Proposed Registration Decision PRD2012-05

Ipconazole

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Overview

Proposed Registration Decision for Ipconazole

Health Canada's Pest Management Regulatory Agency (PMRA), under the authority of the *Pest Control Products Act* and Regulations, is proposing full registration for the sale and use of Ipconazole Technical Fungicide, Vortex FL Seed Treatment Fungicide, Rancona 3.8 FS Fungicide and Rancona Apex Fungicide, containing the technical grade active ingredient ipconazole, to protect against seedling and soil-borne diseases on small grain cereals and corn.

Ipconazole Technical Fungicide (Registration number 29218), Vortex FL Seed Treatment Fungicide (Registration number 29174), Rancona 3.8 FS Fungicide (Registration number 29175; previously known as Ipconazole 3.8 FS Fungicide) and Rancona Apex Fungicide (Registration number 29176; previously known as Crusoe MD Fungicide) are conditionally registered in Canada. The detailed review for Ipconazole Technical Fungicide, Vortex FL Seed Treatment Fungicide, Rancona 3.8 FS Fungicide and Rancona Apex Fungicide can be found in Evaluation Report ERC2011-04: *Ipconazole*. The current applications were submitted to convert Ipconazole Technical Fungicide, Vortex FL Seed Treatment Fungicide, Rancona 3.8 FS Fungicide and Rancona Apex Fungicide from conditional registration to full registration.

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

This Overview describes the key points of the evaluation, while the Science Evaluation section provides detailed technical information on the human health, environmental and value assessments of Ipconazole Technical Fungicide, Vortex FL Seed Treatment Fungicide, Rancona 3.8 FS Fungicide and Rancona Apex Fungicide.

What Does Health Canada Consider When Making a Registration Decision?

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

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

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

to the label directions. Conditions of registration may include special precautionary measures on the product label to further reduce risk.

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

Before making a final registration decision on ipconazole, the PMRA will consider all comments received from the public in response to this consultation document[3]. The PMRA will then publish a Registration Decision[4] on ipconazole, which will include the decision, the reasons for it, a summary of comments received on the proposed final registration decision and the PMRA's response to these comments.

For more details on the information presented in this Overview, please refer to the Science Evaluation section of this consultation document.

What Is Ipconazole?

Ipconazole is a triazole fungicide used to control various fungi species. This active ingredient is used as a seed treatment on small grain cereals and corn to control smuts, bunts, leaf stripe and seed and seedling diseases caused by *Fusarium* spp., *Cochliobolus sativus*, *Rhizoctonia solani*, *Rhizopus* spp., *Cladosporium* spp., *Aspergillus* spp., and *Penicillium* spp. Ipconazole is classified as a Group 3 fungicide that inhibits sterol biosynthesis in fungi.

Health Considerations

Can Approved Uses of Ipconazole Affect Human Health?

Products containing ipconazole are unlikely to affect your health when used according to label directions.

Potential exposure to ipconazole may occur through the diet (food and water), when handling and applying the product, or when entering treated sites. When assessing health risks, two key factors are considered: the levels where no health effects occur and the levels to which people may be exposed. The dose levels used to assess risks are established to protect the most sensitive

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

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

human population (e.g., children and nursing mothers). Only uses for which the exposure is well below levels that cause no effects in animal testing are considered acceptable for registration.

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

A detailed assessment of the toxicology database for ipconazole and its associated end-use products, Rancona 3.8 FS Fungicide, Vortex FL Seed Treatment Fungicide and Rancona Apex Fungicide, can be found in ERC2011-04. In response to issues identified in the conditional registration, the applicant submitted waiver requests to address concerns regarding the cancer assessment, as well as the absence of hormone measurements in the toxicology database. Waiver requests for a short-term immunotoxicity study in rodents and an acute neurotoxicity study in rats were also submitted to address the effects noted on the immune system and potential neurotoxic clinical signs observed at high doses of ipconazole.

A review of the information submitted in the waiver request on the cancer assessment and the effects in endocrine organs was conducted. The information was considered sufficient to address the concerns and no further data are required at this time. The endpoints selected for dietary and occupational risk assessments were revisited to address these conclusions.

Residues in Water and Food

Dietary risks from food and water are not of concern.

Aggregate dietary intake estimates (food plus water) revealed that the general population and children 3-5 years old, the subpopulation which would ingest the most ipconazole relative to body weight, are expected to be exposed to less than 1% of the acceptable daily intake. Based on these estimates, the chronic dietary risk from ipconazole is not of concern for all population sub-groups.

An acute reference dose was determined for the population subgroup of females 13-49 years of age. An aggregate (food and water) dietary intake estimate for females 13-49 years old used less than 1% of the acute reference dose, which is not a health concern.

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

The storage stability data submitted to support the conversion from conditional to full registration are adequate. For the MRLs for this active ingredient, please refer to the Science Evaluation section of ERC2011-04.

Occupational Risks From Handling Vortex FL Seed Treatment Fungicide, Rancona 3.8 FS Fungicide, and Rancona Apex Fungicide

Occupational risks are not of concern when Vortex FL Seed Treatment Fungicide, Rancona 3.8 FS Fungicide, and Rancona Apex Fungicide are used according to the label directions, which include protective measures.

Workers mixing and loading Vortex FL Seed Treatment Fungicide, Rancona 3.8 FS Fungicide, and Rancona Apex Fungicide, or treating seed, as well as workers handling and planting freshly treated seed, can come into direct skin contact with the active ingredient, ipconazole, in these products. Therefore, the labels specify that anyone handling Vortex FL Seed Treatment Fungicide or Rancona 3.8 FS Fungicide, contaminated equipment, or corn seed treated with these products, must wear long pants, a long-sleeved shirt and chemical-resistant gloves. The labels also require that closed mixing/loading equipment be used. For Rancona Apex Fungicide, workers handling the product, contaminated equipment or cereal seed treated with this product must wear long-sleeved coveralls over normal work clothing and chemical-resistant gloves and, for commercial operations, closed mixing/loading equipment is required. Taking into consideration these label statements, the number of applications and the expectation of the exposure period for handlers and workers, the risk to these individuals is not a concern.

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

Environmental Considerations

What Happens When Ipconazole is Introduced Into the Environment?

Environmental risks are negligible when Vortex FL Seed Treatment Fungicide, Rancona 3.8 FS Fungicide, and Rancona Apex Fungicide are used according to label directions, which include precautionary label statements concerning soil incorporation of treated seed and cleanup of spilled seed.

Ipconazole can enter the environment by dislodging from treated seed surfaces during and after seeding. Ipconazole is persistent in the environment, with soil biodegradation being the primary route of transformation. Ipconazole has low mobility in soil, and has low potential to leach to groundwater. Ipconazole is not expected to reach surface waters in any appreciable amounts under the current use pattern, as exposure of surface waters through soil runoff and leaching is expected to be minimal. Some toxicity occurred to laboratory animals exposed to ipconazole; however, the primary environmental risk under the current use pattern is to birds and mammals that may consume treated seed. This risk was determined to be negligible if label statements regarding soil incorporation of treated seed and cleanup of spilled seed are followed. Risk to

other terrestrial and aquatic organisms, and non-target plants is negligible based on low potential for exposure to these organisms.

Value Considerations

What Is the Value of Rancona Apex Fungicide, Rancona 3.8 FS Fungicide, and Vortex FL Seed Treatment Fungicide?

Vortex FL Seed Treatment Fungicide and Rancona 3.8 FS Fungicide are seed treatments for use on field corn, sweet corn and popcorn to provide protection against seed, seedling and soil-borne diseases. Rancona Apex Fungicide is a seed treatment used to control diseases on cereals including wheat, barley, oats, rye and triticale.

Vortex FL Seed Treatment Fungicide and Rancona 3.8 FS Fungicide are alternatives to several older chemicals currently used as corn fungicide seed treatments. As seed treatments, the rate per hectare of all of these products is low and application to the seed reduces exposure to non-target organisms compared to foliar pesticide applications. Rancona Apex Fungicide is a liquid seed treatment with a low concentration of active ingredient and is effective at low rates. Seed and seedling diseases on cereals can be adequately controlled using Rancona Apex Fungicide.

Measures to Minimize Risk

Labels of registered pesticide products include specific instructions for use. Directions include risk-reduction measures to protect human and environmental health. These directions must be followed by law.

The key risk-reduction measures on the labels of Vortex FL Seed Treatment Fungicide, Rancona 3.8 FS Fungicide, and Rancona Apex Fungicide to address the potential risks identified in this assessment are as follows.

Key Risk-Reduction Measures

Human Health

Because there is a concern with users coming into direct contact with ipconazole on the skin or through inhalation of dusts, anyone handling Vortex FL Seed Treatment Fungicide or Rancona 3.8 FS Fungicide, contaminated equipment, or corn seed treated with these products, must wear long pants, a long-sleeved shirt and chemical-resistant gloves. The labels also require that closed mixing/loading equipment be used. For Rancona Apex Fungicide, workers handling the product, contaminated equipment or cereal seed treated with this product, must wear long-sleeved coveralls over normal work clothing and chemical-resistant gloves. Closed mixing/loading equipment is required for the commercial use of Rancona Apex Fungicide.

Environment

The use of Vortex FL Seed Treatment Fungicide, Rancona 3.8 FS Fungicide, and Rancona Apex Fungicide may pose a risk to birds and mammals that consume sufficient amounts of treated seed. Precautionary label statements on the product labels identify and mitigate this risk (i.e., soil incorporation of treated seed and cleanup of spilled treated seed).

Next Steps

Before making a final registration decision on ipconazole, the PMRA will consider all comments received from the public in response to this consultation document. The PMRA will accept written comments on this proposal up to 45 days from the date of publication of this document. Please forward all comments to Publications (contact information on the cover page of this document). The PMRA will then publish a Registration Decision, which will include its decision, the reasons for it, a summary of comments received on the proposed final decision and the Agency's response to these comments.

Other Information

When the PMRA makes its registration decision, it will publish a Registration Decision on ipconazole (based on the Science Evaluation section of this consultation document and ERC2011-04: *Ipconazole*). In addition, the test data referenced in this consultation document and ERC2011-04: *Ipconazole* will be available for public inspection, upon application, in the PMRA's Reading Room (located in Ottawa).

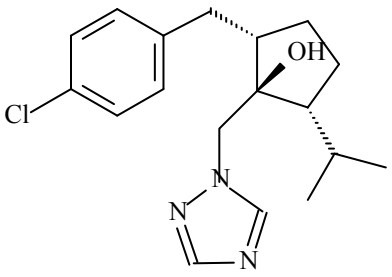
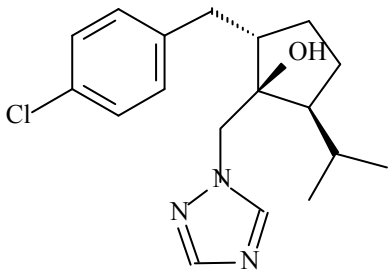
Science Evaluation

Ipconazole

1.0 The Active Ingredient, Its Properties and Uses

Please refer to the Evaluation Report ERC2011-04: *Ipconazole* for the complete chemistry review.

1.1 Identity of the Active Ingredient

Active substance	Ipconazole (ratio of cc to ct isomers is approximately 9:1)
Function	Fungicide
Chemical name	
1. International Union of Pure and Applied Chemistry (IUPAC)	(1RS,2SR,5RS;1RS,2SR,5SR)-2-(4-chlorobenzyl)-5-isopropyl-1-(1H-1,2,4-triazol-1-ylmethyl)cyclopentanol
2. Chemical Abstracts Service (CAS)	2-[(4-chlorophenyl)methyl]-5-(1-methylethyl)-1-(1H-1,2,4-triazol-1-ylmethyl)cyclopentanol
CAS number	125225-28-7 (unstated stereochemistry) 115850-69-6 (cc isomer) 115937-89-8 (ct isomer)
Molecular formula	$C_{18}H_{24}ClN_3O$
Molecular weight	333.9
Structural formula	 cc isomer  ct isomer
Purity of the active ingredient	97.4%

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

Technical Product—Ipconazole Technical Fungicide

Property	Result
Colour and physical state	White powder
Odour	Almond-like odour
Melting range	85.5 – 88.0°C
Boiling point or range	Not applicable
Density	1.18 – 1.26 g/cm^3
Vapour pressure at 20°C	<5.05 x 10^{-5} Pa
Henry's law constant	1.36 x 10^6 for ipconazole cc 7.25 x 10^5 for ipconazole ct
Ultraviolet (UV)-visible spectrum	A major maximum at 222 nm and a minor maximum at 268 nm; no absorbance above 300 nm.
Solubility in water at 20°C	Solvent — cc isomer (mg/L) — ct isomer(mg/L) water — 9.34 — 4.97 pH 5.0 — 9.86 — 5.79 pH 7.0 — 8.68 — 4.60 pH 9.0 — 9.13 — 4.71
Solubility in organic solvents at 20°C (g/L)	Solvent — Solubility acetone — 570 1,2-dichloroethane — 425 dichloromethane — 583 ethyl acetate — 428 heptane — 1.90 methanol — 679 n-octanol — 230 toluene — 156 xylenes — 151
n-Octanol-water partition coefficient (K_{ow})	cc isomer — Log K_{ow} = 4.65 ct isomer — Log K_{ow} = 4.44
Dissociation constant (pK_a)	Unable to determine using the spectrophotometirc method described in OPPTS 830.7370.
Stability (temperature, metal)	Ipconazole Technical Fungicide is stable in the presence of iron, aluminum, iron (II) acetate and aluminum acetate, basic for 14 days at both 20°C and 54°C.

End-Use Product—Vortex FL Seed Treatment Fungicide and Rancona 3.8 FS Fungicide

Property	Result
Colour	Beige
Odour	Very faint odour, reminiscent of latex paint
Physical state	Liquid
Formulation type	Suspension
Guarantee	450 g/L

Property	Result
Container material and description	HDPE bottles or drums
Density at 20°C	1.107 g/mL
pH of 1% dispersion in water	7.0 – 8.5
Oxidizing or reducing action	The product does not contain any oxidizing or reducing agents
Storage stability	Stable for one year under commercial storage conditions
Corrosion characteristics	No corrosion was observed during one year storage
Explodability	Not explosive

End-Use Product—Rancona Apex Fungicide

Property	Result
Colour	Reddish-orange
Odour	Slightly musty odour
Physical state	Liquid
Formulation type	Suspension
Guarantee	4.61 g/L
Container material and description	10 L HDPE jugs and 1000 L LDPE totes
Density at 20°C	1.0 – 1.1 g/mL
pH of 1% dispersion in water	5.0 – 8.0
Oxidizing or reducing action	Not an oxidizing or reducing agent
Storage stability	Stable for one year under commercial storage conditions
Corrosion characteristics	For HDPE bottles, no evidence of perforation, imperfection or discoloration. But for LDPE boxes, the interior has a ring of pink stain. There is no evidence of either decomposition of the product or degradation of the packaging material.
Explodability	Not explosive

1.3 Directions for Use

Directions for use can be found in ERC2011-04, Section 1.3.

1.4 Mode of Action

The mode of action of ipconazole can be found in ERC2011-04, Section 1.4.

2.0 Methods of Analysis

Methods for analysis of the active ingredient, formulations and residue analytical methods for data generation and enforcement purposes can be found in ERC2011-04, Section 2.0.

3.0 Impact on Human and Animal Health

3.1 Toxicology Summary

Only the information submitted in support of the conversion from conditional to full registration is discussed herein. Refer to Report ERC2011-04 for a detailed toxicology assessment of ipconazole.

During the original review, it was concluded that ipconazole did not cause cancer in mice and rats at the doses tested. However, the highest dose tested (13 mg/kg bw/day) in the rat combined chronic/carcinogenicity study was considered to be inadequate based on the marginal effects on body weight gain and the lack of systemic toxicity observed during the study. Ipconazole has irritant properties that resulted in the formation of lesions on the epithelial mucosa of the rodent forestomach. Although these lesions are not toxicologically relevant to humans, consideration of such lesions influenced the dose selection in the long-term study. During the original evaluation, a weight of evidence approach was employed, which involved a review of other related triazole compounds. Overall, ipconazole is not expected to cause hepatocarcinogenic effects in rats below the dose likely to elicit forestomach lesions. However, evidence from other triazoles indicates that rats dosed at or below the maximum tolerated dose (MTD) tend to exhibit greater sensitivity than mice to triazole-mediated oncogenic effects in the endocrine organs (ovaries, testes, thyroid and adrenal) and urinary bladder. Based on these residual uncertainties, a new cancer study, or a detailed rationale outlining why the highest dose tested in the current study was adequate for the assessment of carcinogenic potential, was requested as a condition of registration. In addition, based on the endocrine effects observed in the toxicological database at higher dose levels, a study examining hormone measurements after short-term dosing in rats was also requested. Submission of a short-term immunotoxicity study in rodents and an acute neurotoxicity study in rats was not required at the time of conditional registration; however, these studies were requested since they were required by other regulatory authorities. For the current submission, the applicant submitted waiver requests to address the above-noted data deficiencies.

Oncogenicity study in rats

The doses in the 2-year rat oncogenicity study were 0, 1.3, 3.6, 9.0 mg/kg bw/day in males and 0, 1.9, 4.9, 7.3, 12.6 mg/kg bw/day in females, and no effects on the non-glandular stomach were observed. In two 13-week rat toxicity studies, a dose-response for non-glandular stomach lesions (e.g., epithelial hyperplasia leading to hyperkeratosis, erosion and ulceration) was observed at doses of approximately 26 mg/kg bw/day to 33 mg/kg bw/day and females appeared to be slightly more sensitive to non-glandular stomach lesions than males. The potential occurrence of these effects from 12.6 to 26 mg/kg bw/day was not characterized due to dose selection in the long-term study. The registrant concluded that a slight increase in the dose used in the combined chronic/carcinogenicity study could have potentially compromised the health of the animals due to non-glandular stomach effects. Given the unique nature of the non-glandular stomach lesions observed after short-term dosing with ipconazole and the potential for these lesions to increase

mortality over a longer-term study, the doses selected for the 2-year rat carcinogenicity study were based on reasonable scientific principles.

A re-analysis of the tumour data available for a number of triazole compounds indicated that treatment-related neoplastic lesions in the endocrine organs almost always occurred in the presence of pre-neoplastic lesions. The only two exceptions in rats included a case where thyroid follicular cell adenomas occurred in excess of the MTD and in the case of a threshold response for testicular Leydig tumours. For ipconazole, there were no pre-neoplastic lesions in the organs of rats in the 2-year study up to 13 mg/kg bw/day. In addition, there was no evidence of carcinogenicity in mice at the highest dose tested. Based on a re-consideration of the available information, it was concluded that a new carcinogenicity study in rats at slightly higher doses would not further inform the ipconazole risk assessment and, therefore, the waiver request for a new 2-year rat carcinogenicity study was accepted.

Hormone measurements in rats

A re-consideration of the toxicology data for ipconzole revealed marginal effects in endocrine organs when compared to other triazole compounds. Increased thyroid, prostate and ovary weights were observed after ipconazole treatment and were not associated with correlative histopathology. There were no adverse effects on ovarian follicle counts or reproductive performance in a 2-generation reproductive toxicity study. Treatment-related delayed vaginal opening in F_1 female offspring and decreased pup weights up to postnatal day 25 were observed but there were no effects on sexual maturation in males or on anogenital distance in offspring. Treatment-related increased adrenal weights and associated histopathology (e.g., cortical hypertrophy/hyperplasia, fatty vacuolation) were observed in short-term studies with ipconazole in rats and dogs. In a 13-week oral toxicity study in rats, treatment-related decreases in uterine weight were associated with decreased fluid distension and decreased luminal dilatation. A review of other triazole compounds revealed that treatment-related changes in hormone levels occurred at doses where systemic toxicity, developmental malformations or reproductive organ histopathology were observed. Based on the weight of evidence of the available data, additional hormone measurements in rats are not expected to result in a reference dose lower than those currently established for ipconazole. The waiver request submitted by the applicant was granted.

Toxicity Studies Requested by other Regulatory Authorities

Immunotoxicity:
Effects on the immune system were noted at high doses of ipconazole. The US EPA requested an immunotoxicity study as a condition of registration and since these data were expected to be available, they were also requested by the PMRA to further inform the toxicology assessment. The applicant submitted a waiver request to address these concerns. In dogs, treatment-related effects occurred in the thymus and reddening of the skin was observed in all of the dog toxicity studies. Taken together with the adrenal, thymus and increased white blood cell effects elsewhere in the toxicology database, these findings suggested that ipconazole may cause immune stimulation or autoimmunity at higher doses. Overall, the concern for these effects was low, as there were clear no observed adverse effect levels (NOAELs) in all of the dog toxicity

studies and the next highest dose for potential immunological effects was approximately 10-fold higher than the dose that caused skin reddening in dogs. Based on a re-consideration of the toxicological information, the toxicology reference doses established for ipconazole are considered to be protective of any potential effects on the immune system. Therefore, a short-term immunotoxicity study is not required.

Neurotoxicity:
There was no evidence of neurotoxicity in the acute oral rat study, in the functional observation battery in the 13-week toxicity study in rats, in the 104-week combined chronic/carcinogenicity studies in rats, or in any of the other repeat dosing studies with ipconazole. Some potential neurotoxic clinical signs (e.g. decreased locomotor activity, tip-toe gait) were seen in the acute oral toxicity studies in mice and rats at high doses; however, these effects were generally observed immediately after dosing and tended to occur at doses where mortality was observed.

A limited number of developmental neurotoxicity studies are available for triazole compounds. Among the two available studies, only rat offspring treated with prothioconazole-desthio showed developmental neurotoxicity. The effects occurred in the presence of maternal toxicity and a clear NOAEL for developmental neurotoxicity was established in this study. Developmental malformations occurred at lower doses. Refer to Regulatory Note REG2007-03: *Prothioconazole* and Proposed Regulatory Decision PRD2010-08: *Prothioconazole* for further details.

Overall, it was concluded that there was low concern for neurotoxicity associated with ipconazole based on the fact that there was no evidence of treatment-related neurotoxicity in the toxicological database and no indication of effects on the developing nervous system in the available data, which included several reproductive and developmental toxicity studies. As such, no additional neurotoxicity data are required at this time.

Results of the additional toxicology information submitted for ipconazole and reviewed under the current submission are summarized in Appendix I, Table 1. The toxicology endpoints for use in the human health risk assessment are summarized in Appendix I, Table 2.

Incident Reports

Since April 26, 2007, registrants have been required by law to report incidents, including adverse effects to health and the environment, to the PMRA within a set time frame. Information on the reporting of incidents can be found on the PMRA website. Incidents from Canada and the United States were searched for ipconazole. As of October 25, 2011, there were no reports of adverse health effects for this active in the PMRA Incident Reporting database.

3.1.1 PCPA Hazard Characterization

For assessing risks from potential residues in food or from products used in or around homes or schools, the *Pest Control Products Act* requires the application of an additional 10-fold factor to threshold effects to take into account completeness of the data with respect to the exposure of,

and toxicity to, infants and children, and potential prenatal and postnatal toxicity. A different factor may be determined to be appropriate on the basis of reliable scientific data.

With respect to the completeness of the toxicity database as it pertains to the toxicity to infants and children, extensive data were available for ipconazole. The database contains the full complement of required studies including developmental toxicity studies in rats and rabbits and a reproductive toxicity study in rats. Endocrine organs were targeted at high dose levels after ipconazole treatment. While endocrine activity can be a trigger for a developmental neurotoxicity study, no study was available for ipconazole. A weight of evidence approach concluded that additional hormone measurements in rats after short-term dosing would not impact the reference doses. The endocrine effects observed in the repeat dose toxicity studies occurred at doses above those that are used for risk assessment and there was no evidence of neurotoxicity in adult rats after ipconazole treatment. Based on this information, a developmental neurotoxicity study is not required at the present time.

In a two-generation reproductive toxicity study in rats, treatment-related effects in parents included decreased body weight and/or body weight gain and food consumption. Reproductive effects included increased ovary weight, decreased implantation sites and decreased total offspring number. In offspring, decreased body weight and/or body weight gain and delayed vaginal opening were observed at doses that were toxic to the parents. There was no indication of increased susceptibility of the offspring compared to parental animals in the multi-generation reproductive toxicity study.

In the rat developmental toxicity study, decreased fetal weights and increased incidences of fetal variations such as dilatation of renal pelvis and/or ureter, and left umbilical artery and/or lumbar ribs were noted. These effects were observed in the presence of maternal toxicity (decreased body weight/gain and food consumption during a limited period of time during dosing, increased placental weights). In the rabbit, splitting of the parietal bone, considered a malformation, was observed at maternally toxic doses.

Overall, the database is adequate for determining the sensitivity of the young. There is a low concern for sensitivity of the young and effects on the young are well-characterized. The fetal effects were considered serious endpoints although the concern was tempered by the presence of maternal toxicity. Therefore, the PCPA factor was reduced to 3-fold when using the rabbit developmental toxicity study to establish the point of departure for assessing risk to women of child-bearing age and their fetuses. For exposure scenarios for children, the risk was considered well-characterized and the PCPA factor was reduced to 1-fold.

3.2 Acute Reference Dose

Females 13-49 Years of Age

To estimate acute dietary risk (1 day), the rabbit developmental toxicity study with a NOAEL of 10 mg/kg bw/day was selected for risk assessment. At the lowest observed adverse effect level (LOAEL) of 50 mg/kg bw/day, decreased body weight gains or body weight loss during dosing, decreased food consumption and decreased placental weights were observed in maternal

animals. These findings were associated with decreased fetal weights and increased major malformations, primarily consisting of splitting of the parietal bone. Malformations may result from a single exposure and are therefore relevant to an acute risk assessment. Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability have been applied. As discussed in the PCPA Hazard Characterization section, the PCPA factor was reduced to 3-fold. **The composite assessment factor (CAF) is 300-fold.**

The acute reference dose (ARfD) is calculated according to the following formula:

$$\text{ARfD (females 13-49)} = \frac{\text{NOAEL}}{\text{CAF}} = \frac{10 \text{ mg/kg bw}}{300} = 0.033 \text{ mg/kg bw of ipconazole}$$

General population (excluding females 13-49 years of age)
An acute reference dose for ipconazole was not determined for the general population, including infants and children, because an endpoint of concern attributable to a single exposure was not identified in the oral toxicity studies for this population of interest.

3.3 Acceptable Daily Intake (ADI)

To estimate dietary risk of repeat exposure, the three co-critical studies (12-month dog study, 18-month mouse study, two-generation reproductive toxicity study) with NOAELs of 2 mg/kg bw/day were selected. In the 12-month dog study, treatment-related effects at the LOAEL of 5 mg/kg bw/day consisted of increased reddening of the skin in both sexes and decreased body weight gains in females. In the two-generation reproductive toxicity study, effects at the LOAEL of approximately 8 mg/kg bw/day included decreased body weight, body weight gain and food consumption in parents and offspring. In the 18-month mouse study, there was evidence of increased liver and stomach histopathology at the LOAEL of 24.1 mg/kg bw/day. Collectively, these co-critical studies represent the lowest NOAELs in the database. Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability have been applied. As discussed in the PCPA Hazard Characterization section, the PCPA factor was reduced to 1-fold. **The CAF is 100-fold.**

The acceptable daily intake (ADI) is calculated according to the following formula:

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

The ADI provides margins of 2500 to the dose at which splitting of the parietal bone (a developmental malformation) was observed in rabbits and 1500 to the dose at which decreased fetal weights and developmental variations were observed in rats.

Cancer Assessment

There was no evidence of carcinogenicity and therefore, no cancer risk assessment was necessary.

3.4 Occupational and Residential Risk Assessment

3.4.1 Toxicological Endpoints

Short-term and Intermediate-term Dermal

For short-term and intermediate-term dermal risk assessments for adults, the developmental toxicity study in rabbits was selected. At doses of 50 mg/kg bw/day, decreased fetal weights and increased incidences of major malformations including splitting of the parietal bone were observed in the presence of maternal toxicity. A NOAEL of 10 mg/kg bw/day was established. The short-term dermal toxicity study did not address the endpoint of concern, thus necessitating the use of an oral study for risk assessment.

For occupational scenarios, the target Margin of Exposure (MOE) for this endpoint is 300. Ten-fold factors were applied each for interspecies extrapolation and intraspecies variability. As the worker population could include pregnant women, it is necessary to afford adequate protection of the fetus who may be exposed via its mother. In light of concerns regarding prenatal toxicity (as outlined in the PCPA Hazard Characterization section), an additional 3-fold factor was applied to this endpoint to protect sensitive subpopulations, females 13-49 years of age and their offspring.

Short- and Intermediate-term Inhalation

For short- and intermediate-term inhalation risk assessment for adults, the 28-day inhalation toxicity study in rats was selected. At doses of 8 mg/kg bw/day, treatment-related portal of entry irritation (epithelial hyperplasia and/or metaplasia on epithelial surface of hard palate, larynx, nose and increased inflammatory cells in the mucosa of the trachea and lungs) was observed and was considered to be the most relevant endpoint for occupational and bystander inhalation risk assessment. A NOAEL was not established, as this was the lowest dose tested.

For occupational scenarios, the target MOE for this endpoint is 300. Ten-fold factors were applied each for interspecies extrapolation and intraspecies variability. An additional 3-fold factor was applied to this endpoint for extrapolation from a LOAEL to a NOAEL.

3.4.1.1 Dermal Absorption

Dermal absorption can be found in ERC2011-04, Section 3.4.1.1.

3.4.2 Occupational Exposure and Risk

3.4.2.1 Mixer/loader/applicator Exposure and Risk Assessment

Individuals have potential for exposure to Vortex FL Seed Treatment Fungicide, Rancona 3.8 FS Fungicide, and Rancona Apex Fungicide during mixing, loading and treating seed, contacting contaminated seed treatment equipment and handling and planting treated seed.

Commercial Seed Treatment

Corn seed

Exposure to workers treating corn seed with Vortex FL Seed Treatment Fungicide and Rancona 3.8 FS Fungicide is expected to be of short- to intermediate-term in duration and to occur primarily by the dermal and inhalation routes. Exposure estimates were derived for workers treating corn seed with Vortex FL Seed Treatment Fungicide and Rancona 3.8 FS Fungicide using commercial seed treatment equipment. The exposure estimates are based on treaters and baggers wearing long pants, long-sleeved shirts and chemical resistant gloves.

Chemical-specific data for assessing human exposures during pesticide handling activities were not submitted. Since the label states that Vortex FL Seed Treatment Fungicide and Rancona 3.8 FS Fungicide are intended for use by commercial seed treatment applicators, on-farm seed treatment was not considered in the risk assessment.

For Vortex FL Seed Treatment Fungicide and Rancona 3.8 FS Fungicide applied to corn seed, dermal and inhalation exposure estimates for workers treating and bagging were generated from a surrogate exposure study measuring exposure to workers treating and bagging canola seed treated with the technical grade active ingredient isofenphos.

The surrogate study was conducted to quantify inhalation and dermal exposure of workers during commercial seed treatment of canola seed with Oftanol (containing isofenphos) and Benlate T (containing benomyl and thiram) at an application rate of 12 g isofenphos/kg seed. Monitoring was done for isofenphos only. Workers monitored in this study included a mixer/loader, a treater, a bagger, and a shift foreman. The study was conducted in Alberta. Four workers were monitored three times for a total of 12 replicates. The maximum amount of active ingredient handled per replicate was 92 kg. The average duration of each replicate was 7.4 hours.

Dermal exposure was estimated using passive dosimetry. Deposition was measured using dermal patches attached to the inner and outer clothing of each worker. Deposition to the hands was measured using ethanol hand washes. Total dermal exposure was calculated by extrapolating the patch data to standard body surface areas, and summing all body area results together with the handwash residues. Inhalation exposure was measured using air filters attached to personal air sampling pumps.

The total dermal exposure (patch deposition and hands) was added to the inhalation results for each worker, and normalized for kg active ingredient (a.i.) handled. The mean total exposure was highest for mixer/loader (189.28 µg/kg a.i.), followed by shift foreman (98.02 µg/kg a.i.), treater (33.29 µg/kg a.i.) and bagger (20.54 µg/kg a.i.).

These estimates are based on a closed mixing/loading system with workers wearing long pants, long-sleeved shirts and chemical resistant gloves. Estimates are based on workers with no head covering, and no respirators. The major limitation of this study was that only four workers at one test site were monitored. A greater sample size with additional plants would have allowed for a more accurate comparison between individuals and between plants.

Dermal exposure was estimated by coupling the unit exposure values from the surrogate study with the amount of product handled per day and the dermal absorption value. Inhalation exposure was estimated by coupling the unit exposure values with the amount of product handled per day with 100% inhalation absorption. Exposure was normalized to mg/kg bw/day by using 70 kg adult body weight.

Exposure estimates were compared to the toxicological endpoints (NOAELs) to obtain the MOE; the target MOE is 300.

Studies using canola seed treatment have previously been used as surrogates to represent exposure to workers treating corn seed; however, corn seed is expected to be dustier than canola seed. As such, bridging data were submitted to demonstrate the applicability of using exposure data for workers treating canola to estimate exposure to workers treating corn. A dust-off study was performed that compared the dust-off potential of seeds treated with different formulations (containing another active ingredient) with the dust-off potential of the seeds treated in the surrogate studies. Based on the results of this dust-off study, the surrogate exposure studies on canola seeds treated with isofenphos provide accurate representations of the amount of dust workers would be exposed to by corn seeds treated with Vortex FL Seed Treatment Fungicide or Rancona 3.8 FS Fungicide.

Margins of exposure for all seed treatment workers treating corn with Vortex FL Seed Treatment Fungicide or Rancona 3.8 FS Fungicide are above the target MOE for both dermal and inhalation exposure (Appendix I, Table 3). The personal protective equipment (PPE) for workers in the study is the same as that on the Vortex FL Seed Treatment Fungicide and Rancona 3.8 FS Fungicide labels. Since a closed mixing/loading system was used in the surrogate study, closed mixing/loading was required on the Vortex FL Seed Treatment Fungicide and Rancona 3.8 FS Fungicide labels.

Since the MOEs are significantly higher than the target MOE of 300 for both dermal and inhalation exposure, the surrogate study on canola used in the risk assessment to estimate exposure to corn and the submitted dust-off study are considered acceptable for these two products on corn.

Cereal seed

Exposure to workers treating wheat, barley, oat, rye and triticale seed with Rancona Apex Fungicide is expected to be of short- to intermediate-term in duration and to occur primarily by the dermal and inhalation routes. Chemical-specific data for assessing human exposures during pesticide handling activities were not submitted. Since the label states that Rancona Apex Fungicide is intended for use by commercial and on-farm seed treatment applicators, both of these scenarios were considered in the risk assessment.

Dermal and inhalation exposure estimates for commercial workers treating and bagging cereal seed with Rancona Apex Fungicide were generated from a surrogate exposure study measuring exposure to workers treating and bagging wheat seed treated with Baytan 312 FS containing the active ingredient triadimenol. The study was conducted at three different facilities in Ontario,

Canada, to estimate and compare exposures at large, medium, and small size treatment facilities. Workers were monitored for half-day replicates over two or three days at each facility for a total of 55 half-day replicates. The maximum amount of active ingredient handled per replicate was 21.9 kg. The average duration of each replicate was approximately 3.0–3.5 hours.

Dermal exposure was estimated using dermal patches attached to the inner and outer clothing of each worker. Deposition to the hands and gloves was measured using ethanol hand washes. Total dermal exposure was calculated by extrapolating the patch data to standard body surface areas, and summing all body area results together with the hand wash residues. Inhalation exposure was measured using air filters attached to personal air sampling pumps. All results were corrected for field recovery, where necessary. The study was conducted according to current guidelines, and no major limitations were identified.

Each worker was monitored for half of a work day and wore their normal work clothing, consisting of long pants, long-sleeved shirts and chemical resistant gloves. The total dermal exposure (patch deposition and hands) was added to the inhalation results for each replicate, and normalized for kg a.i. handled. The arithmetic mean value was calculated for each job at each site.

These results are based on half-day replicates for workers wearing long-sleeved shirts, long pants and chemical resistant gloves.

The mixer/calibrator at each facility prepared the treatment mixture by weighing each component by hand, and placing it into a 200 L drum. The mixture consisted of approximately 6 kg of seed colourant, 43 kg Baytan 312 FS, and 156 kg water. The drum served as a temporary mix tank which the worker rolled back and forth to mix the components. The drum was then attached to the treatment equipment. During disassembly, the worker was monitored while disconnecting the hoses and fittings from the drum containing the treatment mixture, cleaning the drum and loading it into a transport van. The study authors stated that these activities and equipment were not typical for most treatment plants, and are not considered relevant for exposure assessment. As such, the mixer/calibrator was excluded when estimating exposure for workers in a commercial seed treatment facility.

The highest mean dermal and inhalation unit exposure values, excluding the mixer/calibrator for medium facilities (689.73 µg/kg a.i handled and 245.74 µg/kg a.i. handled for dermal and inhalation exposures, respectively) were used to estimate exposure to workers treating small cereal grains with Rancona Apex Fungicide.

Margins of exposure for dermal and inhalation exposure for workers treating small cereal grain seed with Rancona Apex Fungicide at commercial seed treatment facilities are above the target of 300 (Appendix I, Table 4) for workers wearing a single layer plus chemical resistant gloves. These estimates are expected to overestimate exposure for most commercial seed treatment workers since a dermal penetration value of 100% was used in the risk assessment.

Since oats are expected to have a higher dust-off potential than wheat, which was used in the surrogate commercial treating study, and the estimated MOEs are relatively close to the target, a suitable dust-off study comparing the dust-off potential of wheat with that of oats was submitted. Based on the results of this dust-off study, the surrogate exposure study on wheat seeds treated with Baytan 312 FS provide an accurate representation of the amount of fine dust workers would be exposed to by oat seeds treated with Rancona Apex, and an overestimate of coarse dust workers would be exposed to by treated oat seeds.

On-farm Seed Treatment and Planting

Exposure to farmers treating small cereal grain seed on-farm and planting treated seed is expected to be of short- to intermediate-term in duration and to occur via the dermal and inhalation routes of exposure. Chemical-specific data measuring exposure to workers treating cereal grains on-farm were not submitted. Dermal and inhalation exposure estimates for farmers treating small grain seeds on-farm with Rancona Apex Fungicide and planting treated seed were generated from a surrogate study measuring exposure to workers treating wheat and barley seed on-farm with Vitaflo 280 Fungicide (containing carbathiin and thiram) and planting treated seed.

The target application rate in the study was 330 mL product/100 kg of seed (57 g a.i./100 kg seed). The maximum proposed application rate of Rancona Apex Fungicide on small grain cereals was 2 g a.i./100 kg seed. The application rate used in this exposure study was higher than that proposed for Rancona Apex Fungicide. The type and amount of seed treated, the treatment equipment and study location are representative of the use pattern; however, the protective equipment used in the study was more protective that the PPE specified on the proposed product label.

Sixteen workers were monitored using inner dosimeters, face/neck wipes and handwash samples to estimate dermal exposure and air sampling tubes to estimate inhalation exposure. The inner dosimeters were worn under a long-sleeved shirt and long pants, additional protective equipment worn included cloth coveralls, a dust mask, goggles, chemical resistant gloves and shoes plus socks. Planting was done with closed cab tractors. Workers handled an average of 4.24 kg a.i. (range 1.74- 6.94 kg a.i.) and planted an average of 54.3 ha (range 26.4- 86.0 ha) of treated seed. The average monitoring period was 9.2 hours and ranged from 6.2 to 13.4 hours.

Overall, the study was well conducted and the data quality is adequate for risk assessment purposes. The mean dermal exposure, when adjusted for the amount of active ingredient handled, as 111.84 g/kg a.i. handled. The hands constituted the majority (approximately 58%) of dermal exposure. Of the residues measured on inner dosimeter sections, the majority was on lower arm sections. The mean inhalation exposure when adjusted for the amount of active ingredient handled was 20.6 g/kg a.i. handled.

Field recovery for air sampling tubes at the low fortification level was low (45.3%). Nine of the sixteen inhalation residue values were corrected for this low field recovery. As well, the air sampling tubes were stored for up to 469 days prior to analysis. Two samples were stored for slightly longer than the field fortified samples. These limitations reduce the confidence in the

inhalation unit exposure value. However, since inhalation exposure is not the principal route of exposure in this study, this study limitation is not expected to have a serious effect on the data.

Margins of exposures for workers treating and planting wheat and barley grain seed with Rancona Apex Fungicide on-farm are above the target of 300 (Appendix 1, Table 5). However, since the protective clothing worn by the workers in the study was higher than that proposed on the Rancona Apex Fungicide label, and it was not possible to extrapolate to other clothing scenarios, coveralls over a single layer of clothing were required during on-farm treatment and planting on the product label for Rancona Apex Fungicide. The requirement to use a closed cab tractor when an exposure assessment is based on this study has recently been re-examined, and depending on the difference between the target MOE and the calculated MOE, the requirement may be waived. In this instance, the calculated MOEs are 23,181 for dermal exposure and 100,683 for inhalation exposure. As these are considerably above the target of 300, no closed cab tractor is required for on-farm workers planting seed with Rancona Apex Fungicide. The exposure to on-farm planters is expected to cover off the exposure to commercial planters, who also require the PPE (coveralls over a single layer and chemical resistant gloves) from the surrogate study.

Oats are expected to have a higher dust-off potential than wheat and barley, which were used in the surrogate on-farm treating and planting study. Since the MOEs for workers treating seed on-farm and planting are significantly higher than the target MOE of 300 for both dermal and inhalation exposure, the registration of on-farm treatment with Rancona Apex Fungicide on oats was supported on a conditional basis pending a study comparing the dust-off potential of wheat treated with Vitaflo 280 Fungicide with that of oats treated with Rancona Apex Fungicide. The applicant submitted a study that compared the relevant products, which demonstrated a lower dust-off potential in oat seeds treated with Rancona Apex Fungicide than wheat seeds treated with two different rates of Vitaflo 280 Fungicide. Thus, the full on-farm registration of Rancona Apex Fungicide on oat and other cereal seeds can be supported from an occupational exposure perspective.

3.4.2.2 Exposure and Risk Assessment for Workers Entering Treated Areas

Workers planting corn seed treated commercially with Vortex FL Seed Treatment Fungicide or Rancona 3.8 FS Fungicide have the potential to be exposed to ipconazole. Exposure is expected to be of short- to intermediate-term in duration and to occur via the dermal and inhalation routes of exposure.

No chemical specific data were submitted by the registrant to represent exposure to workers planting corn seed treated commercially with Vortex FL Seed Treatment Fungicide or Rancona 3.8 FS Fungicide. Dermal and inhalation exposure estimates for workers planting treated seed were generated from a surrogate exposure study measuring exposure to workers planting canola seed treated with isofenphos.

This post-application passive dosimetry study monitored four private growers, each serving as a subject three or four times, for a total of thirteen replicates during loading and planting of canola

seed treated with a mixture containing Oftanol (technical isofenphos) and Benlate T. Monitoring and sample analysis was for isofenphos and its oxygen analog. The study was conducted in Manitoba. Work involved loading the treated seed (25 kg bag) into seed hoppers and planting between 6.7 - 9.0 kg seed/ha using tractor driven planters. The duration of each replicate was between 1.83 - 6.24 hours and each worker handled between 0.86 - 2.81 kg a.i./replicate.

Dermal deposition was measured using patches attached to the inner and outer clothing of each worker. Deposition to the hands was measured using ethanol handwashes. Potential inhalation exposure was measured using air filters attached to personal air sampling pumps. Total exposure was estimated for workers wearing a typical clothing scenario for seed planting including long-sleeved shirt and long pants and wearing chemical resistant gloves while handling the treated seed.

Total dermal exposure was calculated by extrapolating each interior patch data and two exterior patches (upper back and head) to standard body surface areas, and summing results for total body deposition and adding the handwash residues. Inhalation exposure was calculated based on the amount of isofenphos found on the air-sampling filters, the pump flow rate, and an assumed respiratory rate of 29 L/minute (0.029 m^3/minute) for moderate activities. Since workers were not monitored for a full work day, results were normalized to µg/kg a.i. handled. Based on the typical clothing scenario, the mean total exposure (body + hands + inhalation) was 425.28 µg/kg a.i. handled and ranged from 183.55 to 947.02 µg/kg a.i. handled.

The major limitation of this study was that only four workers were monitored. A greater sample size would have allowed for a more accurate comparison between individuals. Other minor limitations did not affect the outcome of the study. Dermal exposure was estimated by coupling the unit exposure values from the surrogate study with the amount of product handled/day and the dermal absorption value. Inhalation exposure was estimated by coupling the unit exposure values with the amount of product handled/day with 100% inhalation absorption. Exposure was normalized to mg/kg bw/day by using 70 kg adult body weight.

Exposure estimates were compared to the toxicological endpoints (NOAELs) to obtain the MOE; the target MOE is 300.

Margins of exposures for workers planting corn seed treated with Vortex FL Seed Treatment Fungicide or Rancona 3.8 FS Fungicide (Appendix I, Table 6) are above the target MOE for both dermal and inhalation exposure for workers wearing long-sleeved shirts, long pants and chemical resistant gloves while handling the treated seed. The requirement to use a closed cab tractor when an exposure assessment is based on this study has recently been re-examined, and depending on the difference between the target MOE and the calculated MOE, the requirement may be waived. In this instance, the calculated MOEs are 48,543 for dermal exposure and 14,950,000 for inhalation exposure. As these are considerably above the target of 300, no closed cab tractor is required for planters of seed treated with Vortex FL Seed Treatment Fungicide or Rancona 3.8 FS Fungicide. Based on the submitted and reviewed dust-off study comparing canola and corn seed, the surrogate study on canola used in the risk assessment to estimate exposure to corn is considered acceptable.

Workers planting cereal grain seeds treated with Rancona Apex Fungicide also have the potential to be exposed to ipconazole. Exposure is expected to be of short- to intermediate-term in duration and to occur via the dermal and inhalation routes of exposure.

Since MOEs for workers treating and planting wheat and barley grain seed on-farm are above the target of 300 (Appendix I, Table 5), exposure for workers planting wheat, barley, oat, rye and triticale treated commercially with Rancona Apex Fungicide is expected to be above the target as well, when all handlers wear coveralls over a single layer and chemical resistant gloves. There are no risks of concern for workers planting treated oat seeds, based on the results of the submitted dust-off study comparing wheat and oat seeds.

3.4.3 Residential Exposure and Risk Assessment

Residential exposure and risk assessment can be found in ERC2011-04, Section 3.4.3.

3.4.4 Bystander Exposure and Risk

Bystander exposure and risk can be found in ERC2011-04, Section 3.4.1.1.

3.5 Food Residues Exposure Assessment

3.5.1 Residues in Plant and Animal Foodstuffs

Please refer to ERC2011-04 for a summary of the previously reviewed data and the rationale for the regulatory decision. The information captured herein only relates to the storage stability data provided to the Agency in support of the conversion from conditional to full registration, and the change in the chronic dietary exposure results due to the modification in the ADI.

The storage stability data requirements identified in ERC2011-04 were submitted and deemed to be adequate. The data demonstrate that the storage conditions and intervals in the wheat and soybean metabolism studies and in the barley and wheat field trials are acceptable.

3.5.2 Dietary Risk Assessment

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

3.5.2.1 Chronic Dietary Exposure Results and Characterization

The following criteria were applied to the basic chronic analysis: 100% crop treated, default processing factors and residues of ipconazole on crops at MRL levels (equivalent to LOQ; 0.01 ppm). Aggregate exposure from food and water is considered acceptable for the total population, including infants and children, and all representative population subgroups. The PMRA

estimates that the basic chronic dietary exposure to ipconazole from all supported ipconazole food uses and water is 0.2% of the ADI for the total population (0.000048 mg/kg bw/day). The highest exposure and risk estimate is for children 3-5 years old at 0.6% of the ADI (0.000114 mg/kg bw/day).

3.5.2.2 Acute Dietary Exposure Results and Characterization

A basic acute dietary exposure assessment was conducted using the MRLs for crop commodities. Aggregate exposure from food and water is considered acceptable and below PMRA's level of concern. Specifically, an acute dietary exposure of 0.25% of the ARfD was obtained for females 13-49 years old. Please refer to ERC2011-04 for details.

3.5.3 Aggregate Exposure and Risk

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

3.5.4 Maximum Residue Limits

Please refer to ERC2011-04 for the proposed MRLs for ipconazole as well as the nature of the residues in animal and plant matrices, analytical methodology and field trial data. The acute and chronic dietary risk estimates are summarized in Appendix I, Table 7.

4.0 Impact on the Environment

4.1 Fate and Behaviour in the Environment

A comprehensive summary of the fate and behaviour in the environment can be found in ERC2011-04, Section 4.1.

4.2 Environmental Risk Characterization

A comprehensive summary of the environmental risk characterization to terrestrial and aquatic organisms can be found in ERC2011-04, Section 4.2.

5.0 Value

5.1 Effectiveness Against Pests

5.1.1 Acceptable Efficacy Claims

A summary of the submitted value data and supported uses for Rancona Apex Fungicide, Rancona 3.8 FS Fungicide and Vortex FL Seed Treatment Fungicide can be found in ERC2011-04, Section 5.1.1.

As a condition of registration for Rancona Apex Fungicide, additional data were requested to confirm efficacy against post-emergence damping-off caused by *Cochliobolus sativus* on wheat, barley, oats, rye and triticale. The claim was subsequently withdrawn by the applicant.

As well, as a condition of registration for Rancona 3.8 FS Fungicide and Vortex FL Seed Treatment Fungicide, additional data were requested to confirm efficacy against seed rot, damping-off and seedling blight caused by *Fusarium* spp. and seed rot and damping-off caused by *Rhizoctonia solani* on corn (sweet, field, popcorn). The data from three efficacy trials conducted on corn in 2009 and 2010 were submitted to satisfy the conditions of registration. The efficacy data demonstrated that Rancona 3.8 FS Fungicide (Vortex FL Seed Treatment Fungicide) controls seed rot / pre-emergence damping-off and seedling blight caused by *Fusarium* spp., and seed rot / pre-emergence damping off caused by *R. solani*. The claims of control of post-emergence damping-off caused by *Fusarium* spp. and *R. solani* were withdrawn by the applicant.

5.2 Phytotoxicity to Host Plants

Information on phytotoxicity can be found in ERC2011-04, Section 5.2

5.3 Economics

Information on economics can be found in ERC2011-04, Section 5.3.

5.4 Sustainability

5.4.1 Survey of Alternatives

Several seed treatments are available for the control of seed rot and seedling blight pathogens on cereals and corn. Differences exist between seed treatments as to the number of crops registered, pests controlled, use restrictions and pricing. For further information on seed treatment alternatives available for cereals and corn, please refer to ERC2011-04, Appendix I, Table 22 (cereals) and Table 23 (corn). Please note that an additional product, Maxim Quattro Seed Treatment (Registration number 29871), containing fludioxonil, metalaxyl-m and s- isomers, azoxystrobin and thiabendazole has been registered to control the supported pests on corn since the publication of ERC2011-04.

5.4.2 Compatibility with Current Management Practices Including Integrated Pest Management

Information on compatibility with current management practices can be found in ERC2011-04, Section 5.4.2.

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

Information on resistance can be found in ERC2011-04, Section 5.4.3.

5.4.4 Contribution to Risk Reduction and Sustainability

Information on risk reduction and sustainability can be found in ERC2011-04, Section 5.4.4.

6.0 Pest Control Product Policy Considerations

6.1 Toxic Substances Management Policy Considerations

A comprehensive summary of the Toxic Substances Management Policy consideration can be found in ERC2011-04, Section 6.1.

6.2 Formulants and Contaminants of Health or Environmental Concern

A comprehensive summary of the Formulants and Contaminants of Health or Environmental Concern can be found in ERC2011-04, Section 6.2.

7.0 Summary

7.1 Human Health and Safety

The toxicology database submitted for ipconazole is adequate to define the majority of toxic effects that may result from exposure. There was no evidence of carcinogenicity in rats or mice and ipconazole is not neurotoxic. In short-term and chronic studies on laboratory animals, the primary targets were the liver, lens (eyes), prostate, adrenals and thymus, with further effects on the endocrine organs and immune system at higher doses. A serious effect was observed in rabbit fetuses but only at a maternally toxic dose. There was no indication of susceptibility of the young in the rat developmental toxicity study or the multi-generation rat reproductive toxicity study. The risk assessment protects against the toxic effects noted above by ensuring that the level of human exposure is well below the lowest dose at which these effects occurred in animal tests.

Commercial and on-farm seed treatment workers handling Vortex FL Seed Treatment Fungicide, Rancona 3.8 FS Fungicide, and Rancona Apex Fungicide and workers handling and planting

treated seed are not expected to be exposed to levels of ipconazole that will result in an unacceptable risk when these products are used according to label restrictions. Adequate dust-off data were submitted to bridge the surrogate studies to the proposed uses and fulfill the occupational exposure conditions of registration. The personal protective equipment and use restrictions required on the product labels are adequate to protect workers treating seed commercially and on-farm, as well as workers bagging and planting treated seed.

The nature of the residue in plants and animals is adequately understood. The residue definition for enforcement is ipconazole. The residue definition for risk assessment is ipconazole and 1,2,4-T in animals and ipconazole, 1,2,4-T and the conjugate triazole metabolites (e.g., TA, TAA and TP) in plants. The uses of ipconazole on cereal grains and the import of peanuts, soybeans and crops in crop subgroup 6C (dried shelled pea and bean, except soybean) do not constitute an unacceptable chronic or acute dietary risk (food and drinking water) to any segment of the population, including infants, children, adults and seniors. Sufficient crop residue data have been reviewed to recommend MRLs to protect human health.

7.2 Environmental Risk

The primary environmental risk of the use of Vortex FL Seed Treatment Fungicide, Rancona 3.8 FS Fungicide, and Rancona Apex Fungicide as a seed treatment is to birds and mammals that may consume the treated seed. This risk was determined to be negligible if label statements regarding burial and cleanup of spilled treated seed are followed. Risk to other terrestrial and aquatic organisms, and non-target plants, is negligible based on low potential for exposure to these groups.

7.3 Value

The claims of control of seed rot / pre-emergence damping-off and seedling blight caused by *Fusarium* spp., and seed rot / pre-emergence damping off caused by *Rhizoctonia solani,* on corn are acceptable based on the submitted scientific data. The claims of control of post-emergence damping-off caused by *Cochliobolus sativus* on wheat, barley, oats, rye and triticale, and post-emergence damping-off caused by *Fusarium* spp. and *R. solani* on corn, were withdrawn by the applicant.

8.0 Proposed Regulatory Decision

Health Canada's PMRA, under the authority of the *Pest Control Products Act* and Regulations, is proposing full registration for the sale and use of Ipconazole Technical Fungicide, Vortex FL Seed Treatment Fungicide, Rancona 3.8 FS Fungicide and Rancona Apex Fungicide, containing the technical grade active ingredient ipconazole, to protect against seedling and soil-borne diseases on small grain cereals and corn.

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

List of Abbreviations

µg	microgram(s)
a.i.	active ingredient
ADI	acceptable daily intake
ARfD	acute reference dose
bw	body weight
CAF	composite assessment factor
CAS	Chemical Abstracts Service
cm^3	centimetre(s) cubed
F_1	first filial generation
FDA	*Food and Drugs Act*
g	gram(s)
ha	hectare(s)
HDPE	high density polyethylene
IUPAC	International Union of Pure and Applied Chemistry
kg	kilogram(s)
K_{ow}	*n*–octanol-water partition coefficient
L	litre(s)
LDPE	low density polyethylene
LOAEL	lowest observed adverse effect level
LOQ	limit of quantitation
m^3	metre(s) cubed
mg	milligram(s)
mL	millilitre(s)
MOE	margin of exposure
MRL	maximum residue limit
MTD	maximum tolerated dose
nm	nanometre(s)
NOAEL	no observed adverse effect level
Pa	pascal(s)
PCPA	*Pest Control Product Act*
p*K*a	dissociation constant
PMRA	Pest Management Regulatory Agency
PPE	personal protective equipment
ppm	parts per million
st. dev.	standard deviation
US EPA	United States Environmental Protection Agency
UV	ultraviolet

Appendix I Tables and Figures

Table 1 Toxicity Profile of Technical Ipconazole

Study Type/Animal/PMRA #	Study Results
Waiver request PMRA #1980937	The applicant provided a scientific rationale to support the adequacy of the dose tested in the long-term rat carcinogenicity study with ipconazole. The document also included a scientific justification that hormone, immunotoxicity and acute neurotoxicity data are not required.

Table 2 Toxicology Endpoints for Use in Health Risk Assessment for Ipconazole

Exposure Scenario	Study	Point of Departure and Endpoint	CAF[1] or Target MOE
Acute dietary general population	Not required		
Acute dietary females aged 13-49	Developmental toxicity study in rabbits	NOAEL = 10 mg/kg bw Decreased body weight gains or body weight loss during dosing, decreased food consumption and decreased placental weights in maternal animals. Decreased fetal weights and increased major malformations, primarily consisting of splitting of the parietal bone in fetuses.	300
	ARfD = 0.033 mg/kg bw		
Repeated dietary	Co-critical studies: 12-month dog study, 18-month mouse study, two-generation reproductive toxicity study	NOAEL = 2 mg/kg bw 12-month dog: increased reddening of the skin in both sexes and decreased body weight gains in females. two-generation reproductive toxicity: decreased body weight, body weight gain and food consumption in parents and offspring. 18-month mouse: liver and stomach histopathology	100
	ADI = 0.02 mg/kg bw/day		
Short-term and intermediate-term dermal[2]	Developmental toxicity study in rabbits	NOAEL = 10 mg/kg bw/day Decreased body weight gains or body weight loss during dosing, decreased food consumption and decreased placental weights in maternal animals. Decreased fetal weights and increased major malformations, primarily consisting of splitting of the parietal bone in fetuses.	300

Exposure Scenario	Study	Point of Departure and Endpoint	CAF[1] or Target MOE
Short- and Intermediate-term inhalation[3]	28-day inhalation toxicity study in rats	LOAEL = 8 mg/kg bw/day Portal of entry irritation (epithelial hyperplasia and/or metaplasia on epithelial surface of hard palate, larynx, nose and increased inflammatory cells in the mucosa of the trachea and lungs)	300
Cancer	Not required		

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 assessments

2 Since an oral NOAEL was selected, a dermal absorption factor of 100% (default value) was used in a route-to-route extrapolation

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

Table 3 Summary of Exposure and Risk Estimates for Commercial Seed Treatment Workers Treating Corn with Vortex FL Seed Treatment Fungicide or Rancona 3.8 FS Fungicide

Subpopulation and Route	Unit Exposure[1] (g/kg a.i. handled)	Amount a.i. handled[2] (kg)	Exposure [3] (g/kg bw/day)	MOE[4]
Mixer/loader - Closed Transfer - Long-sleeve shirt, long pants; chemical resistant gloves				
Dermal	187.8	1.5	4.02	2 490
Inhalation	1.49	1.5	0.032	250 000
Coater - Long-sleeve shirt, long pants; chemical resistant gloves				
Dermal	32.3	1.5	0.69	14 500
Inhalation	0.96	1.5	0.021	381 000
Bagger - Long-sleeve shirt, long pants; chemical resistant gloves				
Dermal	20.4	1.5	0.44	22 700
Inhalation	0.11	1.5	0.0024	3 330 000
Shift Foreman - Long-sleeve shirt, long pants; chemical resistant gloves				
Dermal	97.5	1.5	2.09	4 790
Inhalation	0.50	1.5	0.011	727 000

1 Commercial Seed Treatment Plant Worker Exposure Study with OFTANOL Seed Treatment on Canola.

2 Based on an application rate of 2.5 g a.i./100 kg seed x 60 000 kg seed treated/day.

3 Exposure (g/kg bw/day) = kg a.i. handled/day x unit exposure (g/kg a.i. handled) x 100% penetration/70 kg bw

4 Based on an oral NOAEL of 10 mg/kg bw/day for dermal exposure and an inhalation LOAEL of 8 mg/kg bw/day. The target for both dermal and inhalation exposure is 300.

Table 4 Summary of Exposure and Risk Estimates for Commercial Workers Treating Cereal Seed with Rancona Apex Fungicide

Subpopulation and Route	Unit Exposure[1] (g/kg a.i. handled)	Amount a.i. handled[2] (kg)	Exposure [3] (g/kg bw/day)	MOE[4]
Clothing Scenario: long-sleeved shirts, long pants, chemical resistant gloves				
Dermal	689.73	1.6	15.76	635
Inhalation	245.74	1.6	5.62	1423

1 Commercial Treater Exposure Study with Baytan 312 FS Seed Treatment on Grain Seeds (Dean, 1993).

2 Based on an application rate of 2.0 g a.i./100 kg seed x 80 000 kg seed treated/day.

3 Exposure (g/kg bw/day) = kg a.i. handled per day x unit exposure (g/kg a.i. handled) x 100% penetration/70 kg bw

4 Based on an oral NOAEL of 10 mg/kg bw/day for dermal exposure and an inhalation LOAEL of 8 mg/kg bw/day. The target for both dermal and inhalation exposure is 300.

Table 5 Summary of Exposure and Risk Estimates for On-Farm Workers Treating and Planting Cereal Seed Treated with Rancona Apex Fungicide

Subpopulation and Route	Unit Exposure[1] (g/kg a.i. handled)	Amount a.i. handled[2] (kg)	Exposure [3] (g/kg bw/day)	MOE[4]
Dermal	111.84	0.27	0.43	23 200
Inhalation	20.6	0.27	0.079	101 000

1 On-farm Treater and Planter Exposure Study with Vitaflo 280 Fungicide on Cereal Seeds.

2 Based on an application rate of 2.0 g a.i./100 kg seed x 13 500 kg seed treated and planted/day.

3 Exposure (g/kg bw/day) = kg a.i. handled per day x unit exposure (g/kg a.i. handled) x 100% penetration/70 kg bw

4 Based on an oral NOAEL of 10 mg/kg bw/day for dermal exposure and an inhalation LOAEL of 8 mg/kg bw/day. The target for both dermal and inhalation exposure is 300.

Table 6 Summary of Exposure and Risk Estimates for Workers Planting Corn Seed Treated with Vortex FL Seed Treatment Fungicide or Rancona 3.8 FS Fungicide

Subpopulation and Route	Unit Exposure[1] (g/kg a.i. handled)	Amount a.i. handled[2] (kg)	Exposure [3] (g/kg bw/day)	MOE[4]
Dermal	424.2	0.034	0.206	48 500
Inhalation	1.11	0.034	0.000535	14 950 000

1 Seed Planting Worker Exposure Study with Oftanol Seed Treatment on Canola.

2 Based on an application rate of 2.5 g a.i./100 kg seed x 1350 kg seed planted/day.

3 Exposure (g/kg bw/day) = kg a.i. handled per day x unit exposure (g/kg a.i. handled) x 100% penetration/70 kg bw

4 Based on an oral NOAEL of 10 mg/kg bw/day for dermal exposure and an inhalation LOAEL of 8 mg/kg bw/day. The target for both dermal and inhalation exposure is 300.

Table 7 Food Residue Chemistry Overview of Metabolism Studies and Risk Assessment

DIETARY RISK FROM FOOD AND WATER			
	POPULATION	**ESTIMATED RISK % of ACCEPTABLE DAILY INTAKE (ADI)**	
		Food and Water	
Basic chronic non-cancer dietary risk **ADI = 0.02 mg/kg bw/day** **Estimated chronic drinking water concentration = 0.029 μg a.i./L**	**All infants < 1 year**	0.3	
	Children 1-2 years	0.5	
	Children 3-5 years	0.6	
	Children 6-12 years	0.4	
	Youth 13-19 years	0.3	
	Adults 20-49 years	0.2	
	Adults 50+ years	0.1	
	Total population	0.2	
Basic acute dietary exposure analysis, 95th percentile **Estimated acute drinking water concentration = 0.12 μg a.i./L**	**POPULATION**	**ESTIMATED RISK % of ACUTE REFERENCE DOSE (ARfD)**	
		Food Only	**Food and Water**
ARfD = 0.033 mg/kg bw	**Females 13–49 years**	0.25	0.25

Table 8 Use (label) Claims Proposed by Applicant and Whether Acceptable or Unsupported

Proposed Use Claim	Supported/unsupported
Control of seed rot / pre-emergence damping-off and seedling blight caused by *Fusarium* spp. and seed rot / pre-emergence damping off caused by *Rhizoctonia solani* on corn.	Supported.
Control of post-emergence damping-off caused by *Fusarium* spp. and *Rhizoctonia solani* on corn.	Withdrawn by the applicant.
Control of post-emergence damping-off caused by *Cochliobolus sativus* on wheat, barley, oats, rye and triticale.	Withdrawn by the applicant.

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

The MRLs for ipconazole can be found in ERC2011-04.

References

A. List of Studies/Information Submitted by Registrant

1.0 Human and Animal Health

PMRA Document Number Reference

1980937 2009, Ipconazole Technical Registration Number 27942, Response to Deficiencies Identified by the Pest Management Regulatory Agency (PMRA), DACO: 4.4.4,4.5.12,4.8

1981015 2009, Ipconazole - Nature of the Residues in Plants; Response to PMRAs Request for Storage Stability Supporting Data, DACO: 6.3

1981030 2009, Supplemental Compilation: Chemtura Response to PMRA Regulatory Decision Letter for Submission Number 2007-2308, Registration Number 29175 (RANCONA 3.8 FS Fungicide), DACO: 7.4.1,7.4.2

1980968 2010, Determination of The Dust Off Potential of Wheat Seed Treated With Baytan 30 FF or Vitaflo 280 Versus Oat Seed Treated with Rancona Apex, Project Number MF 08-050. DACO: 5.14

1965959 2010, Laboratory Dust-off Study of Different Cereal, Pulse, Oilseed and Corn Seeds treated with Penflufen Based Seed Treatment Formulations – Addendum 1. Project Number BYFCAN007. DACO: 5.14

2.0 Value

PMRA Document Number Reference

1981119 2010. Vortex FL Seed Treatment Fungicide - Additional Data to Support Registration. DACO: 10.2.3.1, 10.2.3.2