Pest Management Regulatory Agency
Agence de réglementation de la lutte antiparasitaire

Proposed Regulatory Decision Document PRDD2004-06

Triticonazole

The technical grade active ingredient (TGAI) triticonazole and the associated end-use products (EPs), Charter Seed Treatment (contains triticonazole as active ingredient) and Charter PB Seed Treatment (contains triticonazole and thiram as active ingredients), for the control of selected diseases caused by fungal pathogens on wheat, barley and oats are proposed for full registration under Section 13 of the Pest Control Products (PCP) Regulations.

This Proposed Regulatory Decision Document (PRDD) provides a summary of the data reviewed and the rationale for the proposed full registration of these products. The Pest Management Regulatory Agency (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 the Publications Coordinator at the address below.

(publié aussi en français)

29 December 2004

This document is published by the Alternative Strategies and Regulatory Affairs Division, Pest Management Regulatory Agency. For further information, please contact:

Publications Coordinator
Pest Management Regulatory Agency
Health Canada
2720 Riverside Drive
A.L. 6605C
Ottawa, Ontario
K1A 0K9

Internet: pmra_publications@hc-sc.gc.ca
www.pmra-arla.gc.ca
Information Service:
1 800 267-6315 or (613) 736-3799
Facsimile: (613) 736-3758

ISBN: 0-662-39023-7 (0-662-39024-5)
Catalogue number: H113-9/2004-6E (H113-9/2004-6E-PDF)

Foreword

The submissions for full registration of the active ingredient (a.i.) triticonazole and the end-use products (EPs), Charter Seed Treatment and Charter PB Seed Treatment, fungicides developed by Bayer CropScience Inc. for use on wheat, barley and oats against fungal diseases, have been reviewed by Health Canada's Pest Management and Regulatory Agency (PMRA).

The PMRA has carried out an assessment of available information in accordance with Section 9 of the PCP Regulations and has found it sufficient pursuant to Section 18(b) to allow a determination of the safety, merit and value of the a.i. triticonazole and the EPs, Charter Seed Treatment, and Charter PB Seed Treatment. The Agency has concluded that the use of the a.i. triticonazole and the EPs, Charter Seed Treatment and Charter PB Seed Treatment, in accordance with the label, has merit and value consistent with Section 18(c) of the PCP Regulations and does not entail an unacceptable risk of harm pursuant to Section 18(d). Therefore, based on the considerations outlined above, the use of the a.i. triticonazole and the EPs, Charter Seed Treatment and Charter PB Seed Treatment, are proposed for full registration, pursuant to Section 13 of the PCP Regulations.

Methods for analyzing of triticonazole residues in various environmental media can be provided to research institutions and monitoring agencies upon request to the PMRA.

The PMRA will accept written comments on this proposal up to 45 days from the date of publication of this document to allow interested parties an opportunity to provide input into the proposed registration decision for this product.

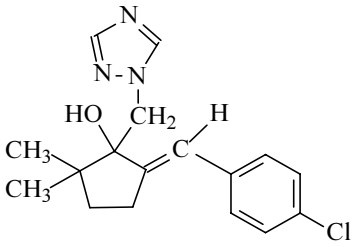
Note: Charter PB Seed treatment, a new flowable (aqueous suspension) ready-to-apply (RTA) seed treatment co-formulation is also discussed here. Charter PB is intended for the control or suppression of the most prevalent seed and soil-borne fungal diseases of wheat, barley and oat seeds in Canada, and contains triticonazole and thiram at guaranteed concentrations of 1.25% and 12.5%, respectively. Thiram is currently registered for use on wheat, barley and oat seeds at application rates ranging from 28.9 g a.i./100 kg seed to 108.6 g a.i./100 kg seed. The proposed application rate for Charter PB is 360 mL product/100 kg seed (5 g a.i. triticonazole/100 kg seed, and 50 g a.i. thiram/100 kg seed). Therefore, the proposed application rate of thiram is within the current use pattern. The risk assessment for all thiram requested uses will be addressed through the upcoming re-evaluation of thiram.

Table of Contents

1.0 The active substance, its properties and uses

1.1 Identity of the active substance and preparation containing it (OECD 2.1.1)

TGAI Identification

Active substance	Triticonazole
Function	Fungicide
Chemical name	
IUPAC	(±)-(E)-5-(4-chlorobenzylidene)-2,2-dimethyl-1-(1H-1,2,4-triazol-1-ylmethyl)cyclopentanol
CAS	5-[(4-chlorophenyl)methylene]-2,2-dimethyl-1-(1H-1,2,4-triazol-1-ylmethyl)cyclopentanol
CAS number	131983-72-7
Molecular formula	$C_{17}H_{20}ClN_3O$
Molecular weight	317.8
Structural formula	
Purity of active	92.5% nominal (87.4–96.0%)
Identity of relevant impurities of toxicological, environmental or other significance	The technical grade triticonazole does not contain any impurities or microcontaminants known to be Toxic Substances Management Policy (TSMP) Track 1 substances as identified in Appendix II of DIR99-03.

1.2 Physical and chemical properties (OECD 2.1.2)

Technical product: Triticonazole

Property	Result	Comment
Colour and physical state	White powder	
Odour	Odourless	
Melting point or range	139–140.5°C	
Boiling point or range	Not applicable	
Specific gravity	1.326–1.369 at 20°C	
Vapour pressure	$< 1 \times 10^{-5}$ Pa at 50°C	Non-volatile
Henry's Law constant	$< 3.8 \times 10^{-5}$ Pa^{-3} m. mol^{-1}	Not volatile from water and moist surfaces
UV–visible spectrum	λmax at 212 and 263 nm; no absorbance above 320 nm	Low potential for phototransformation
Solubility in water at 20°C	8.4 mg/L	Low solubility and solubility is independent of pH
Solubility in organic solvents at 20°C	**Solvent** **g/L** dichloromethane 191 ethyl acetate 48.6 n-hexane 0.19 Toluene 12.6 Methanol 18.2 Acetone 17.4 2-propanol 7.60	
n-octanol–water partition coefficient (K_{ow})	log K_{ow} = 3.29 at 20°C	Potential for bioconcentration/ bioaccumulation
Dissociation constant (pK_a)	Does not dissociate	No dissociable functionality based on structure
Stability (temperature, metal)	Slight decomposition at 180°C	

End-use product: Charter Seed Treatment fungicide

Property	Result
Colour	Opaque dark pink
Odour	Odourless
Physical state	Liquid
Formulation type	Aqueous suspension
Guarantee	Triticonazole: 25 g/L (nominal)
Container material and description	Non-permeable polyethylene or polyethylene lined metal is anticipated; sizes 1, 4, 10, 100, and 1000 L
Specific gravity	1.069 g/mL
pH	7.63
Oxidizing or reducing action	No reaction with water, hexane, monoammonium phosphate or zinc; mild reaction with potassium permanganate
Storage stability	No change after 1 year ambient or 2 years in dark
Explodability	Does not have any components or properties that are explosive

End-use product: Charter PB Seed Treatment

Property	Result
Colour	Pink
Odour	Odourless
Physical state	Liquid
Formulation type	Aqueous liquid suspension
Guarantee	Triticonazole 1.25% (nominal) (1.19–1.31%) Thiram 12.5% (min.)
Formulants	The product does not contain any List 1 formulants or formulants known to be TSMP Track 1 substances.
Container material and description	Plastic container and polyethylene lined metal drums
Bulk density	1.1226 at 25°C
pH of 1% dispersion in water	4.49 at 25°C

Property	Result
Oxidizing or reducing action	The formulation does not react with water, hexane, monoammonium phosphate or zinc; mild reaction with potassium permanganate.
Storage stability	No change after 1 year in dark. Stability supported by surrogate data for a similar formulation, Fondation Lite.
Explodability	The product does not have any explosive properties.

1.3 Details of uses

Charter Seed Treatment was proposed for use at 5 g a.i./100 kg seed on specific cereal crops to control the following:

- common bunt (*Tilletia caries*) and loose smut (*Ustilago tritici*) of wheat;
- covered smut (*Ustilago hordei*), false loose smut (*Ustilago nigra,* or *Ustilago avenae*) and true loose smut of barley (*Ustilago nuda*); and
- covered smut (*Ustilago kolleri*) and loose smut (*Ustilago avenae*) of oats.

In addition, the following claims were made:

- control of seed rot caused by *Fusarium* spp.;
- control of seedling blights caused by seed and soil-borne *Fusarium* spp.;
- suppression of *Fusarium* crown and root rot; and
- suppression of common root rot and control of seedling blight caused by *Cochliobolus sativus* on both wheat and barley.

Claims that were not supported include control of seedling blight caused by soil-borne *Fusarium* spp. on wheat and barley as well as that caused by *Cochliobolus sativus* on wheat and barley.

2.0 Methods of analysis

2.1 Methods for analysis of the active substance as manufactured

A high performance liquid chromatographic (HPLC) method was used for the determination of the active substance and a (similar) HPLC method was used to determine the significant structurally related impurities (content $\geq$0.1%) in the technical product. The methods have been shown to have satisfactory specificity, linearity, precision and accuracy.

2.2 Method for formulation analysis (OECD IIIA5.2.1)

An HPLC method was submitted for the simultaneous determination of triticonazole and thiram. The method was assessed to be specific, precise and accurate for use as an enforcement analytical method.

2.3 Methods for residue analysis

2.3.1 Methods for environmental residue analysis

A summary of the analytical methods for detection of triticonazole and its transformation products in soil and biota (barley, wheat, cereal straw, green plant, beef, poultry, egg, fat and milk) are provided in Appendix III, Table 11.

2.3.2 Multiresidue methods for residue analysis

A gas chromatographic method using a nitrogen phosphorus detector (GC/NPD), European Multiresidue Analytical Method DFG S19, was proposed for enforcement purposes to quantify residues of triticonazole in plant matrices. The principle of the method is homogenization/extraction of plant samples with aqueous acetonitrile and cleanup by solvent partitioning into ethyl acetate and cyclohexane and Gel Permeation Chromatography (GPC). The resulting GPC eluate is fractionated on a silica gel column and fractions are analyzed by GC/NPD. The method limits of quantitation (LOQ) were set at 0.005 ppm (pea seed and pod and wheat grain) and 0.01 ppm (wheat straw). The method/detector response was linear (correlation coefficient = 0.991748) within the range of 0.01–0.5 ppm. The average recoveries ranged from 90 to 120% (SD ≤23%) when samples were spiked at levels ranging from 0.005 to 0.025 ppm. Confirmation was provided by GC/MS/MS. The independent laboratory validation (ILV) of the multiresidue analytical method was successfully completed. This multiresidue analytical method was considered acceptable for enforcement purposes.

2.3.3 Methods for residue analysis of plants and plant products

Residues of triticonazole in cereals were determined by gas chromatography using a thermionic detector (GC/TID), Method AR 92-92(E). The principle of the method is homogenization/extraction with acetone:water (4:1 v/v) followed by cleanup using C18 and amino solid phase extraction and quantitation of residues using GC/TID. Quantitation is carried out by external standardization. The method LOQs for triticonazole were reported to be 0.01 ppm and 0.05 ppm for grain and straw, respectively. The detector response was found to be linear in the range of 10–150 µg/L (correlation coefficient = 0.998). This method was validated using barley grain, barley straw and wheat straw samples spiked at LOQ, 5× LOQ (grain only) and 10× LOQ. The method gave good recoveries for the analysis of barley grain samples (97–119%; mean = 109 ± 10%; n = 6) and samples of barley and wheat straw (69–120%; mean = 96 ± 17%; n = 11).

A gas chromatographic method using a mass selective detector (GC/MS), Report # P91/151, was proposed for data gathering to analyze residues of triticonazole and its associated hydroxy metabolites (RPA 406341, RPA 404886 and RPA 406780) in cereal straw and green plants. The principle of the method is homogenization/extraction with acetone followed by cleanup using C18 and amino solid phase extraction and quantitation of residues using GC/MS. The reported method limit of detection (LOD) and LOQ for each analyte were 0.01 ppm and 0.06 ppm, respectively for plant material. The response of the mass selective detector appeared to be linear over the range of 0–1 µg/mL but non linear over the range of 1–10 µg/mL (correlation coefficients not provided). Limited method validation indicated that when control plant material was spiked at levels ranging from 0.04 to 0.20 ppm, recoveries for the parent and hydroxy metabolites were as follows:

- triticonazole—23–44% (overall mean = 31 ± 11; n=3);
- RPA 406341—61–81% (overall mean = 68 ± 12; n=3);
- RPA 404886—86–101% (overall mean = 95 ± 8; n=3); and
- RPA 406780—70–175% (overall mean = 114 ± 54; n=3).

Low recoveries of triticonazole were apparently a result of losses due to early elution in the solid phase extraction (SPE) cleanup procedure; these low recoveries were because the aqueous contained residual acetone.

The LC/MS or LC/MS/MS analytical method MS 148.02 was proposed for data gathering and enforcement purposes to quantify residues of triticonazole and metabolites RPA 404886 and RPA 406341 in plant matrices. The principle of the method is extraction with acetone and water, then clean up by SPE or liquid/liquid partitioning with dichloromethane. The resulting extract is redissolved in solvent and analyzed/quantitated by LC/MS or LC/MS/MS. The LOQs for LC/MS were 0.01 ppm for grain and 0.04 ppm for forage and straw; the LOQ for LC/MS/MS was 0.005 ppm for grain, forage and straw. The method/detector response was linear (correlation coefficient $\geq$ 0.997) within the range of 0.02–0.5 ppm (LC/MS) and 0.002–0.25 ppm (LC/MS/MS). The average recoveries of triticonazole ranged from 77 to 122% for all plant matrices when samples were spiked at levels ranging from 0.02 to 0.5 ppm (LC/MS) and 0.002–0.5 ppm (LC/MS/MS). ILV of the method using wheat forage was successfully completed.

2.3.4 Methods for residue analysis of food of animal origin

A gas chromatographic method using an electron capture detector (GC/ECD), Analytical Method AR 104-94(E), was proposed for data gathering and enforcement purposes to quantify residues of triticonazole in animal tissues. The method involves maceration/extraction with acetone or acetonitrile and clean up by solvent partitioning with hexane, a C_{18} and/or amino SPE. The resulting eluate is re-dissolved in solvent and analyzed/quantitated by GC/ECD. The LOQs were set at 0.05 ppm (eggs, beef and poultry tissues and fat) and 0.01 ppm (milk). Average recoveries of triticonazole in beef and poultry tissue, milk and eggs spiked at 0.01 and 0.05 mg/kg ranged from 85 to 97%

with standard deviations ranging from 6 to 11%. ILV of this method using beef and poultry tissue, milk and eggs was successfully completed.

2.3.5 Chemistry conclusions (OECD 3.1)

The product chemistry data for triticonazole technical used in the proposed EPs is completed. Batch data were provided in support of the specifications. Based on the raw materials, the manufacturing process used and the chemical structures of the active and impurities, the technical substance is not expected to contain any toxic microcontaminants as identified in Section 2.13.4 of DIR98-04 or any TSMP Track 1 substances as identified in Appendix II of DIR99-03. The required physical and chemical properties of technical material and of the EPs were determined using acceptable methods. An HPLC method was used for the determination of actives in the formulation. The method is found to be suitable for use as enforcement analytical methods.

3.0 Impact on human and animal health

3.1 Integrated toxicological summary

Triticonazole administered orally to rats was rapidly absorbed and metabolised via hydrolysis. Elimination occurred rapidly mainly via feces and partly via urine. Triticonazole had limited tissue accumulation; highest tissue levels occurred in the liver, adrenals, fat, skin and fur. Metabolism was almost complete with only trace amounts of the parent compound recovered unchanged from the feces. Differences in metabolism and excretion between males and females were minor and quantitative rather than qualitative in nature.

Acute toxicity – technical grade triticonazole
Technical triticonazole was of low acute toxicity via the oral and dermal routes; was slightly acutely toxic via the inhalation route; and a minimal irritant to eyes. It was not dermally irritating nor a skin sensitizer.

Primary Display Panel: **"CAUTION POISON"**.
Secondary Display Panel: Harmful if inhaled. Avoid inhaling or breathing dust.

Acute toxicity – CHARTER

Charter was of low acute toxicity via the oral, dermal and inhalation routes; a slight irritant to skin and minimal irritant to eyes; and not a skin sensitizer.

The proposed draft label is adequate.

Acute toxicity – CHARTER PB

CHARTER PB seed treatment appeared to be of low acute oral and dermal toxicity. It is slightly toxic by the inhalation route. The product is mildly irritating to eyes and slightly irritating to skin. The test material is a skin a sensitizer by the Buehler test.

Primary Display Panel:
CAUTION POISON, EYE IRRITANT AND POTENTIAL SKIN SENSITIZER

Secondary Display Panel: May irritate eyes. Avoid contact with eyes. Potential skin sensitizer.

Subchronic and chronic dietary/oral studies—In these studies conducted in mice, rats and dogs, the dog was identified as the most sensitive species. Toxicity manifested in adrenal cortical histopathology, lenticular cataracts, effects on testes and prostate weights and on clinical chemistry parameters (cholesterol and albumin). However, in a developmental study in rabbits following exposure via gavage, significantly increased mortality was observed after seven to nine days of treatment indicating rabbits are considerably more sensitive to the toxicity of triticonazole than are dogs, rats and mice. Rats demonstrated the least sensitivity to the toxic effects of triticonazole among the four species tested. No evidence of toxicity was observed in rats following dermal exposure at the limit dose of 1000 mg/kg bw/day.

Toxicity appeared to be cumulative in rats where long-term exposure produced similar pathological effects but at lower dose levels. There was no definitive indication of gender sensitivity observed in all three species tested. However, following short-term dietary exposure to triticonazole in rats, effects on body weight, adrenal gland and liver were demonstrated in males at a lower dose level than in females.

The adrenal gland and liver were identified as the target organs in mice, rats and dogs. In rats and dogs, triticonazole caused histopathological changes in the cortex of the adrenal gland following short- and long-term exposure where, as in mice, increased adrenal weights were not accompanied by any corresponding histopathology. Effects in the liver in all three species ranged from effects on weight, microsomal enzyme levels and/or histopathological changes.

Triticonazole was not genotoxic or oncogenic in mice and female rats; thyroid adenomas were noted in only the male rats at high doses. However, adenomas are a benign tumor; there were no thyroid follicular cell carcinomas (malignant) observed in any animal. Furthermore, there were no other indications of thyroid toxicity observed in this study and there were no other treatment-related tumors observed in male or female rats or in any other species tested (mice, dogs, rabbits). The genotoxicity studies all yielded negative results. Hence, the thyroid adenomas observed only in male rats are considered of minimal concern with respect to human health because rodents are well known to be more sensitive physiologically to thyroid hormone perturbations than are humans.

Triticonazole also caused changes in reproductive organs in dogs, rats and mice; effects on ovaries, testes or prostate weights unaccompanied by any corresponding histopathology were observed following short-term exposure only. Decreased uterine weights were also observed in rats and mice following short-term dietary exposure with histopathological changes observed only in the rats. No effects in reproductive organs were observed in rodents following chronic dietary exposure. However, the potential toxic effect of triticonazole on reproductive parameters of both males and females are highlighted in the rat reproduction study where increases in ovary weights, vacuolation of ovarian cells, decreased mating and fertility indices; decreased litter size and livebirth index were also observed. No age-related sensitivity was observed as effects in the offspring (decreased viability index and pup body weight) were seen to occur only at maternally toxic doses in rats. Effects on reproductive performance (rats), reproductive organ toxicity (dogs, rats, mice) and offspring toxicity (rats) may be the result of possible perturbations of endocrine system mediated by adrenal gland toxicity.

Triticonazole was not teratogenic in rats or rabbits. Although skeletal anomalies such as elongation of the acromion processes and supernumerary ribs occurred in rabbit and rat fetuses, no evidence of age related sensitivity was observed as effects in the offspring occurred only at or above maternally toxic doses.

Triticonazole was not neurotoxic following long-term exposure in rats; nor were there any developmental anomalies of the nervous system noted in the developmental toxicity studies in rats and rabbits. No behavioural nor neurological effects were observed in the offspring in the two-generation reproductive toxicity study. In addition, the 13-week subchronic-neurotoxicity study in rats demonstrated no effects in the functional observation battery nor on motor activity testing.

Lenticular cataracts and degeneration of the lens were observed in all male and ¾ of the female dogs following a one-year oral exposure. The mode of action of triticonazole is through inhibition of sterol demethylation. Thus, the apparent effect on cholesterol and on organs/tissues that are involved in steroid synthesis may be related to the inhibition of synthesis of cholesterol. One postulated mechanism contends that inhibition of HMG-CoA reductase, a target for antihyperlipidemic drugs, may produce some of the ocular effects observed in this study. However, the absence of mechanistic data as well as a lack of a structure-activity relationship between triticonazole and known HMG-CoA reductase inhibitors render it impossible to determine a definitive site of action.

A possibility exists that, at high doses, triticonazole may cause endocrine effects in mice, rats and dogs. The significant reduction in mating and fertility indices in rats noted at high doses of the F_1 parental generation may be an indication of cumulative toxicity in both sexes. It may also be correlated with the observation of increased ovary weights and associated vacuolation of ovarian cells in females and with perturbations of the endocrine function of the adrenal gland as evidenced by adrenal pathology in both sexes. Adrenal gland weights were decreased in F_0 and F_1 females. Histopathological examination of the adrenals in both sexes showed that adrenal effects were more severe in females. In male

dogs, following a one-year oral exposure of triticonazole, the toxicologically significant alterations in the testes and prostate weights combined with the histopathological effects on the adrenal cortex correlated with the decrease in serum cholesterol reported at the same dose level, which suggests an effect on steroid metabolism. Decreased uterine weights were observed in rats and mice following short-term dietary exposure and thyroid adenomas were noted in male rats following chronic exposure.

3.2 Determination of acceptable daily intake (ADI)

The recommended ADI for triticonazole is 0.008 mg/kg bw/day. The most appropriate study for selection of toxicity endpoints for chronic dietary exposure was the 52-week study with a NOAEL of 2.5 mg/kg bw/day in dogs; target organ toxicities were observed as adrenal cortical cell vacuolation, decreased cholesterol and albumin levels, changes in testes and prostate organ weights at and above 25 mg/kg bw/day and lenticular cataracts at 25 mg/kg bw/day. An additional safety factor (SF) of 3× (in addition to the usual 100-fold for interspecies and intraspecies variation) was deemed necessary, due to observed effects on reproductive performance (rats)/reproductive organ toxicity (dogs and rats)/offspring toxicity (rats) as a result of possible perturbations of endocrine system via the adrenal gland. In the absence of any evidence of age-related sensitivity, an SF of 300-fold was applied to the NOAEL of 2.5 mg/kg bw/day as follows:

$$\text{ADI for triticonazole} = \frac{\text{NOAEL}}{\text{SF}} = \frac{2.5}{300} = 0.008 \text{ mg/kg bw/day.}$$

The **ADI of 0.008 mg/kg bw/day** provides the following margins of safety (MOSs):

6750 – for reproductive performance/offspring toxicity
[NOAEL = 54 mg/kg bw/day]

3675 – for the development of thyroid follicular cell adenomas in male rats following chronic dietary exposure to triticonazole [NOAEL = 29.4 mg/kg bw/day in males]

3125 – for lenticular cataracts in 1-year dog study
[NOAEL = 25 mg/kg bw/day]

625 – for developmental toxicity
[elongated acromion process in rabbit fetuses, NOAEL = 5 mg/kg bw/day]

3.3 Acute reference dose (ARfD)

3.3.1 Acute toxicity – females (13+)

Based on the increased incidences of skeletal anomalies, i.e., elongation of the acromion process and delayed ossification of the metacarpals and phalanges (rabbit) and supernumerary ribs (rat), observed in teratogenicity studies following exposure to triticonazole (effects observed at maternally toxic doses), an ARfD was deemed necessary for the sub-population of females (13+). The recommended ARfD is 0.017 mg/kg bw/day based on the lowest developmental NOAEL of 5 mg/kg bw/day in the rabbit teratogenicity study, and utilizing an uncertainty factor of 300.

An additional SF of 3× (in addition to the usual 100-fold for interspecies and intraspecies variation) was deemed necessary, due to the following:

- possible hormonal perturbations occurring during organogenesis and resulting in skeletal abnormalities; no hormone assays were performed in any studies;
- occurrence of skeletal abnormalities at dose levels where only minimal maternal toxicity was observed; and
- lack of available information to determine whether the observed skeletal abnormalities were a transient phenomenon or whether they persisted through postnatal development into adulthood.

3.3.2 Acute toxicity – general population

In the context of the low order of acute toxicity of triticonazole following exposure by oral, dermal and inhalation routes, it is not necessary to propose an acute reference dose for the general population.

3.4 Toxicological endpoint for assessment of occupational, residential and bystander risks

Complete and acceptable toxicology data were available for review of the new TGAI triticonazole.

- Triticonazole was of low acute toxicity in rats via the dermal route of exposure and no significant systemic toxicity was observed at a limit dose of 2000 mg/kg bw. In a short-term (23-day) dermal toxicity study in rats, no evidence of toxicity was observed at the limit dose of 1000 mg/kg bw/day, where a full range of parameters were investigated including clinical signs, body-weight gain, hematology and clinical chemistry, macroscopic and microscopic pathology.

- Triticonazole has been shown to be rapidly and extensively metabolized and excreted in the rat with no evidence of bioaccumulation following repeat oral exposures.

- The dose–response curve for triticonazole toxicity has been well characterized in several species (mouse, rat, dog) following subchronic and chronic oral administration. There was no definite indication of gender sensitivity.

- In subchronic and chronic oral studies, noted toxicologically significant effects were adrenal cortical histopathology in rats and dogs, altered clinical chemistry parameters (decreased cholesterol and albumin) and lenticular cataracts in dogs and liver effects in rats and mice.

- In subchronic and chronic dietary/oral studies conducted in mice, rats and dogs, the dog was identified as the most sensitive species. The rat appeared to be the least sensitive to triticonazole toxicity among all of the species tested.

- Subchronic oral exposure in rats and dogs produced a similar range of effects at comparative effect levels. Chronic toxicity studies showed qualitatively similar toxicity and target organ as in the subchronic toxicity studies. However, toxicity appeared to be cumulative in rats where long-term exposure produced effects at lower dose levels. In the reproduction studies, toxicity was cumulative as more toxic effects were noted in the second generation. Triticonazole was not tumorigenic in mice or female rats and was not mutagenic or clastogenic.

- Tumorigenicity was noted in the thyroids of male rats (benign tumours) at doses of 204 mg/kg bw/day with a NOAEL at 29.4 mg/kg bw/day. A threshold margin of exposure (MOE) approach was used. The mechanism of tumorigenicity was consistent with a non-genotoxic, mitogenic process, whereby thyroid toxicity (follicular cell hypertrophy) may be the critical determinant in the formation of thyroid follicular cell adenomas.

- Triticonazole is a reproductive toxicant at high doses with effects on reproductive performance in rats, on reproductive organs in rats and dogs, and on rat pup mortality and body weight. It was not teratogenic and no increased susceptibility of fetuses to in utero exposure to triticonazole was demonstrated in the developmental toxicity studies in rats and rabbits. Triticonazole was not neurotoxic.

- Exposure of on-farm applicators and seed handlers would be of a short-term duration (i.e., 2 or 3 days to a few weeks per year) and would be predominately via the dermal route (90–95% of exposure). As such, the subchronic 23-day dermal toxicity study in rats was considered the most relevant study for toxicity endpoint selection. A full range of parameters were investigated including clinical

signs, body-weight gain, hematology and clinical chemistry, and macroscopic and microscopic pathology.

- Exposure of commercial seed treaters would be of an intermediate term (i.e., 1–6 months over the course of a year, with most treating occurring between February and May), with predominant human exposure occurring via the dermal route (99%). As such, a longer duration than the 23-day dermal toxicity was considered appropriate since increased toxicity was observed in rats following increased duration of exposure. The one-year dog study (NOAEL = 2.5 mg/kg bw/day) was considered as the most relevant study, as the dog was identified as the most sensitive species with toxicity manifesting as adrenal cortical histopathology, lenticular cataracts, effects on testes and prostate weights and on clinical chemistry parameters (cholesterol and albumin).

- A MOE of 300 is recommended to account for intraspecies (10×) and interspecies (10×) differences and an additional safety factor (3×) for reproductive performance/reproductive organ toxicity (testes, prostrate, ovary, uterus) effects and organ toxicity.

An in vivo dermal absorption study was provided to estimate potential dermal penetration of triticonazole. Male Sprague-Dawley rats were administered nominal doses of 0.15 and 3.0 mg/cm^2 of ^{14}C-triticonazole and monitored up to 72 h post-dosing. Four animals were treated for each group at each dose level, and sacrifices were made at 8, 24 and 72 h after application of the dose. The skin site of all animals was washed after 8 h. Mean dermal absorption values were as follows:

- 56.38% absorption after 8 h, 41.97% after 24 h, and 35.84% after 72 h at the low dose; and
- 14.79% absorption after 8 h, 7.41% after 24 h, and 9.81% after 72 h at the high dose.

The 24-h low dose absorption rate of 42% is recommended for this use scenario, as exposure is expected to be daily when it occurs, and a wash was conducted at 8 h post-dosing, which would simulate showering after the workday.

Dermal absorption of triticonazole was also evaluated in vitro using non-viable human and viable rat epidermal preparations. Skin preparations were determined to be of adequate integrity. Two dose levels were used: 2970 µg/cm² (neat formulation) and 148.5 µg/cm² (1:20 aqueous dilution). Five replicates were used per species per dose level. Samples from the receptor cell were analyzed for triticonazole at regular intervals up to 24 hours. Mean percent dermal absorption was determined for rat and human skin at 8 and 24 hours post dose. The percent dermal absorption is presented in Table 3.4.1.

Table 3.4.1 Percent dermal absorption for rat and human skin

	8-hour exposure		24-hour exposure	
	Neat dilution	**1:20 dilution**	**Neat dilution**	**1:20 dilution**
Rat epidermis	0.10 ± 0.025%	0.65 ± 0.20%	0.39 ± 0.10%	2.61 ± 0.61%
Human epidermis	0.15 ± 0.07%	0.12 ± 0.06%	0.32 ± 0.10%	0.77 ± 0.23%

As skin wash, donor and receptor cell washes, and skin bound residues were not performed, the total recoveries were not calculated; this is considered a major limitation of the study. While in vitro dermal absorption studies alone are not sufficiently validated for use in deriving estimates or systemic exposure for risk assessments (draft North American Free Trade Agreement [NAFTA] Harmonization Position Paper on Methodology Issues, 18 January 1999), a well conducted in vitro study may have some utility as bridging data between species. While the in vitro data suggest that human epidermis was approximately four times less permeable to triticonazole than rat skin, there were several design flaws that preclude the use of the in vitro study in a quantitative manner. Consequently, the PMRA has opted to retain the dermal absorption value for triticonazole of 42% as determined in the in vivo dermal absorption study.

3.5 Impact on human or animal health arising from exposure to the active substance or to impurities contained in it

Charter is a new seed treatment fungicide for the control of various seed-borne diseases in wheat, oats and barley. It contains 25 g/L of the active ingredient triticonazole. It is proposed for use in both commercial and on-farm treating facilities. No mixing is required as Charter is a ready-to-use product. The proposed application rate for Charter is 5 g a.i./100 kg seed (50 mg a.i./kg seed). The proposed application rate of triticonazole is twice the rate that has been granted temporary registration. The quantity of a.i. handled in a day depends on the amount of seed treated and will be different for commercial and on-farm facilities. The amount of seed treated will depend on the size of the facility and the seed being treated.

Charter PB is a new flowable (aqueous suspension) ready-to-apply (RTA) seed treatment formulation that is intended for the control or suppression of the most prevalent seed and soil-borne fungal diseases of wheat, barley and oat seeds in Canada. Charter PB will be used in commercial facilities as well as in on-farm gravity flow or mist type treatment machines. Charter PB contains triticonazole and thiram at guaranteed concentrations of 1.25% and 12.5%, respectively. The proposed application rate for Charter PB is 360 mL product/100 kg seed (5 g a.i. triticonazole/100 kg seed and 50 g a.i. thiram/100 kg seed). Thiram is registered for application to wheat, barley, and oat seeds at application rates ranging from 28.9 g a.i./100 kg seed to 108.6 g a.i./100 kg seed. Therefore, the proposed application rate of thiram is within the current use pattern. An exposure and risk

assessment for all thiram requested uses will be addressed through the upcoming re-evaluation of thiram.

In commercial facilities, one to three people would generally be involved in seed treating. Typical tasks include mechanical and manual loading of chemical and seed into the mixing auger, supervising application equipment, bagging, sewing filled bags, moving bags to pallets, bulk loading treated seed to trucks or seeding equipment as well as cleaning seed treatment area, equipment and seed storage bins. The same person or different people may carry out all or some of these tasks. Application is generally via a closed, calibrated metering system fed to an auger to be mixed with seed. Loading can either be open pouring or closed via hard-couple linkage. Clean-up of auger and treating equipment is performed daily and is necessary before a different type of seed is treated. Typically a Canadian commercial seed-treating facility can treat approximately 46 000 kg of seed in a day but a range of between 3000 and 200 000 kg of seed can be treated. Based on the proposed application rate, approximately 2.3 kg a.i. can typically be handled in a day. Application at a commercial facility can be daily or based on demand for treated seed. Commercial seed treatment occurs over several months (1–6 months), with most seed being treated between February and May.

The applicant conducted a survey to determine actual use pattern of Charter Seed Treatment. The applicant collected and evaluated data collected from 55 cooperative seed treatment facilities in Alberta. Based on data collected from the 55 seed treatment facilities, in the 1999/2000 season, an average of 15 869 kg of wheat and 16 461 kg of barley were treated per day, for a total of 31 738 kg/day and a range of 4084 to 115 864 kg/day. The survey results indicate that the current PMRA default of 46 000 kg seed/day is representative and adequate to protect health of workers in all facilities.

The busy season for commercial seed treatment was from April to May and was approximately 45 to 60 days. The survey results also indicated that seed are not treated on a daily basis, and that the predominant activity of the seed treatment facilities was seed cleaning. Based on the survey results, the applicant concluded that the average use of Charter Seed Treatment per facility was 707 L (17 675 g triticonazole), which, at the present treatment rate of 2.5 g a.i./100 kg seed, would treat approximately 704 000 kg seed/season. Most facilities treat seed for only 2 hours/day (Alberta Manager's Association of Co-op Seed Plants). Based on treating seed for 2 hours/day, it is estimated that between 60 and 100 days would be required to treat 704 000 kg of seed. Therefore, based on the survey results that indicate that peak season use could be up to 60 days, and the fact that most facilities have the potential to use the product for a longer period of time, exposure in commercial facilities is considered to be of intermediate duration (i.e., 1 to 6 months).

On-farm treating generally involves one person and is conducted once per year. Seed is treated as needed during the sowing of crops, with only the amount of seed needed being treated. The seeding rate for wheat, oats and barley is approximately 110 kg seed/ha and

approximately 80 ha/day of wheat can be sown. Therefore, approximately 8800 kg of seed will be treated in a day resulting in 0.44 kg a.i. handled/day assuming an application rate of 50 mg a.i./kg seed. Less hectares per day would be sown with oats and barley resulting in less a.i. handled per day. Typically on-farm treatment would be done over a few days to a few weeks in spring just prior to or during seeding the fields. Therefore, exposure of on-farm applicators and seed helpers wold be short-term in duration. On the farm, seed may be treated and planted by a variety of methods including gravity flow or mist-type seed treatment equipment or using a treat-on-the-go air seeder. In rare instances, some small operations may mix manually with a paddle in a barrel or hopper. Exposure may occur while loading the product, while handling treated seed (e.g., levelling the seed in small hoppers) or during equipment cleaning and maintenance.

3.5.1 Occupational exposure and risk

3.5.1.1 Handler exposure and risk

A commercial seed treatment passive-dosimetry study was submitted as a surrogate to estimate exposure when treating seeds at a commercial facility. The study was conducted using two formulations of carbathiin: Vitaflo-280, and Vitavax Single, both of which are currently registered for seed treatment use in Canada. The study was conducted at two Canadian sites: a seed treatment and bagging facility in using Vitaflo-280 formulation, and a bulk seed treatment facility using Vitavax Single formulation. The varieties of seed treated during the monitoring periods included wheat, barley, oats and peas. Seed was treated at the recommended rates for Vitavax and Vitaflo formulations (613 and 417 mg a.i./kg seed, respectively), rates much higher (8–12 times) than that proposed for Charter (50 mg a.i./kg seed). Results showed overall mean exposures (dermal + inhalation) from both sites of 1514.6 μg/kg a.i. (standard deviation [SD] 2981.2). The very large standard deviations demonstrate the large differences in exposure potential in seed treatment facilities. Hands received approximately 86% of the total dermal exposure, whereas inhalation accounted for only 1% of total exposure. Workers receiving the highest exposures were those who were in direct contact with the treated seed, either during clean up, or from entering storage or transfer areas containing treated seed. One of the replicates had an excessively high dermal exposure from jumping into a truck of treated seed. It is uncertain whether this would be typical behaviour. With such a small sample size (12 replicates), it is difficult to characterize typical exposures. That this behaviour was observed in the study indicates that such behaviour may re-occur. Such high end exposures could also result during accidental exposure (e.g., spillage). Consequently, the PMRA feels that it is important to consider all exposures, even high end exposures observed in the surrogate exposure study. Study limitations included the small number of individuals monitored at each site, and the problems observed with the field recovery results. Due to the study limitations, the PMRA considers the surrogate data to be low quality, and, therefore, used the arithmetic mean as the measure of central tendency.

Exposure estimates for commercial workers handling Charter or Charter PB were based on the surrogate exposure values (dermal deposition of 1503.7 µg/kg a.i. handled, and inhalation exposure of 10.9 µg/kg a.i. handled), an application rate of 5.0 g a.i./100 kg seed, a throughput of 46 000 kg seed/day and a dermal absorption value of 42%.

An assessment of the Pesticide Handlers Exposure Database (PHED), Version 1.1, was submitted to quantify exposure to triticonazole when conducting on-farm seed treatment with Charter or Charter PB. The PHED is a database of generic mixer/loader/applicator passive dosimetry data, which facilitates the generation of scenario specific exposure estimates. This PHED assessment conforms to the NAFTA guidelines for using and reporting PHED data. The PHED subsets compare well to the proposed formulation and use pattern and is therefore acceptable as surrogate data for estimating exposure to triticonazole for on-farm seed treatment. The PHED estimate is based on a worker wearing one layer of clothes (e.g., long-sleeved shirt, pants) and gloves while mixing and loading Charter or Charter PB. The personal protective equipment (PPE) recommended on the label is coveralls and gloves for workers handling Charter, Charter PB or treated seed. Because application to seed is done using a calibrated metering system and is largely closed, application exposure is expected to be negligible. Based on this data, a potential exposure of 0.28 μg a.i./kg bw/day was estimated for a 70-kg farmer loading 0.44 kg/day of triticonazole to treat 8800 kg of wheat seed using closed application equipment. The primary route of exposure was dermal; only 4.5% was by inhalation. Based on a qualitative assessment, there will be some additional exposure from other activities related to the seeding operation, but this exposure is likely to be less than that associated with handling and pouring Charter or Charter PB. Exposure for treating other cereal seeds (i.e., barley and oats) would be the same or less, as fewer seeds would be treated.

The triticonazole exposure values and MOEs for commercial seed treaters and on-farm seed treaters are presented in Table 3.5.1.2.1. All exposure estimates are based on wearing one layer of clothing and wearing gloves when appropriate. The target MOE for all scenarios is 300.

The MOE for commercial treaters was 119. The one-year dog study with a NOAEL of 2.5 mg/kg bw/day was used in the risk assessment because it had a relevant duration, and the dog was identified as the most sensitive species. The MOE of 119 is considered unacceptable. However, an acceptable MOE can be achieved by allowing a maximum of 20 000 kg seed to be treated per day.

The MOE for on-farm applicators is greater than 3.5×10^6 and is considered adequate. The 23-day dermal rat study with a NOAEL of 1000 mg/kg bw was used for the risk assessment for these exposure scenarios, because it had a relevant duration and route of exposure. However, the rat is also the least sensitive species. It was felt though, that MOEs greater than 1000 would be protective even though the least sensitive species (rat) was used as a model for toxicity.

3.5.1.2 Post-application exposure and risk

Post-application exposure can occur as a result of handling treated seed. Treated seed to be sown in fields is added to hoppers on the seeders either manually (smaller bags of treated seed) or mechanically with augers and forklifts (large bags of treated seed or bulk seed containers). The largest potential for exposure from handling treated seed is from when seeds are loaded into the seeder hoppers and when levelling the treated seed in the hopper by hand. Once in the hopper, there is little contact with treated seed. Typically sowing of fields would occur for a few days to a few weeks in the spring and would depend on the crop and size of field to be seeded. Therefore, post-application exposure to triticonazole from handling treated seed would only occur for a few days to a few weeks each year. The seeding rate for wheat, oats and barley is 110 kg seed/ha and approximately 80 ha/day of wheat can be sown. Therefore, approximately 8800 kg of seed will be sown in a day resulting in approximately 0.44 kg a.i. being handled indirectly in a day, assuming an application rate of 50 mg a.i./kg seed. Fewer hectares per day would be sown with oats and barley resulting in less a.i. handled per day.

Two surrogate passive dosimetry studies were submitted to estimate exposure to triticonazole when sowing fields with seed treated with Charter. One study, conducted in France, used winter wheat seed treated with a test product containing a marker for exposure. The estimated potential exposure for triticonazole for workers handling treated seed when sowing fields is 0.26 mg/kg bw/day. This is based on a 70-kg worker handling 8800 kg of seed treated with triticonazole at a rate of 50 mg a.i./kg seed. The hands accounted for 91% of the potential exposure, while inhalation accounted for only 1%. The triticonazole exposure estimate was extrapolated from a surrogate exposure value of 42.29 mg/kg a.i. handled. The study limitations included a low number of replicates, low number of Quality Assurance (QA)/Quality Control (QC) samples and limited information on the formulation used in the study.

Another surrogate study to estimate exposure to triticonazole when sowing fields with treated seed was also submitted. This study was conducted in the United Kingdom in October 1993 and was reviewed previously. Baytan treated seed was used; triadimenol was the active ingredient monitored in this study. The normalized exposure derived from this study was 12.8 mg a.i./kg a.i. handled. This gives an extrapolated potential exposure estimate for triticonazole of 0.08 mg a.i./kg bw/day based on a 70-kg worker handling 8800 kg of seed treated with triticonazole at a rate of 50 mg a.i./kg seed. Dermal exposure accounted for 98% of the total potential exposure.

Despite some limitations, the two studies were collectively considered adequate to estimate potential exposure. In averaging the two exposure values for handling treated seed, potential exposure would be 0.09 mg/kg bw/day.

The triticonazole exposure value and MOE for treated seed handlers are presented in Table 3.5.1.2.1. The exposure estimate is based on wearing one layer of clothing and wearing gloves when appropriate. The MOE seed handlers is greater then 5560 and is

considered adequate. The 23-day dermal rat study with a NOAEL of 1000 mg/kg bw was used for the risk assessment for these exposure scenarios, because it had a relevant duration and route of exposure. However, the rat is also the least sensitive species. It was concluded that MOEs greater than 1000 would be protective even though the least sensitive species (rat) was used as a model for toxicity.

Table 3.5.1.2.1 Exposure estimates and MOEs for seed treatment workers handling Charter Seed Treatment and Charter PB Seed Treatment, and for farmers handling treated seed

Scenario	Unit exp [a] (mg/kg a.i.)	Seed handled (kg/day)	Rate (kg a.i./ 100 kg seed)	Amt handled (kg a.i./day)	Daily dose (mg/kg bw/day) [b]	MOE [c]
Applicator exposure and risk						
Commercial treatment	0.642	46 000	0.005	2.3	2.11×10^{-2}	119
On-farm treatment	0.045	8800	0.005	0.44	2.83×10^{-4}	3.5×10^{6}
Post-application exposure and risk						
Handling treated seed	26.5	8800	0.005	0.44	0.17	5560

a For intermediate-term exposure (commercial application), an oral toxicity study was used and exposure estimates are corrected for dermal absorption (42%); inhalation absorption was assumed to be 100%. Because the MOE for short-term exposure (on-farm application) is based on a dermal toxicity study, exposure estimates are based on dermal deposition only (inhalation exposure is considered to be very low compared to dermal deposition).

b Calculated as: (Unit Exposure [µg/kg a.i.]) × (Amount Handled [kg a.i./day])/body weight (70 [kg]).

c The MOE for commercial treatment is based on a NOAEL of 2.5 from the dog chronic dietary exposure study; MOE for on-farm seed treatment and handling of treated seed is based on NOAEL of 1000 from the 23 day rat dermal toxicity study. The target MOE is 300.

3.5.2 Residential exposure and risk

As the proposed products are commercial-class products not used on residential sites, residential handler and post-application assessments were not required.

3.5.3 Bystander exposure and risk

Given the proposed commercial and agricultural use scenarios, exposure and risk to bystanders should be minimal.

4.0 Residues

4.1 Food residue summary

4.1.1 Methods for residue analysis of plants and plant products

Residues of triticonazole in the forage, grain and straw samples from the field trials were determined by GC/TID [Method AR 92-92(E)]. The method LOQs for triticonazole were reported to be 0.01 ppm and 0.05 ppm for grain and straw, respectively. This method was validated with spiked samples of barley grain, barley straw and wheat straw samples, and found to give good recoveries with good repeatability.

A GC/MS (Report # P91/151) analytical method was proposed for data gathering to analyze residues of triticonazole and its associated hydroxy metabolites (RPA 406341, RPA 404886 and RPA 406780) in cereal straw and green plant. The method LOD and LOQ for each analyte were estimated at 0.01 ppm and 0.06 ppm, respectively. Limited method validation demonstrated low recoveries of the parent compound (23–44%).

The LC/MS or LC/MS/MS analytical method MS 148.02 was proposed for data gathering and enforcement purposes to quantify residues of triticonazole and metabolites RPA 404886 and RPA 406341 in plant matrices. The LOQs for LC/MS were 0.01 ppm for grain and 0.04 ppm for forage and straw; the LOQ for LC/MS/MS was 0.005 ppm for grain, forage and straw. The average recoveries of triticonazole ranged from 71 to 122% for all plant matrices spiked at levels ranging from 0.02 to 0.5 ppm (LC/MS) and 0.002–0.5 ppm (LC/MS/MS). ILV of the method using wheat forage was successfully completed. The analytical method was considered acceptable for enforcement purposes.

4.1.2 Methods for residue analysis of food of animal origin

The GC/ECD analytical method AR 104-94(E) was proposed for data gathering and enforcement purposes to quantify residues of triticonazole in animal tissues. The LOQs were 0.05 ppm (eggs, beef/poultry tissues and fat) and 0.01 ppm (milk). The recoveries ranged from 75 to 109% when samples of beef and poultry tissues, milk and eggs were spiked at levels ranging from 0.05 to 0.25 ppm. ILV of this method was successfully completed. The analytical method was considered acceptable for enforcement purposes.

4.1.3 Nature of the residue in plants

In the cereal metabolism studies, [^{14}C-phenyl]-triticonazole formulated as an emulsifiable concentrate was applied as a seed treatment to winter wheat and barley at rates of 180 g a.i./100 kg seed and 240 g a.i./100 kg seed, respectively. Similarly, [^{14}C-triazole]-triticonazole was applied to spring wheat and barley at rates of 190 g a.i./100 kg seed and 300 g a.i./100 kg seed, respectively. Wheat and barley were harvested at preharvest intervals (PHIs) of 134 and 240 days. Total radioactive residues (TRRs) in winter wheat grain (0.01 ppm) and winter barley grain (0.05 ppm) were very

low. In the barley chaff (both labels), TRRs ranged from 1.07 to 1.43 ppm. In barley straw, TRRs were 1.69 ppm (phenyl label) and 2.35 ppm (triazole label). TRRs in wheat chaff were 0.15 ppm (phenyl label) and 1.05 ppm (triazole label). TRRs in wheat straw ranged from 2.08 to 2.23 ppm (both labels).

Extractable residues in grain, chaff and straw ranged from 76 to 89% of the TRR in barley and 60–87% of the TRR in wheat. Bound residues in winter cereals ranging from 11 to 25% of the TRR, were subjected to mild acid hydrolysis followed by strong acid hydrolysis and Soxhlet extraction. Unextractable residues in spring cereals, which accounted for 15–40% of the TRR, were subjected to extractions with water and organic solvents and Soxhlet extractions with various organic solvents. These extraction procedures released an additional 2–52% of the TRRs. The parent, triticonazole, was the predominant residue in winter barley grain, winter and spring barley straw, spring wheat chaff and winter and spring wheat straw. The major metabolites (>10% TRR) identified in barley grain and barley and wheat chaff and straw were the hydroxy metabolites, RPA 404766, RPA 406780, RPA 404886, RPA 406341. The unidentified metabolite A was also detected in all cereal matrices at levels greater than 9.0% TRR.

Based on the findings of the wheat and barley metabolism studies, the ROC for cereal crops for enforcement and risk assessment purposes may be defined as the parent, triticonazole.

4.1.4 Confined accumulation in rotational crops

[^{14}C-phenyl] triticonazole was applied as a spray at a rate of 285.9 g a.i./ha, incorporated into the soil and aged for approximately one month (representing seed failure), five months (crop failure) and one year (second year crops). Lettuce, radish and wheat were planted as secondary crops. Residues of triticonazole were very low (<0.05 ppm) in all raw agricultural commodities (RACs) of the rotational crops (radish, leaf lettuce and wheat) at all plantback intervals. Therefore, it appears unlikely that residues of triticonazole and its related metabolites in soil will be readily taken up by rotational crops.

4.1.5 Nature of the residue in animals

In the dairy cow metabolism study, [^{14}C-phenyl] triticonazole was administered orally to two lactating dairy cows for seven consecutive days at doses equivalent to 1 mg/kg feed/day and 10 mg/kg feed/day. The majority of the administered dose (AD) was excreted in the feces (50.2–51.3% of the AD) and urine (29.8–33.8% of the AD). At the low dose, TRRs in milk were below the LOD (<0.001 ppm) while at the high dose, TRRs accounted for 0.005% of the AD. Therefore, it appears that there was minimal transfer and accumulation of triticonazole and its metabolites in milk. Among all tissues analyzed, TRRs were the highest in liver (low dose—0.021 ppm; high dose—0.238 ppm) followed by kidney (low dose—0.003 ppm; high dose—0.035 ppm). TRRs in skeletal

muscle and fat (omental and perirenal) were nondetectable (< 0.004 ppm) at both dose levels; therefore, these tissues were not further analyzed.

Approximately 96% of the TRR in kidney (high dose) was extractable and the predominant residues consisted of triticonazole and a mixture of the hydroxy metabolites RPA 404766 and RPA 404886, which were not resolved. In liver, only 24% of the TRR was extractable at the low dose and 55% of the TRR at the high dose. The major metabolite in liver (high dose) was the hydroxy metabolite RPA 406780. The nature of the unextractable residues in liver was not further elucidated. The overall low level of tissue residues appears to indicate that neither the parent triticonazole or any of its hydroxy or acid metabolites are likely to accumulate in bodytissues.

Ten laying hens were administered [^{14}C-phenyl] triticonazole orally for 14 consecutive days at doses equivalent to 1 m/kg feed/day and 10 mg/kg feed/day. Hens were sacrificed 23.5 hours after the last dose of triticonazole. At both dose levels, radioactivity was rapidly eliminated in the excreta (85–107% of the AD).

- At the low dose, the radioactivity in the tissues accounted for 0.06% of the AD (0.035 ppm in liver and <0.003 ppm in each of muscle and fat) while the radioactivity in egg white and egg yolk each accounted for 0.18% of the AD (0.004–0.025 ppm).

- At the high dose, the ^{14}C -residues in tissues represented 0.03% of the AD (0.155 ppm in liver, 0.003 ppm in muscle and 0.036 ppm in fat) while ^{14}C-residues in egg white and egg yolk represented 0.16% of the AD (0.1 ppm) and 0.12% of the AD (0.19 ppm), respectively.

Approximately 54–93% of the TRR was extractable from egg samples (yolk and white) and 55–77% of the TRR was extractable from liver samples. The predominant residues in eggs consisted of triticonazole and RPA 404886 (yolk only). In liver extracts, the major residues consisted of triticonazole, RPA 406972 (acid) and RPA 404886. The nature of the unextractable residues in eggs and liver (22–45% TRR; 0.045–0.09 ppm, high dose) was not further elucidated. The nature of the skin, muscle and fat TRRs was not further elucidated.

Based on the dairy cow and poultry metabolism studies, triticonazole appears to be rapidly absorbed and eliminated (mainly via feces) with minimal tissue accumulation. The ROC was defined as the parent, triticonazole.

4.1.6 Supervised residue trials and residue decline studies

Supervised residue field trials were conducted in 1995 and 1996 in 11 locations representing major cereal growing regions of Canada: Ontario, Manitoba, Saskatchewan and Alberta.

Triticonazole flowable formulations were applied as seed treatments to wheat, barley and oats at rates ranging from 10 to 35 g a.i./100 kg seed. Samples of forage were collected for analysis 30 days following emergence while samples of grain and straw were collected at normal plant maturity, ranging from 77 to 116 days following emergence. There were no measurable residues of triticonazole in grain (≤0.01 ppm), straw and forage (≤0.05 ppm). Therefore, when cereal seeds are treated at a rate of 2.5 g a.i./100 kg seed, residues of triticonazole in forage, mature grain and straw are unlikely to exceed the method LOQs.

As triticonazole is to be applied as a seed treatment, no residue decline studies were required.

4.1.7 Freezer storage stability

In the freezer storage stability study, control samples of maize grain, winter wheat grain and winter wheat straw were spiked with triticonazole at 0.01, 0.01 and 0.05 ppm, respectively, and stored at –20°C for 0, 3, 6 and 12 months. The data indicated that residues of triticonazole were stable for 12 months.

The dairy cattle and laying hen metabolism studies were stored for less than 6 months. Furthermore feeding studies were not required on the basis that measurable residues of triticonazole in milk, eggs, meat and meat byproducts are not anticipated when livestock are exposed to feed treated according to the label. Therefore, the requirement for freezer storage stability data for animal matrices was waived.

4.1.8 Processing studies

According to the supervised field trials, residues in wheat, barley and oat grains did not exceed the method LOQ (0.01 ppm) when treated at highly exaggerated rates. Therefore, no processing studies were required.

4.1.9 Meat/Milk/Poultry/Eggs

According to the supervised residue trials, residues of triticonazole in livestock feed items (forage, hay and straw) did not exceed 0.05 ppm when seeds were treated at highly exaggerated rates. The dairy cattle and poultry metabolism studies demonstrated that there were no residues of triticonazole detected at levels greater than 0.01 ppm in the milk and 0.05 ppm in meat and meat byproducts, when administered a diet representing 5–333× the maximum theoretical dietary burden. Because residues of triticonazole are unlikely to accumulate in milk, eggs, beef/poultry meat and meat byproducts, feeding studies were not required.

4.1.10 Dietary risk assessment

The use of triticonazole as a seed treatment on wheat, barley and oats does not pose an unacceptable dietary risk to any segment of the population, including infants, children, adults and seniors.

5.0 Fate and behaviour in the environment

For a summary, see Appendix III, tables 4 and 5.

5.1 Physical and chemical properties relevant to the environment

Triticonazole was determined to have low solubility in water (8.4 mg a.i./L), and is relatively non-volatile under field conditions (vapour pressure of $<0.1\times10^{-5}$ Pa). Its Henry's Law constant [1/H: 6.4×10^{7}] indicates that it is not volatile from water and moist surfaces. The UV-visible absorption spectrum (λ_{max} 212 and 263 nm) indicates that phototransformation is unlikely under natural light. The octanol–water partition coefficient (log K_{ow}) is 3.29 indicating that triticonazole has potential to bioaccumulate/bioconcentrate. Dissociation is not expected to occur at environmentally relevant pHs, based on the molecular structure and lack of relationship between pH and solubility in water (Appendix III, Table 1).

The log K_{ow} of RPA 404766, RPA 406341, and RPA 407922, triticonazole's transformation products, were calculated to be 0.9, 1.5, and 1.3, respectively. These values indicate that these transformation products have limited potential for bioaccumulation/bioconcentration.

5.2 Abiotic transformation

Triticonazole is stable to hydrolysis at pH 5, pH 7, and pH 9.

The photolytic DT_{50} of triticonazole in water was determined to be 4.9 days under continuous irradiation. The major transformation product was the *cis*-isomer (RPA 406203) of triticonazole, which was detected at 42–48% of the applied radioactivity after 6 days (Appendix III, Figure 1). Photo-isomerization will be limited to the photic zone of aquatic systems.

The vapour pressure ($<0.1\times10^{-5}$ Pa) and the Henry's Law constant [1/H: 6.4×10^{7}] indicate that triticonazole is not volatile under field conditions.

5.3 Biotransformation

At 22–25°C in four aerobic soils, laboratory DT_{50} values for triticonazole were 145–554 days, indicating that triticonazole is moderately persistent to persistent according to the classification of Goring et al. (1975). Transformation of triticonazole is a

slow process, and four major transformation products were identified (RPA 407922, RPA 406341, RPA 404766 and RPA 406780) (Appendix III, Figure 2). Unextractable residues accounted for 6–18% of the applied radioactivity at study termination (357–365 days).

RPA 407922 was detected in one soil (clay loam) and was stable at ~12% of the applied radioactivity. RPA 406341 was detected in all four soils and was generally stable at 3–11% of the applied radioactivity in three of the soils. It was still increasing in the Speyer 2.2 soil at study termination (to 15% of the applied radioactivity). RPA 404766 was detected in one soil (clay) and was still increasing at study termination (to 9.5% of the applied radioactivity). RPA 406780 was detected in three soils and was generally stable at 3–10% of the applied radioactivity. It was still increasing in the sandy loam soil at study termination (to 7% of the applied radioactivity).

At 20°C in three aerobic soils, laboratory first-order half-lives of RPA 406341 were 165 days (clay loam), 193 days (sandy loam) and 330 days (loam soils), indicating that RPA 406341 is moderately persistent to persistent according to the classification of Goring et al. (1975). The DT_{90} values were 548 days (clay loam), 640 days (sandy loam) and 1097 days (loam). No major transformation products were detected, and less than 5% of the applied was evolved as carbon dioxide over the 120 days in all three soils. There was an increase in the amount of radioactivity associated with soil as time progressed. Unextractable residues accounted for 21.7% (clay loam), 20.7% (sandy loam) and 12.2% (loam soil) of the applied on day 120.

At 20°C in three aerobic soils, laboratory DT_{50} values of RPA 407922 were found to be 0.5, 0.8, and 1.1 days in two clay loam soils (clay loam 1 and clay loam 2), and loamy sand, respectively, indicating that RPA 407922 is non-persistent according to the classification of Goring et al. (1975). The DT_{90} values were found to be 1.8 days for clay loam 1, 5.7 days clay loam 2 and 4.1 days loamy sand.

An unidentified polar major transformation product was detected in all three soils with the maximum concentration of 10–15% of applied on Day 28. There was an increase in the amount of radioactivity associated with soil as time progressed. Unextractable residues accounted for 81% (clay loam 1), 71% (clay loam 2) and 70% (loamy sand) of the applied at day 100. At the final 100 day time point, 4% (clay loam 1), 7% (clay loam 2) and 5% (loamy sand) of the applied radioactivity had been mineralised to carbon dioxide.

Biotransformation in anaerobic systems is not an important route of transformation of triticonazole in the environment (DT_{50} = 554 days). Triticonazole is classified as persistent under anaerobic conditions.

5.4 Mobility

Based on laboratory studies of adsorption/desorption on a range of soils, triticonazole has low to moderate mobility ($K_{oc\text{-}ads}$ = 184–812) in soils according to the classification of McCall et al. (1981). Adsorption/desorption studies for two major transformation products, RPA 406341 and RPA 407922, on four soils showed that RPA 406341 has moderate to high mobility ($K_{oc\text{-}ads}$ 61–163), while RPA 407922 has low to moderate mobility ($K_{oc\text{-}ads}$ 407–1305) (Appendix III, Table 2).

In both non-aged and aged soil column leaching studies, 99% of the applied radioactivity remained in the soil columns, with the exception of sandy soil where 70% and 27% of the applied radioactivity was detected in the leachates of unaged and aged soil, respectively. These results indicate that triticonazole residues have the potential to leach in sandy soils. An assessment of the potential for triticonazole and two of its transformation products (RPA 406341 and RPA 407922) to contaminate groundwater conducted according to the method of Gustafson (1989) indicates that triticonazole and RPA 406341 are "leachers", while RPA 407922 is a "non-leacher". The groundwater ubiquity scores [GUS] were 3.8 (triticonazole), 5.6 (RPA 406341) and 0.06 (RPA 407922) (Appendix III, Table 3). Therefore, triticonazole and RPA 406341 are expected to leach to groundwater based on their persistence and limited adsorption.

5.5 Dissipation and accumulation under field conditions

The terrestrial field dissipation study of Charter (EP of triticonazole), applied as a single broadcast application of 10 g a.i./ha to bare soil under Western Canadian field conditions, was conducted at one site near the town of Fort Qu'Appelle, Saskatchewan, in Ecozone 9.2. The first-order half-life and DT_{90} of triticonazole were estimated to be 144 and 470 days, respectively, which indicates that triticonazole dissipates slowly and is moderately persistent under Western Canadian field conditions according to the classification of Goring et al. (1975). At 357 days post-application, the total carryover of triticonazole residues was approximately 12% of the applied amount (1.09 µg/kg soil on Day 357), indicating low potential for carryover. RPA 404766 and RPA 406341 residues were only detected at 0.5% and 1.1% of the applied, respectively, at this time.

The results of this study are consistent with the results obtained from soil dissipation studies conducted in Europe, and the United States, which indicate that triticonazole is moderately persistent (according to the classification of Goring et al. 1975). There was no opportunity to assess leaching potential of triticonazole and its transformation products under Canadian field conditions due to low irrigation, which limited the vertical movement of the product (rainfall was approximately 50% of the historical values for this location and not supplemented with irrigation to reach the average historical value), and low application rate, which resulted in non-detectable residues. Laboratory studies of adsorption/desorption, leaching, and assessment of the potential to contaminate groundwater (GUS method), indicate that triticonazole and RPA 406341 may have the potential to leach under certain conditions (coarse texture soils, such as sand, sandy loam

and loamy sand). In American field trials, however, with application rates of 187 and 636 g a.i./ha, the residues of triticonazole and its transformation products did not leach below the 30 cm soil profile. The proposed low application rate for the seed treatment (8 g a.i./ha) and binding of residues to soil with time will limit the leaching potential. No major transformation products were detected under Canadian conditions; however, the European field studies showed that triticonazole transformed to RPA 406341, a major transformation product, that achieved a maximum of 11% of applied amount at 6–10 months of application. Dissipation kinetics of the transformation products under the Canadian field study could not be determined due to very low concentrations.

5.6 Bioaccumulation

The log K_{ow} of triticonazole is 3.29, which indicates a potential for bioconcentration/bioaccumulation. In absorption studies with the rat, metabolism of triticonazole was almost complete with only trace amounts of the parent compound recovered unchanged. Triticonazole had limited tissue accumulation and the highest tissue concentrations occurred in the skin and fur. Based on these studies, triticonazole is not expected to bioaccumulate in wild mammals.

Bioaccumulation of triticonazole was studied in bluegill sunfish (*Lepomis macrochurus*) under flow-through conditions at a nominal concentration of 89 µg/L for 28 days, followed by a 14-day depuration period.

Bioconcentration factors (BCFs), based on TRR and taking into account the kinetics of uptake and depuration, were 9.2 (in edible tissue), 115 (in inedible tissue) and 73 (in whole fish). The BCF for triticonazole was 2.3 in whole fish. The fact that the BCF determined for parent compound was much lower than the TRR-based BCF indicates that triticonazole is metabolized very quickly in fish (Appendix III, Figure 3). The depuration half-life was 0.86 days in whole fish. These results indicate that triticonazole undergoes rapid metabolism and depuration in fish and, therefore, is unlikely to bioaccumulate.

5.7 Summary of fate and behaviour in the terrestrial environment

Laboratory studies of transformation of triticonazole in soil showed that hydrolysis is not an important route of transformation in the terrestrial environment. Biotransformation is a route of transformation of triticonazole in soil under aerobic conditions, although this is a slow process (DT_{50} 145–554 days), indicating moderate persistence to persistence in soil according to the classification of Goring et al. (1975) (Appendix III, Table 4). Soil biotransformation results in the formation of four major transformation products (RPA 406780, RPA 406341, RPA 407922 and RPA 404766), which undergo further biotransformation. At 20°C in three aerobic soils, laboratory first-order half-lives of RPA 406341 were 165 days (clay loam soil), 193 days (sandy loam soil), and 330 days (loam soil), indicating that RPA 406341 is moderately persistent to persistent according to the classification of Goring et al. (1975). The DT_{90} values were 548, 640 and 1097 days, respectively, for the clay loam, sandy loam and loam soils. No major transformation

products were detected, and less than 5% of the applied was evolved as carbon dioxide over the 120 days of the study in all three soils. There was an increase in the amount of radioactivity associated with soil as time progressed. Unextractable residues accounted for 21.7%, 20.7% and 12.2% of the applied in clay loam, sandy loam and loam soils, respectively, on day 120. At 20°C in three aerobic soils, laboratory DT_{50} values of RPA 407922 were found to be 0.5, 0.8, and 1.1 days in clay loam 1, clay loam 2, and loamy sand, respectively, indicating that RPA 407922 is non-persistent according to the classification of Goring et al. (1975). The DT_{90} values were found to be 1.8, 5.7 and 4.1 days for clay loam 1, clay loam 2, and loamy sand, respectively.

An unidentified polar major transformation product was detected in all three soils with the maximum concentration of 10–15% of applied on Day 28. There was an increase in the amount of radioactivity associated with soil over the time. Unextractable residues accounted for 81%, 71% and 70% of the applied for clay loam1, clay loam2, and loamy sand, respectively, at day 100. At the final 100 day time point, 4%, 7% and 5% and of the applied radioactivity had been mineralised to carbon dioxide for clay loam1, clay loam2 and loamy sand, respectively.

Under anaerobic conditions, triticonazole undergoes negligible biotransformation and is persistent.

The results of adsorption/desorption studies indicate that triticonazole has low to moderate mobility in a range of soils ($K_{oc\text{-}ads}$ = 184–812) according to the classification of McCall et al. (1981). RPA 407922 also has low to moderate mobility in soils ($K_{oc\text{-}ads}$ = 407–1305), while RPA 406341 is more mobile than the parent compound, showing moderate to high mobility ($K_{oc\text{-}ads}$ = 61–163). Column leaching studies using non-aged and aged soils demonstrated that triticonazole has the potential to leach in sandy soils. An assessment of the potential for triticonazole and its transformation products (RPA 406341 and RPA 407922) to contaminate groundwater conducted according to the method of Gustafson (1989) indicates that triticonazole and RPA 406341 are “leachers”, while RPA 407922 is a “non-leacher”. Therefore, triticonazole and RPA 406341 have the potential to leach under certain conditions (coarse texture soils, such as sand, sandy loam and loamy sand).

A Canadian study of terrestrial field dissipation of the formulation product, Charter, illustrated that triticonazole dissipates with the first-order half-life of 144 days, which indicates that it is moderately persistent under Western Canadian field conditions according to the classification of Goring et al. (1975). At 357 days post-application, the total carryover of triticonazole residues was approximately 12% of the applied amount (1.09 µg/kg soil on day 357), indicating low potential for carryover. RPA 404766 and RPA 406341 residues were only detected at 0.5% and 1.1% of the applied, respectively, at this time.

The results of this study are consistent with the results obtained from soil dissipation studies conducted in Europe, and the United States, which indicate that triticonazole is

moderately persistent (according to the classification of Goring et al. 1975). There was no opportunity to assess leaching potential of triticonazole and its transformation products under Canadian field conditions due to low irrigation, which limited the vertical movement of the product (rainfall was approximately 50% of the historical values for this location and not supplemented with irrigation to reach the average historical value), and low application rate, which resulted in non-detectable residues. Laboratory studies of adsorption/desorption, leaching, and assessment of the potential to contaminate groundwater (GUS method), indicate that triticonazole and RPA 406341 may have the potential to leach under certain conditions (coarse texture soils, such as sand, sandy loam and loamy sand). In American field trials, however, with application rates of 187 and 636 g a.i./ha, the residues of triticonazole and its transformation products did not leach below the 30 cm soil profile. The proposed low application rate for the seed treatment (8 g a.i./ha) and binding of residues to soil with time will limit the leaching potential. No major transformation products were detected under Canadian conditions; however, the European field studies showed that triticonazole transformed to RPA 406341, a major transformation product, that achieved a maximum of 11% of applied amount at 6–10 months of application. Dissipation kinetics of the transformation products under the Canadian field study could not be determined due to very low concentrations.

5.8 Summary of fate and behaviour in the aquatic environment

Under the proposed use pattern (seed treatment, and treated seed incorporated into the soil), there is little potential for exposure of surface water through surface runoff, spray drift or accidental overspray. Therefore, exposure of aquatic environments is not of concern for this seed treatment formulation. However, triticonazole is stable to hydrolysis (Appendix III, Table 5). In the photic zone of aquatic systems, triticonazole will undergo photo-isomerization to its *cis*-isomer (DT_{50} = 4.9 days).

5.9 Expected environmental concentrations

5.9.1 Soil

The expected environmental concentration (EEC) of triticonazole in soil was calculated by the reviewer to be 0.004 mg a.i./kg dry soil immediately after application, assuming a soil bulk density of 1.5 g/cm^3, a soil depth of 15 cm, and a scenario in which the maximum Canadian label rate of 8 g a.i./ha is applied once to bare soil.

5.9.2 Aquatic systems

Under the proposed use pattern, the potential exposure of surface water through surface runoff, spray drift and accidental overspray is unlikely. Therefore, EECs in water and surface runoff were not calculated.

5.9.3 Vegetation and other food sources

The EECs of triticonazole were calculated in the diet of bobwhite quail (27.5 mg a.i./kg dw), mallard duck (35 mg a.i./kg dw), rat (10 mg a.i./kg dw), and mouse (25 mg a.i./kg dw) (Appendix III, Table 6). Grain as the food item and its relative contribution (as % diet) to the dietary EEC for each species (Urban and Cook 1986) and a scenario in which the maximum label rate of 50 mg a.i./kg seed were used.

6.0 Effects on non-target species

6.1 Effects on terrestrial organisms

Technical triticonazole showed no toxicity to earthworms in an acute study. No adverse effects were observed at the highest dose tested (1000 mg a.i./kg soil) (Appendix III, Table 7).

Technical triticonazole was not acutely toxic to the bobwhite quail or mallard duck administered a single dose of 2000 mg a.i./kg bw by gavage. Therefore, triticonazole is categorized as practically non-toxic (LD_{50} >2000 mg a.i./kg bw) to birds on an acute oral basis in accordance with the United States Environmental Protection Agency (USEPA) descriptive categorization (USEPA 1985a). Similarly, triticonazole was not toxic to bobwhite quail or mallard duck administered dietary doses for five consecutive days. Therefore, triticonazole is categorized as practically non-toxic (LC_{50} >5000 mg a.i./kg diet) to birds on a short-term dietary basis in accordance with the USEPA descriptive categorization (USEPA 1985b). In avian reproduction studies, no treatment-related effects were observed in mallard duck (NOEC 1000 mg a.i./kg diet); however, dietary administration to adult bobwhite quail adversely affected egg production and hatchling survival (NOEC 250 mg a.i./kg diet).

The acute oral LD_{50} of technical triticonazole was > 2000 mg/kg bw in rats. Therefore, triticonazole is categorized as practically non-toxic (LD_{50} >2000 mg/kg bw) to wild mammals on an acute oral basis in accordance with the USEPA descriptive categorization (USEPA 1985c). The adrenal gland and liver were identified as target organs in rats and mice following short- or long-term dietary exposure to technical triticonazole. The short-term dietary NOEC values were 250 mg a.i./kg diet for the female rat (13-week study) and 1500 mg a.i./kg diet for the mouse (42-day study). The long-term NOEC values were 750 mg a.i./kg diet for the rat (100-week study) and 150 mg a.i./kg diet for the mouse (78-week study). The short-term NOEC values for mortality were 5000 and 12 500 mg a.i./kg diet for the mouse and rat, respectively. The corresponding long-term NOEC values for mortality were 1500 and 5000 mg a.i./kg diet. In a multi-generation reproductive study with the rat, increases in ovary weights, vacuolation of ovarian cells, decreased mating and fertility indices as well as decreased litter size and live-birth index were observed. The NOEC value for parental, offspring and reproductive toxicity in rats was 750 mg a.i./kg diet.

6.2 Effects on aquatic organisms

6.2.1 Acute toxicity to freshwater organisms

Technical triticonazole was moderately toxic to freshwater invertebrates in accordance with the USEPA descriptive classification (USEPA 1985d) (Appendix III, Table 8). The 48-hour LC_{50} value was 9 mg a.i./L for *Daphnia magna* (NOEC 3.2 mg a.i./L). Long-term exposure to technical triticonazole at 3.0 mg a.i./L resulted in a reduction of reproductive output and mean total length of *Daphnia magna* adults (21-day NOEC 1.3 mg a.i./L).

Technical triticonazole was not toxic to freshwater fish at the maximum achievable test concentrations (limited by its low solubility in water). The 96-hour LC_{50} values for rainbow trout and bluegill sunfish were empirically estimated to be > 3.6 and > 8.9 mg a.i./L, respectively. No adverse effects were observed in bluegill sunfish at the highest dose tested (8.9 mg a.i./L); however, erratic swimming was observed in rainbow trout at 2.3 mg a.i./L (NOEC 1.4 mg a.i./L).

The early life-stage study with sheepshead minnow indicates that adverse effects on larval growth may occur at concentrations as low as 0.051 mg a.i./L (34-day NOEC 0.021 mg a.i./L).

6.3 Effects on biological methods of sewage treatment

Data are not required.

6.4 Risk characterization

6.4.1 Environmental behaviour

Triticonazole is stable to abiotic transformation processes in the terrestrial environment. Triticonazole and its transformation product RPA 406341 are subject to slow biotransformation in aerobic soils (DT_{50} = 145–554 days for triticonazole and 165–330 days for RPA 406341), and are moderately persistent to persistent in soils under the laboratory conditions according to the classification of Goring et al. (1975). Triticonazole's other transformation product, RPA 407922, however, is non-persistent (DT_{50} = 0.5–1.1 days) under aerobic soil. Under anaerobic conditions, triticonazole undergoes negligible biotransformation and is persistent. Triticonazole and RPA 407922, have low to moderate mobility in a range of soils ($K_{oc\text{-}ads}$ = 184–812 for triticonazole, 407–1305 for RPA 407922), while RPA 406341 shows moderate to high mobility in soils ($K_{oc\text{-}ads}$ = 61–163). Results of laboratory soil column leaching studies showed that triticonazole has the potential to leach in a sandy soil, and an assessment of leaching potential of triticonazole and its transformation products, RPA 406341, and 407922, conducted according to the method of Gustafson (1989), indicated that triticonazole and RPA 406341 are "leachers", while RPA 407922 is a "non-leacher". The results of the Canadian terrestrial field dissipation study, at application rate of 10 g a.i./ha on a bare soil

with more than 70% sand, are consistent with the results obtained from soil dissipation studies conducted in Europe, and the United States, which indicate that triticonazole is moderately persistent (according to the classification of Goring et al. 1975) with DT_{50} of 144 days. At 357 days post-application, the total carryover of triticonazole residues was approximately 12% of the applied amount (1.09 µg/kg soil on Day 357), indicating low potential for carryover. RPA 404766 and RPA 406341 residues were only detected at 0.5% and 1.1% of the applied, respectively, at this time. There was no opportunity to assess leaching potential of triticonazole and its transformation products under Canadian field conditions due to low irrigation that limited the vertical movement of the product (rainfall was approximately 50% of the historical values for this location and not supplemented with irrigation to reach the average historical value), and low application rate that resulted in non-detectable residues. In the American field trials, however, with application rates of 187 and 636 g a.i./ha, the residues of triticonazole and its transformation products did not leach below the 30 cm soil profile. The proposed low application rate for the seed treatment (8 g a.i./ha) and the binding of residues to soil with time will limit the leaching potential.

In aquatic systems, triticonazole is subject to phototransformation (photo-isomerization to its *cis*-isomer) (DT_{50} = 4.9 days), which would be limited to the photic zone of aquatic systems. Under the proposed use pattern, however, aquatic exposure to triticonazole is limited.

Triticonazole and its metabolites are not expected to bioaccumulate in terrestrial or aquatic organisms based on the following:

- the lack of bioaccumulation of triticonazole and TRRs in whole fish (BCF 2.3, and 73, respectively);
- the rapid depuration of residues in fish (DT_{50} = 0.86 days); and
- the limited accumulation of triticonazole in skin and fur of rats.

6.4.2 Terrestrial organisms

Earthworms—Based on the comparison of the calculated EEC in soil (0.004 mg a.i./kg dry soil) and the LC_{50} and NOEC (>1000 mg a.i./kg soil and 1000 mg a.i./kg soil, respectively) the lethal and sublethal risk of triticonazole to earthworm is negligible. The short-term risk quotient (RQ) values for earthworm mortality and sublethal effects are <0.000 004 (EEC/LC_{50}) and 0.000 004 (EEC/NOEC), respectively.

Birds and mammals—Wild birds and mammals could be exposed to triticonazole residues as a result of consumption of contaminated seeds. The risk assessment procedure is directed at risks to individuals, as there are currently no commonly used criteria for judging the significance of effects for population-level processes. The diets of wild birds, such as bobwhite quail and the mallard duck, consist of 55% and 70% seeds, respectively. The diets of wild mammals, such as rat and mouse, consist of 20% and 50% seeds, respectively. Using the triticonazole maximum application rate of 50 mg a.i./kg seed

(EEC), the estimated ingestion of triticonazole via contaminated seeds is 27.5, 35.0, 10.0 and 25.0 mg a.i./kg dw diet for bobwhite quail, mallard duck, rat and mouse, respectively.

The acute oral risk to birds was assessed using the following:

- NOEL estimates for each respective species from the applicable studies;
- food consumption estimates (bobwhite quail: 0.015 kg dw/ind/d; mallard duck: 0.099 kg dw/ind/d) from the applicable studies;
- mean body weight (bobwhite quail: 197 mg; mallard duck: 1060 mg) estimates from the applicable studies; and
- the predicted EEC in each birds's diet.

Based on the predicted daily intake (DI) (DI = food consumption [FC] × EEC: bobwhite quail—0.41 mg a.i./ind/d; mallard duck—3.47 mg a.i./ind/d), the maximum number of days of intake of triticonazole by a bobwhite quail and a mallard duck to reach their respective NOELs ($NOEL_{(ind)}$/DI) was 955 days (bobwhite quail) and 306 days (mallard duck). Therefore, birds are not at risk on an acute basis.

In the assessment of the acute risk to rats, default values were used for food consumption (i.e. 0.06 kg dw/ind/d) and body weight per individual (i.e., 350 mg/ind). The EEC in a typical rat (seeds only) was 10.0 mg a.i./kg dw. Based on the predicted DI of 0.60 mg a.i./ind/d and the NOEL of 200 mg/kg bw, the maximum number of days of intake of triticonazole by a rat to reach NOELs ($NOEL_{(ind)}$/DI) was 117 days. Therefore, small wild mammals are not at risk on an acute basis.

The following RQs and assessments were determined (Appendix III, Table 10):

- The dietary RQ values for bobwhite quail and mallard duck are sublethal effects are 0.02 and 0.027 (EEC/NOEC), respectively. Therefore, the risk of sublethal effects of triticonazole to birds is negligible following dietary exposure.

- The reproductive RQ values (EEC/NOEC) for bobwhite quail and mallard duck are 0.11 and 0.035, respectively. Therefore, the risk of reproductive effects of triticonazole to birds is low to negligible.

- The dietary RQ value for rat (EEC/NOEC) is 0.04, indicating that the risk of sublethal effects of triticonazole to mammals is negligible following dietary exposure.

- The chronic RQ value for mouse (EEC/NOEC) is 0.17, indicating that the risk of chronic effects of triticonazole to mammals is low.

Therefore, the risk of triticonazole, used as a seed treatment, poses negligible to low risk to wild birds and wild mammals on an acute, dietary, chronic and reproductive basis.

6.4.3 Aquatic organisms

Based on the proposed use pattern, no exposure to aquatic environments is expected.

6.5 Risk mitigation

The following statement is required under **"DIRECTION FOR USE"** to minimize the potential for leaching:

> "The use of this chemical may result in contamination of groundwater, particularly in areas where soils are permeable (e.g. sandy soil) and/or the depth to the water table is shallow."

Based on available data, no restrictions on the application of Charter Seed Treatment Fungicide are required for the protection of earthworms, birds or wild mammals. However, environmental hazard statements are required on the label for protection of non-target terrestrial and aquatic habitats.

The "**ENVIRONMENTAL PRECAUTIONS**" section must be revised to read as follows:

> "Ensure seeds are properly incorporated into soil. **DO NOT** feed treated seed to wildlife or domestic birds, or allow the animals to be exposed to treated seed. If treated seed is spilled outdoors or in areas accessible to birds, promptly clean up or bury the seeds to prevent ingestion. Ensure proper disposal of any surplus treated seed not intended for later planting. **DO NOT** contaminate domestic or irrigation water supplies, lakes, streams, ponds or any body of water with the chemical, used containers, treated seed or bags that have held treated seed. **DO NOT** contaminate water by cleaning of their equipment or disposal of waste. Unused or leftover treated seed should not be stored where there is a chance it will be mixed with untreated seed."

7.0 Efficacy

7.1 Effectiveness

7.1.1 Intended uses

Charter Seed Treatment was originally proposed for application at 5 g a.i./100 kg seed to control common bunt (*Tilletia caries*) and loose smut (*Ustilago tritici*) of wheat; true loose smut of barley (*Ustilago nuda*); and covered smut (*Ustilago kolleri*) and loose smut (*Ustilago avenae*) of oats. Subsequently, applications were made to add the following claims to the product label:

- control of seed rot caused by *Fusarium* spp.;
- control of seedling blights caused by seed and soil-borne *Fusarium* spp.;
- suppression of *Fusarium* crown and root rot;
- suppression of common root rot and control of seedling blight caused by *Cochliobolus sativus* on both wheat and barley; and
- control of covered smut (*Ustilago hordei*) and false loose smut (*Ustilago nigra,* or *Ustilago avenae*) on barley.

7.1.2 Mode of action

Triticonazole, the active ingredient in Charter Seed Treatment, inhibits a demethylation step during fungal sterol biosynthesis. This active falls within the Group 3 Fungicides as described by the Fungicides Resistance Action Committee (FRAC), and is one of several demethylation inhibitor (DMI) triazole fungicides available.

7.1.3 Crops

Charter Seed Treatment is proposed for use on wheat, barley and oats.

7.1.4 Effectiveness against pests

7.1.4.1 Smuts and bunts – wheat, barley and oats

A total of 32 efficacy trials and 24 crop tolerance trials conducted in Canada were submitted for the original claims of controlling common bunt (*Tilletia caries*) and loose smut (*Ustilago tritici*) of wheat; true loose smut of barley (*Ustilago nuda*); and covered smut (*Ustilago kolleri*) and loose smut (*Ustilago avenae*) of oats. Charter was applied to seed at full and half rates and was compared with commercial standard treatments containing tebuconazole or carbathiin. Charter was effective in controlling wheat common bunt and loose smut resulting in means of 93% and 96% control, respectively. It also reduced barley loose smut, providing 80% control, and 100% control of oat loose smut and covered smut. This performance was typically better than the commercial standards tested at the same time. In comparative trials, there was typically no significant

difference between the efficacy of the proposed rate (5 g a.i./100 kg seed) and the half-rate (2.5 g a.i./100 kg seed) of triticonazole; therefore the 2.5 g a.i. rate is considered to be the lowest effective rate (LER) for control of smuts and bunts.

7.1.4.2 Control of seed rot (*Fusarium* spp.) on wheat and barley

Data was presented on *Fusarium*-inoculated wheat seed only, and results were extended to include barley. Five laboratory germination trials, and eleven field emergence trials were submitted for review. Three of the five lab trials showed a significant increase in percent germination with Charter at 2.5 or 5.0 g a.i./100 kg seed rates, or any other fungicide commercial standard, compared to the untreated seed. Only one trial showed an increase in germination with the 5.0 g a.i. Charter rate over the 2.5 g a.i. rate. The field trials were not as supportive as the laboratory results. Of the 11 field emergence studies, 9 showed no significant increase in emergence with the use of Charter at any rate, or any commercial standard, compared to the untreated seed. No differences were found in emergence counts between seeds treated with Charter at the 2.5 g a.i. rate, and the other commercial standards. The claim that Charter Seed Treatment will control wheat and barley seed rot caused by *Fusarium* spp., when applied at 2.5 g a.i./100 kg seed, was supported.

7.1.4.3 Control of seedling blight caused by seed-borne *Fusarium* sp. on wheat and barley

The 11 field trials used to assess control of wheat seed rot were also used to assess the seedling blight claim, and the results were extended to barley. Plant stand counts were assessed 12–14 days after emergence. Only 1 of the 11 trials showed a significant increase in plant stand for Charter at 2.5 g a.i. (average increase of 13.5%), and 2 trials for the 5.0 g a.i. rate (average increase of 11.8%), compared to the check plants. Charter at 2.5 g a.i. performed as well as the commercial standards in most of the trials. The claim that Charter Seed Treatment will control wheat and barley seedling blight caused by seed-borne *Fusarium* spp., when applied at 2.5 g a.i./100 kg seed, was supported.

7.1.4.4 Control of seedling blight caused by soil-borne *Fusarium* sp. on wheat and barley

Results from the 11 soil-inoculated *Fusarium* trials demonstrated that Charter did not provide consistent disease control compared to the untreated, inoculated control. The average increase in plant stand was 6.4% for Charter at the proposed rate, and 9.3% for the commercial standard. Of these trials, only one demonstrated that applying Charter or any other fungicide, resulted in a significantly greater plant stand count compared to the untreated seeds. Of the remaining trials, there was no definite trend to indicate that Charter provided consistent levels of control. The claim that Charter Seed Treatment will control wheat and barley seedling blight caused by soil-borne *Fusarium* sp., when applied at 2.5 g a.i./100 kg seed, was not supported.

7.1.4.5 Control of covered smut (*Ustilago hordei* sp. *avenae*) on barley

No data was presented to support this claim, but a rationale was provided. Based on the data previously presented on covered smut of oats (*Ustilago kolleri*), and the fact that these two pathogens are similar with respect to their biology, the claim was accepted at the 2.5 g a.i./100 kg seed rate.

7.1.4.6 Control of false loose smut (*Ustilago nigra*) on barley

No data was presented to support this claim, but a rationale was provided. Based on the data previously presented on loose smut of oats (*Ustilago avenae*), the claim was accepted at the 2.5 g a.i./100 kg seed rate.

7.1.4.7 Suppression of fusarium crown and root rot on wheat and barley

Five wheat and six barley field trials were submitted to support this claim. Plant crown and roots were examined and disease incidence recorded, as well as disease severity being rated on a 0–5 scale, which was then converted to a percent value. The data showed moderate disease pressures in most of the trials. Of the 11 trials, 5 found no significant decrease in crown or root rot with any of the fungicides tested, including Charter at 2.5 or 5.0 g a.i./100 kg seed, compared to the untreated, inoculated check. The remaining trials showed a significant decrease in crown and root rot, with there being do difference between Charter at the 2.5 g a.i. rate and the commercial standards. The claim that Charter Seed Treatment will suppress Fusarium crown and root rot on wheat and barley was supported at the 2.5 g a.i./100 kg seed rate.

7.1.4.8 Control of seedling blight caused by *Cochliobolus sativus* on wheat and barley

Eight Manitoba trials (five on barley, three on wheat) were submitted that tested Charter at 2.5 and 5.0 g a.i./100 kg seed, and compared them to an untreated check and other commercial standards. Plant stand counts, made 14–27 days after emergence, were used as an indirect way of assessing this claim. The trials failed to demonstrate a consistent, significant increase in stand counts with Charter at either rate, compared to plots sown with untreated seeds, while seeds treated with a commercial standard did show an increase in stand counts. This claim was not supported.

7.1.4.9 Suppression of common root rot caused by *Cochliobolus sativus* on wheat and barley

Seven trials (four on wheat, three on barley) compared Charter applied at 2.5 and 5.0 g a.i./100 kg seed, and rated root rot disease incidence and severity (0–5 scale, and severity values were then converted to percent disease severity). Disease pressure in the barley trials were low, and moderately low in the wheat trials. Results show that Charter at both rates did suppress root rot disease to levels similar to those of the commercial standards, and disease levels were lower than in the check plots. Trends also indicate that the higher Charter rate, 5.0 g ai, provided a greater level of suppression of common root

rot than the lower rate of 2.5 g a.i./100 kg seed. The claim that Charter Seed Treatment will suppress common root rot of wheat and barley caused by *Cochliobolus sativus*, was supported at the 5.0 g a.i./100 kg seed rate.

7.1.5 Total spray volume

Charter seed treatment is a liquid concentrate that must be diluted with water to provide adequate application volume to ensure good seed coverage. It is recommended to mix two parts water with one part Charter. However, any directions regarding water dilutions should be followed according to the manufacturers instructions on the seed treatment application equipment.

7.2 Phytotoxicity to target plants (including different cultivars) or to target plant products

No phytotoxicity was noted on any of the target plants (wheat, barley or oats) that were tested at the proposed application rate. Higher rates (up to 36 times the proposed rate) resulted in no observable phytotoxic effect on any of the cereal varieties tested.

7.3 Observations on undesirable or unintended side effects

No data were submitted to assess side effects on beneficial and other non-target organisms, on succeeding crops, as well as on other plants or parts of treated plants used for propagating purposes (i.e., seed, cutting, runners). However, no adverse effects are expected based on the use pattern (seed treatment).

7.3.1 Impact on succeeding crops

No data was submitted to assess this. No adverse effects are expected based on the use pattern (seed treatment).

7.3.2 Impact on adjacent crops

No data was submitted to assess this. No adverse effects are expected based on the use pattern (seed treatment).

7.4 Economics

No data was submitted to assess the economics of Charter Seed Treatment.

7.5 Sustainability

7.5.1 Survey of alternatives

7.5.1.1 Non-chemical control practices

Various methods of non-chemical disease control practices can be incorporated into a good integrated pest management (IPM) strategy. This includes choice of disease-resistant varieties, and certified disease-free seeds, as well as being aware of crop rotation options to limit the duration of a pathogen in a specific field. In addition, good sanitation practices should be followed when storing unused seed over winter, limiting the use of equipment from fields known to harbour disease, to disease-free fields and in removing diseased plant debris from the field after harvest.

7.5.1.2 Chemical control practices

The fungicide seed treatment products listed in Table 5.5.1.2.1 are registered to control or suppress some or all of the same crops and pathogens proposed for use on the Charter Seed Treatment label. Products are arranged according the FRAC Group and the active ingredient.

Table 5.5.1.2.1 Registered fungicide seed treatment products

FRAC group	Fungicide active ingredient	Product and registration number
M3	Maneb	Agsco DB-Red L Liquid Seed Fungicide Seed Treatment (27144)
M3	Mancozeb	Dithane—45 Seed Protectant Concentrate (27616)
P	2 (thiocyanomethylthio) benzothiazde	Busan 30 Liquid Seed Treatment Fungicide (10662)
	Formaldehyde	Formalin Fungicide (6998)
3	Hexaconazole	Proseed Seed Treatment Fungicide (25892)
3	Tebuconazole	Raxil 250 FL Flowable Fungicide (26138); Raxil 312 FS Seed Treatment Fungicide (25762); Raxil SP Soluble Pack Systemic Fungicide Seed Protectant (26137)
3, M	Tebuconazole, thiram	Raxil Thiram Flowable Fungicide (27566)
3, 4	Difenoconazole, metalaxyl-M	Dividend XL Fungicide (25778); Dividend XL RTA Fungicide (25777)

FRAC group	Fungicide active ingredient	Product and registration number
4	Metalaxyl, metalaxyl-M	Apron FL Seed Treatment Fungicide (Reg. No. 24262); Apron XL LS Seed Treatment Fungicide (25585)
7	Carbathiin	Vitaflo 250 Liquid Suspension (13429); Vitavax FL (27550)
7, M	Carbathiin, thiram	Vitaflo 280 Fungicide (11423); Vitaflo 280 Liquid Suspension (undyed) (22473); Vitaflo 220 Liquid Suspension (21174); Vitavax 200 Flowable Fungicide (27555); Vitavax Powder Systemic Seed Protectant (27959)
12	Fludioxonil	Maxim 480 FS Colourless Seed Treatment Fungicide (27001)

7.5.2 Contribution to risk reduction

Seed treatments, in general, are considered to have less inherent risk than foliar-applied fungicides, given the following reasons:

(a) There is usually a lower quantity of active ingredient required to be applied to the seed.

(b) There is only one application made per year.

(c) By applying a fungicide product to the seed, there is less of a chance for pathogens to develop within the field, which in turn will lead to a reduced need for foliar applications.

7.5.3 Information on the occurrence or possible occurrence of the development of resistance

Disease resistance to active ingredients within Group 3 Fungicides have been documented and characterized over the past 20 years. Problems occur after several years of intensive use, and performance has been noted to decline during this time, especially with repeated foliar applications. Within the Group 3 Fungicides, it was noticed that there is positive cross-resistance amongst the DMI fungicides, and among the “morpholine” fungicides, but no cross-resistance between these two groups. FRAC defines the active ingredients within the Group 3 Fungicides as having a “medium risk” for developing disease resistance. Because Charter is to be applied as a seed treatment, used in small quantities at only one time during the year, it is not expected that the use of Charter Seed Treatment will increase the risk of disease resistance development.

7.6 Conclusions

Earlier evaluations assessed the smut and bunt disease claims and supported their use at the lowest effective rate of 2.5 g a.i./100 kg seed. Subsequently, additional claims for control of *Fusarium* diseases were made, and these claims were also supported at the 2.5 g a.i. rate. However, for the claim of suppression of common root rot on wheat and barley caused by *Cochliobolus sativus*, the data showed a clear trend that the higher Charter rate of 5.0 g a.i./100 kg seed was required. Because this product is a seed treatment, and not a foliar-applied fungicide, the product can only be applied at one rate to control all of the diseases listed on the product label. Therefore, because 5.0 g a.i. was the highest rate supported, this rate will be recommended for application on wheat, barley and oats to control or suppress the supported diseases (Table 7.6.1).

Table 7.6.1 Disease claims supported/not supported for Charter Seed Treatment at 5.0 g a.i./100 kg seed

Disease claims that were supported for Charter Seed Treatment

Wheat

- Control of seed rot caused by *Fusarium* spp.
- Control of seedling blight caused by seed-borne *Fusarium* spp.
- Control of loose smut
- Control of common bunt
- Suppression of *Fusarium* crown and root rot
- Suppression of common root rot caused by *Cochliobolus sativus*

Barley

- Control of seed rot caused by *Fusarium* spp.
- Control of seedling blight caused by seed-borne *Fusarium* spp.
- Control of true loose smut
- Control of false loose smut
- Control of covered smut
- Suppression of *Fusarium* crown and root rot
- Suppression of common root rot caused by *Cochliobolus sativus*

Oats

- Control of loose smut
- Control of covered smut

Claims that were not supported for Charter Seed Treatment

- Control of seedling blight caused by soil-borne *Fusarium* spp.
- Control of seedling blight caused by *Cochliobolus sativus* on wheat and barley

8.0 Toxic Substances Management Policy considerations

During the review of technical triticonazole and the associated EPs, Charter Seed Treatment and Charter PB Treatment, the PMRA has taken into account the federal Toxic Substances Management Policy[1] and its Regulatory Directive DIR99-03[2], and has concluded the following:

- Triticonazole does not meet the criteria for persistence under the proposed use pattern. Although its highest value for half-life in laboratory aerobic study in soil (544 days) is above the TSMP Track 1 cut-off criterion for soil (≥182 days), the corresponding value under the Canadian field conditions is 144 days. Triticonazole will undergo photo-isomerization to its *cis*-isomer (DT_{50} 4.9 days) in aquatic systems. Therefore, its half-life is below the TSMP Track 1 cut-off criterion for water (≥182 days). With respect to the proposed use pattern for Charter, the exposure of the aquatic systems to triticonazole is limited. Triticonazole is non-volatile from moist soil and water surfaces, based on values for vapour pressure and Henry's Law constant, therefore, atmospheric contamination is not considered to be a route of exposure with the proposed use.

- Triticonazole does not meet the criterion for bioaccumulation. The log K_{ow} is 3.29, which is below the TSMP Track 1 cut-off criterion of log $K_{ow} \geq 5$. The BCF values in whole fish are 2.3 for triticonazole and 73 for TRRs, which are below the TSMP Track 1 cut-off criterion of BCF ≥ 5000. In addition, no bioaccumulation was observed in the rat metabolism study.

- The toxicity of triticonazole is summarized in sections 3.0 and 6.0.

- In aerobic soil systems, triticonazole forms persistent transformation products in soil (RPA 406341 with a DT_{50} up to 330 days. RPA 407922, RPA 404766, and RPA 406780—no half-life was reported for the last three; however, their residues did not decline during the study period).

- Based on their polarity and log K_{ow} (≤1.5), the four aerobic soil transformation products are unlikely to bioaccumulate.

---

1 The federal Toxic Substances Management Policy is available through Environment Canada's website at www.ec.gc.ca/toxics

2 Regulatory Directive DIR99-03, *The Pest Management Regulatory Agency's Strategy for Implementing the Toxic Substances Management Policy*, is available through the Pest Management Information Service. Phone: 1 800 267-6315 within Canada or (613) 736-3799 outside Canada (long distance charges apply); Fax: (613) 736-3758; E-mail:pmra_infoserv@hc-sc.gc.ca; or through our website at www.pmra-arla.gc.ca.

- Technical triticonazole does not contain any impurities of toxicological concern as identified in Section 2.14 of DIR98-04 nor any TSMP substances as listed in Appendix II of DIR99-03.

- The EP does not contain any formulants that are known to contain TSMP Track 1 substances.

Therefore, the use of Charter Seed Treatment Fungicide, containing triticonazole, is not expected to result in the entry of TSMP Track 1 substances into the environment. The proposed registration of triticonazole and Charter Seed Treatment Fungicide is, therefore, consistent with the PMRA's strategy for implementing the TSMP.

9.0 Proposed regulatory decision

The PMRA has carried out an assessment of available information in accordance with Section 9 of the PCP Regulations and has found it sufficient pursuant to Section 18.(b), to allow a determination of the safety, merit and value of technical grade triticonazole and its EPs, Charter Seed Treatment and Charter PB Seed Treatment, manufactured by Bayer CropScience Inc. The Agency has concluded that the use of the active ingredient triticonazole or the EPs, Charter Seed Treatment and Charter PB Seed Treatment, in accordance with the label has merit and value consistent with Section 18(c) of the PCP Regulations and does not entail an unacceptable risk of harm pursuant to Section 18(d). Therefore, based on the considerations outlined above, the use of the active ingredient triticonazole or the EPs, Charter Seed Treatment and Charter PB Seed Treatment, for the control of various fungal diseases on wheat, barley and oats are proposed for full registration pursuant to Section 13 of the PCP Regulations.

List of abbreviations

AD	administered dose
ADI	acceptable daily intake
a.i.	active ingredient
ARfD	acute reference dose
BCF	bioconcentration factor
bw	body weight
CAS	Chemical Abstracts Service
C_{max}	peak plasma concentration
d	day(s)
DMI	demethylation inhibitor
DT_{50}	time required for non first-order 50% dissipation
dw	dry weight of diet
EEC	expected environmental concentration
EP	end-use product
F_0	parental generation
$F_0/_1$	parental generation/1st generation offspring
F_1	1st generation offspring
FRAC	Fungicides Resistance Action Committee
GC	gas chromatography
GC/ECD	gas chromatograph equipped with an electron capture detector
GC/MS	gas chromatography mass selective detection
GC/TID	gas chromatography using a thermionic detector
GPMT	guinea pig maximization test
GUS	groundwater ubiquity score
H	Henry's Law constant
HDT	highest dose tested
ILV	independent laboratory validation
K	Freudlich coefficient*K*
oc-ads	adsorption quotient normalized to organic carbon
K_{ow}	*n*-octanol–water partition coefficient
LC_{50}	lethal concentration 50%
LC/MS	liquid chromatography/mass spectrometry
LD_{50}	lethal dose 50%
LER	lowest effective rate
LOAEL	lowest observed adverse effect level
LOD	limit of detection
LOQ	limit of quantitation
MAS	maximum average score (for 24, 48 and 72 h)
MIS	maximum irritation score
MOE	margin of exposure
MOS	margin of safety
MRL	maximum residue limit
MS	mass spectrometry
LC/MS	Liquid chromatograph with mass spectrometric detection

LC/MS/MS	Liquid chromatograph with tandem mass spectrometric detection
MSD	mass selection detection
MTD	maximum tolerated dose
N/A	not applicable
NAFTA	North American Free Trade Agreement
ND	not determined
NOAEL	no observed adverse effect level
NOEC	no observable effect concentration
NOEL	no observable effect dose level
NR	not reported
NZW	New Zealand white
OC	organic carbon
OEAS	Occupational Exposure Assessment Section
OECD	Organisation for Economic Co-operation and Development
OPPTS	Office of Prevention, Pesticides and Toxic Substances
PCP	pest control product
pH	$-\log_{10}$ hydrogen ion concentration
PHED	Pesticide Handlers Exposure Database
PHI	preharvest interval
pK_a	acid dissociation constant
PPE	personal protective equipment
ppm	parts per million
PRDD	Proposed Regulatory Decision Document
QA	quality assurance
QC	quality control
RAC	raw agricultural commodity
ROC	residue of concern
RSD	relative standard deviation
RTA	ready-to-apply
SD	standard deviation
SF	safety factor
SPE	solid phase extraction
STMR	supervised tiral median residue
TGAI	technical grade active ingredient
TRR	total radioactive residue
TSMP	Toxic Substances Management Policy
µg	microgram
µL	microlitre
USEPA	United States Environmental Protection Agency
UV	ultraviolet
w/v	weight per volume

Appendix I Toxicology

Figure 1 Proposed metabolic pathway of triticonazole in the rat

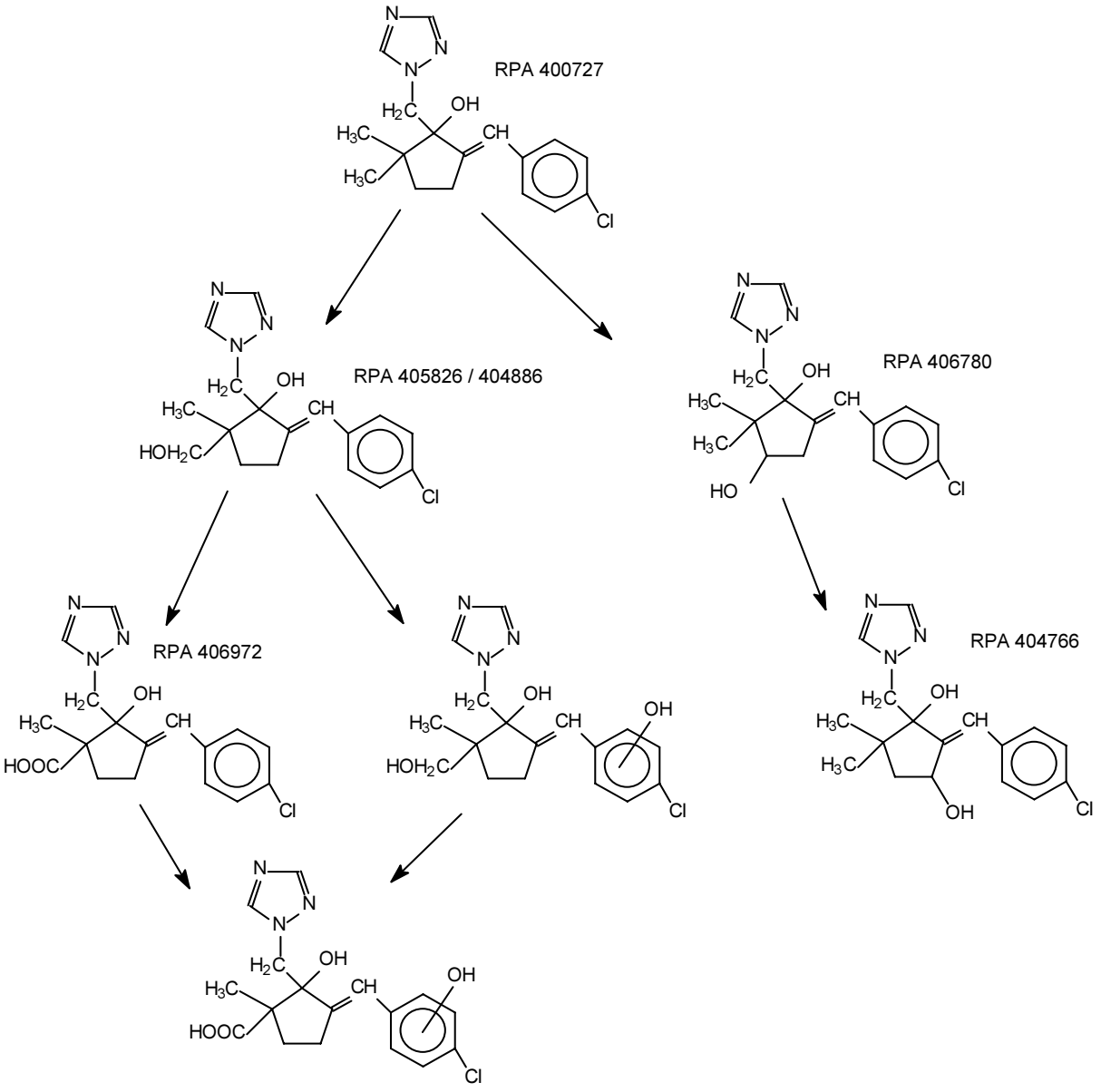


Table 1 Toxicology summary

METABOLISM

Absorption: Single or repeated doses of 5 mg/kg bw of RPA 400727 in rats were readily and extensively absorbed.

Distribution: The plasma C_{max} was reached at 0.6 hours (5 mg/kg bw) and 1.6–2 hours (500 mg/kg bw) in both sexes. Tissue residues after each of the three protocols were low, were not dose proportional, and no indication of accumulation was observed. The highest residues were found in the liver, skin and fur (500 mg/kg bw); in adrenals and in plasma in males; and adrenals and fat in females (5 mg/kg bw).

Excretion: Rapidly and almost completely eliminated within 48 hours. By Day 7, 3–15% (males) and 5–32% (females) were excreted via the urine; 81–96% (males) and 65–96% (females) were excreted via the feces. Terminal biological half-life was 95–118 hours.

Metabolism: Metabolised, and subsequently excreted primarily in the feces as unconjugated metabolites. The terminal biological half-life was 95–118 hours. Repeated dosing over 14 days did not alter the pharmacokinetic profile of the compound. Differences in metabolism and excretion between males and females were minor and quantitative rather than qualitative. The major fecal metabolites were identified as RPA 405826 and RPA 406972 (5 mg/kg bw) and RPA 405826 (500 mg/kg bw). Urine from all three dose groups was found to contain up to 12 metabolites, four of which (RPA 406972/404766/406780/406341) accounted for the bulk of the radio label. These were identified only as derivatives of the parent compound.

STUDY	SPECIES/STRAIN/ DOSES	LD_{50} (mg/kg bw) LC_{50} (mg/L)	SIGNIFICANT EFFECTS/COMMENTS
ACUTE STUDIES–Technical (RPA 400727)			
Oral	Rat(CD) 5/sex @2000 mg/kg (limit test)	LD_{50} > 2000	**Low acute toxicity** ↓motor activity and ataxia in all animals.
Dermal	Rat (CD) 5/sex @2000 mg/kg (limit test)	LD_{50} > 2000	**Low acute toxicity** Dermal irritation noted at administration site.
Inhalation	Rat (CD) 5/sex @1.40 mg/L (max. attainable conc.)	LC_{50} > 1.40	**Slight acute toxicity** Excessive salivation.
Dermal irritation	Rabbit (NZW) 0.10 g dose unwashed: 3/sex;	MAS = 0	**Non-irritant**
Eye irritation	Rabbit (NZW) 6 males 0.1 g dose (1991) Rabbit (NZW) 6 females 0.1 g dose (1997)	MIS (1hour) = 4.7 MIS (1hour) = 2.7	**Minimal irritant** Iridial inflammation (2/6); conjunctival erythema (5/6) and erythema (2/6), resolved by 48 hours **Minimal irritant** Conjunctival erythema and discharge (6/6), resolved by 24 hours.

STUDY	SPECIES/STRAIN/ DOSES	LD_{50} (mg/kg bw) LC_{50} (mg/L)	SIGNIFICANT EFFECTS/COMMENTS
Skin sensitization	Guinea pig (Dunkin Hartley) 10/sex **Buehler** [Ind: 50% w/v a.i. (0.25 ml); Challenge: 10% and 50% a.i. in propylene glycol] **GPMT** (Ind. 0.1 ml of 5% w/v a.i. followed by 50% w/v propylene glycol; Challenge with 10% and 50% a.i. in propylene glycol)	**Buehler** – No evidence of sensitization. **GPMT** – Some slight erythema after induction. 50% a.i. and 10% a.i. groups showed no reaction after challenge.	**Not a sensitizer**
ACUTE STUDIES – Impurity (RPA 402570)			
Oral	Rat(CD) 5/sex @2000 mg/kg (limit test)	LD_{50} > 2000	**Low acute toxicity** No deaths. No clinical signs.
Dermal	Rat (CD) 5/sex @2000 mg/kg (limit test)	LD_{50} > 2000	**Low acute toxicity** No deaths or clinical signs. No signs of dermal irritation noted at admin. site.
ACUTE STUDIES – CHARTER EP			
Oral	Rat – Crl:CD BR 5/sex	LD_{50} > 2000 mg/kg ♂ and ♀	**Low acute toxicity**
Dermal	Rat – Crl:CD BR 5/sex	LD_{50} > 2000 mg/kg bw ♂ and ♀	**Low acute toxicity**
Inhalation (nose only)	Rat – Crl:CD BR 5/sex	LC_{50} > 1.7 mg/kg	**Slight acute toxicity** Excessive salivation.
Skin irritation	Rabbit – NZW 2 males and 1 female (0.5 g)	MIS= 1.0 at 1 hour MAS= 0.33 (average from 24, 48 and 72 hours)	**Slightly irritating**
Eye irritation	Rabbit – NZW 1 male, 2 females (0.1 ml) unwashed eye)	MIS = 7.3 at 1 and 24 (reversible by Day 7)	**Mildly irritating**
Dermal sensitization (Buehler)	Guinea Pigs – Hartley 10/sex 100% induction 100% challenge	Positive response	**Skin sensitizer**

STUDY	SPECIES(STRAIN)/ DOSES	NOAEL/LOAEL (mg/kg bw/day)	SIGNIFICANT EFFECTS/COMMENTS
SHORT TERM/SUBCHRONIC			
42-day dietary	Mouse (CD-1); 12/sex/group; 0, 10, 30, 100, 250 or 500 ppm (♂:0, 1.5, 4.3, 15.5, 36.9 or 73.1 mg/kg bw/day, and ♀: 0, 2.0, 5.9, 19.1, 45.5 or 99.2 mg/kg bw/day).	NOAEL = 500 ppm (73.1 ♂/99.2♀) LOAEL = Not determined.	**500 ppm:** ↑liver weight (slight) and hepatocyte hypertrophy (♂); considered as an adaptive response. Note: supplementary study.

STUDY	SPECIES(STRAIN)/ DOSES	NOAEL/LOAEL (mg/kg bw/day)	SIGNIFICANT EFFECTS/COMMENTS
SHORT TERM/SUBCHRONIC			
42-day dietary	Mouse (CD-1); 12/sex/group; 0, 500, 1500, 5000, 15 000 or 50 000 ppm (♂: 0, 77.7, 233, 851 or 3270 mg/kg bw/day and ♀: 0, 98.8, 286, 982 or 4091 mg/kg bw/day). [Compound consumption (mg/kg bw/day) could not be determined for the 50 000 ppm group because all animals died within the first week of the study.]	NOAEL = 1500 ppm (233♂/286♀) LOAEL = 5000 ppm (851 ♂/982♀)	**5000 ppm:** ↑liver weight; liver histopathology [hepatocyte hypertrophy, fatty vacuolation, multiple nuclei and focal mineralization (♂)] ≥ **15 000 ppm:** ↓body-weight gain and food intake, mortality and clinical signs (piloerection, pallor, hunched posture); bile duct proliferation (♂), ↓uterus weight (no histopathology) **50 000 ppm:** Mortality (100% by day 6)
13-week dietary	Mouse (CD-1); 12/sex/group; 0, 2500, 5000 or 8000 ppm (♂: 0, 382.8, 807.6 or 1426.2 mg/kg bw/day, and ♀: 0, 503.8, 969.2 or 1657.6 mg/kg bw/day).	NOAEL = Not determined. LOAEL = 2500 ppm (382.8♂/503.8♀)	≥ **2500 ppm:** ↓body-weight gain and food efficiency; enlarged livers; ↑liver weight; hepatocyte hypertrophy, hepatocytic fatty vacuolation and necrosis; bile plug formation (♂), ↓uterus weight (no histopathology) ≥ **5000 ppm:** ↑hepatocyte mitotic activity; bile plug formation (♀)
4-week dog (determina-tion of maximum tolerated dose [MTD])	Dog (Beagle) 1/sex **Group 1**: increasing doses of 10, 20, 40, 80, 160, 640 mg/kg bw/day; doses held for 3 days at each level, and 320 and 1000 mg/kg bw/day; doses held for 6 days **Group 2**: 1000 mg/kg bw/day for 3 days, untreated for 11 days followed by 14 days at 500 mg/kg bw/day **Group 3:** 300 mg/kg bw/day for 14 days (capsule)	MTD: 300 mg/kg bw/d	**Group 1:** ≥ **40 mg/kg bw/d:** ↓body-weight gain (♂) ≥ **80 mg/kg bw/d:** ↓body-weight gain (♀) **1000 mg/kg bw/d:** overt clinical signs (♂) **Group 2 (1000/500 mg/kg bw/d):** weight loss, ↑liver weight, ↑hepatic enzyme parameters, overt clinical signs of intoxication (ataxia, torpor, tremors, disorientation and convulsions); one male at 1000/500 mg/kg bw/day killed in extremis following the second dose. **Group 3 (300 mg/kg bw/d):** ↑liver weight, ↑hepatic enzyme parameters. Clinical signs in dogs treated at 300 mg/kg bw/day cleared within the first few days of dosing.
1 year dog	Dog (Beagle) 4/sex 0, 2.5, 25 or 150 mg/kg bw/day (capsule)	NOAEL = 2.5 LOAEL = 25	≥ **25 mg/kg bw/d:** ↓body-weight gain (♀), ↓albumin (♂), ↑ALP (♀), vacuolation of adrenal cortical cells (zona fasciculata) (♂/♀) **150 mg/kg bw/d:** ↓body-weight gain (♂), clinical signs, ↓cholesterol (♂/♀), ↓albumin (♂), ↑ALP (♂), lenticular cataracts (4/4 ♂ and 3/4 ♀), ↑Abs. and rel. testes weight, ↓abs. and rel. prostate weight in ♂,

STUDY	SPECIES(STRAIN)/ DOSES	NOAEL/LOAEL (mg/kg bw/day)	SIGNIFICANT EFFECTS/COMMENTS
SHORT TERM/SUBCHRONIC			
23-day dermal	Rat [Crl:CD (SD)BR Vaf Plus] 5/sex/group, 0, 100, 300 or 1000 mg/kg bw/day	NOAEL = 1000 LOAEL = Not determined	No systemic treatment-related effects at any dose level tested. Dermal irritation was not observed at any dose level tested.
14-day gavage; comparative study	Rat (Sprague-Dawley CD); 5/sex/group; RPA 400727 (technical active) or RPA 402570 (impurity of synthesis): 0, 10, 100 or 1000 mg/kg bw/day	NOAEL = 100 LOAEL = 1000 [For RPA 400727 and RPA 402570]	**1000 mg/kg bw/d:** RPA 400727 (technical active): ↑liver weight and hepatocyte vacuolation (♀); thickened glandular gastric (♂) and forestomach (♀) epithelium. RPA 402570 (impurity): ↑liver weight and hepatocyte vacuolation; hyperkeratosis and acanthosis in the forestomach (♂).
4-week dietary	Rat (F-344); 5/sex/group; 0, 500, 1500, 5000, 15 000 or 50 000 ppm (♂: 0, 50.1, 152.3, 513.2, 1494 or 4802 mg/kg bw/day, and ♀: 0, 52.4, 151.3, 489.4, 1476 and 4945 mg/kg bw/day)	Males: NOAEL = 1500 ppm (152.3) LOAEL = 5000 ppm (513.2) Females: NOAEL = 5000 ppm (489.4) LOAEL = 15 000 ppm (1476)	≥ **500 ppm:** ↓uterus weight (no histopathology) ≥ **5000 ppm:** ↓body-weight gain, food intake and food efficiency (♂), ↓prostate weight (no histopathology) ≥ **15 000 ppm:** ↓food efficiency; ↑liver weight; hepatocyte vacuolation; necrosis (♂); ↓uterus weight with reduced uterine endometrial stroma; **50 000 ppm:** General clinical signs of toxicosis, ↓body-weight gain(♀), ↓serum glucose, ketonuria, hepatocyte hypertrophy; ↓prostate weight, ↓ovary weight (no histopathology).
13-week dietary	Rat (CD); 10/sex/group; 0, 25, 250, 12 500 and 25000 ppm (♂: 0, 2.0, 19.8, 1117.0 or 2309.3 mg/kg bw/day, and ♀: 0, 2.2, 22.3, 1183.5 and 2368.8 mg/kg bw/day).	**Males:** NOAEL < 25 ppm (<2.0) LOAEL = 25 ppm (2.0) **Females:** NOAEL = 250 ppm (22.3) LOAEL=12 500 ppm (1183.5)	≥ **25 ppm:** Adrenocortical fatty vacuolation (♂) ≥ **250 ppm:** hepatocyte hypertrophy (♂). ≥ **12 500 ppm:** Generalized hair loss, ↓body-weight gain, food intake and food efficiency;↑serum cholesterol (♀), ↑liver weight; hepatocyte hypertrophy (♀), fatty vacuolation (♀); degeneration of the adrenal zona reticularis (♀); adrenocortical fatty vacuolation.
CHRONIC TOXICITY/ONCOGENICITY			
78-week dietary	Mouse (CD-1) 68/sex/group 0, 15, 150 or 1500 ppm (♂: 0, 1.8, 17.4 or 202.2 mg/kg bw/day, and ♀: 0, 2.1, 20.1 or 209.5 mg/kg bw/day)	**Chronic effects:** NOAEL = 150 ppm (17.4♂/20.1♀) LOAEL = 1500 ppm (202.2♂/209.5♀)	**1500 ppm:** ↑liver weight, enlarged livers; hepatocyte hypertrophy (♂) and fatty vacuolation; ↓body-weight gain (♀), ↓food efficiency (♂), ↑adrenal weight (♂/♀ at interim sacrifice only; no histopathology) No treatment-related oncogenic effects at any dose level tested.

STUDY	SPECIES(STRAIN)/ DOSES	NOAEL/LOAEL (mg/kg bw/day)	SIGNIFICANT EFFECTS/COMMENTS
SHORT TERM/SUBCHRONIC			
100-week dietary	Rat (CD-1) 80/sex/group 0, 5, 25, 750 or 5000 ppm (♂: 0, 0.2, 1.0, 29.4 or 203.6 mg/kg bw/day, and ♀: 0, 0.3, 1.3, 38.3 or 286.6 mg/kg bw/day)	**Chronic effects**: NOAEL = 750 ppm (29.4♂/38.3♀) LOAEL = 5000 ppm (203.6♂/286.6♀) **Oncogenicity** **Males:** NOAEL = 750 ppm (29.4) LOAEL = 5000 ppm (203.6) **Females:** NOAEL = 5000 ppm (286.6) LOAEL = Not determined	**5000 ppm:** ↓ body-weight gain and food efficiency (♀), multinucleated cells in the adrenal (♀), chronic inflammation of adrenal (♀), hepatocyte fatty vacuolation (♀), ↑ incidence of thyroid follicular cell adenomas (♂).
REPRODUCTION/DEVELOPMENTAL TOXICITY			
Multi-generation	Rat (Crl:CD® BR), 2 generations, (1 litter/gen) 28/sex/dose 0, 5, 25, 750 or 5000 ppm via diet (♂: 0, 0.3, 1.6, 49.4 or 307.2 and ♀: 0, 0.4, 1.8, 54.7 or 386.6 mg/kg bw/day).	**Systemic toxicity:** NOAEL = 750 ppm (49.4♂/54.7♀) LOAEL = 5000 ppm (307.2♂/386.6♀) **Offspring toxicity:** NOAEL = 750 ppm (54.7) LOAEL = 5000 ppm (386.6) **Reproductive toxicity:** NOAEL = 750 ppm (54.7) LOAEL = 5000 ppm (386.6)	**Parents:** **5000 ppm:** ↑maternal deaths (F_0♀); ↓parental body weight ↓body-weight gain, ↓food consumption (F_0♀, F_1♂ + ♀), ↑liver weight and liver pathology, ↓adrenal weight and adrenal pathology ($F_{0/1}$ ♀); adrenal pathol ($F_{0/1}$ ♀) **Offspring:** **5000 ppm:** ↓ $F_{1/2}$ pup body weight; ↓viability index $F_{1/2}$ pups **Reproductive parameters:** **5000 ppm:** ↓fertility and mating indices F_1; ↑gestation interval F_0, ↑ovary weight and pathology (vacuolation) (F_1♀), ↑stillborn pups (F_0), ↓litter size (F_1), ↓live birth index $F_{1/2}$ pups.
Teratogenicity	Rat (Crl:CD® BR) 25 females/dose 0, 40, 200 or 1000 mg/kg bw/day, by gavage (in methyl cellulose) on gestation days 6–15.	**Maternal:** NOAEL =1000 (HDT) **Developmental:** NOAEL = 1000 (HDT)	**Maternal toxicity:** **1000:** marginal ↓body weight, ↓body-weight gain, ↓feed consumption, not considered adverse **Developmental toxicity:** **1000**: ↑incidence of 14th rib/pairs of ribs (variation not considered to be adverse) **Not teratogenic**

STUDY	SPECIES(STRAIN)/ DOSES	NOAEL/LOAEL (mg/kg bw/day)	SIGNIFICANT EFFECTS/COMMENTS
SHORT TERM/SUBCHRONIC			
Teratogenicity	Rabbit (NZW) 20/dose 0, 5, 25, 50 or 75 mg/kg bw/day by gavage (in methyl cellulose) on gestation days 6–19	**Maternal:** NOAEL = 5 LOAEL = 25 **Developmental:** NOAEL = 5 LOAEL = 25	**Maternal toxicity:** **≥ 25:** ↓body-weight gain and food consumption; **≥ 50:** ↑maternal deaths, ↑respiration rate; **75:** slight ↑in pre- and post- implantation loss **Fetal toxicity:** **≥ 25:** ↑elongation acromion process **≥ 50:** ↑various skeletal abnormalities (↑incidence of delayed ossification of digits). **Not teratogenic**
NEUROTOXICITY			
Acute (Range-finding and time-to-peak-effect)	Rat (Crl:CD® BR),4/sex/dose 0, 50, 1000 or 2000 mg/kg bw	Doses for definitive acute study determined to be 80, 400 and 2000 mg/kg bw	Time-to-peak-effect is 3 hr post-dosing. Dose-related increase in motor activity greatest at 3 hrs post dose. No effects on FOB tests.
Acute	Rat (Crl:CD® BR), 10/sex/dose, via single gavage dose of 0, 80, 400 or 2000 mg/kg bw; observed for 15/16 days post dose	**Neurotoxicity:** NOAEL = 2000 mg/kg bw (the highest dose tested)	No treatment related effects on mortality, clinical signs, body weight, brain size or gross/histologic pathology or neuropathology. No effects on functional observation battery.
Subchronic	Rat (Crl:CD® BR), 10/sex/dose 0, 500, 2500 or 10 000 ppm (♂: 0, 32.5, 170.0 or 695.1 mg/kg bw/day, and ♀: 0, 38.5, 199.4 or 820.3 mg/kg bw/day) via diet for 90 days	**Neurotoxicity:** NOAEL > 695♂/820♀	No mortalities of clinical signs of toxicity. No effects on functional observation battery nor neuropathology at highest dose tested.
GENOTOXICITY			
STUDY	**SPECIES/STRAIN or CELL TYPE**	**DOSES EMPLOYED**	**SIGNIFICANT EFFECTS/COMMENTS**
Technical Active (RPA 400727)			
Reverse mutation	S. *typhimurium*, ± S9	25, 79, 250, 790, 2500 µg/plate	Negative
Gene mutation	Chinese hamster V79 cells ± S9	62.5, 125, 250, 500, 1000 µg/ml	Negative

STUDY	SPECIES/STRAIN or CELL TYPE	DOSES EMPLOYED	SIGNIFICANT EFFECTS/COMMENTS
Chromosome aberration	Human lymphocytes ± S9	+ S9: 125, 250, 500 µg/ml; - S9: 10, 20, 40, 50, 60 µg/ml	Negative Negative
Micronucleus test	Mouse	25, 125, 625 mg/kg bw	Negative
Unscheduled DNA synthesis	Rat	7.8, 15.6, 31.3, 62.5, 125 µg/ml	Negative
Impurity (RPA 402570)			
Reverse mutation	S. *typhimurium*, ± S9	100, 250, 500, 1000, 2500 µg/plate	Negative

Acute toxicity ARfD

Females (13+): Based on the increased incidences of skeletal anomalies i.e. elongation of the acromion process and delayed ossification of the metacarpals and phalanges (rabbit) and supernumerary ribs (rat) observed in teratogenicity studies following exposure to triticonazole (effects observed at maternally toxic doses), an ARfD was deemed necessary for the sub-population of females (13+). The recommended ARfD is 0.017 mg/kg bw/day based on the lowest developmental NOAEL of 5 mg/kg bw/day in the rabbit teratogenicity study, and utilizing an uncertainty factor of 300.

General population

In the context of the low order of acute toxicity of triticonazole following exposure by oral, dermal and inhalation routes, it is not necessary to propose an ARfD for the general population.

Recommended ADI is 0.008 mg/kg bw/day. The most appropriate study for selection of toxicity endpoints for chronic dietary exposure was the 52-week study with a NOAEL of 2.5 mg/kg bw/day in dogs where target organ toxicities were observed as adrenal cortical cell vacuolation, decreased cholesterol and albumin levels, changes in testes and prostate organ weights at and above 25 mg/kg bw/day and lenticular cataracts at 25 mg/kg bw/day. An additional (× 3) safety factor (in addition to the usual 100-fold for interspecies and intraspecies variation) was deemed necessary, due to observed effects on reproductive performance (rats)/reproductive organ toxicity (dogs and rats)/offspring toxicity (rats) as a result of possible perturbations of endocrine system via the adrenal gland.

Appendix II Residues

Table 1 Integrated food residue chemistry summary

DIRECTIONS FOR USE OF PESTICIDE ON BARLEY, OATS AND WHEAT						
Crop	**Formulation/type**	**Interval (day)**	**Rate**	**# / season**	**Maximum rate**	**PHI (days)**
barley	liquid flowable	N/A	2.5 g a.i./100 kg seed	N/A	2.5 g a.i./100 kg of seed	N/A
oats						
wheat						
Label restrictions: Do not use treated seed for food, feed or oil processing.						

PHYSICOCHEMICAL PROPERTIES	
Water solubility at 20°C	8.4 mg/L
Solvent solubility	**Solvent** — **Solubility (g/L)** Hexane — 0.12 Methanol — 18.2 Acetone — 74.5 Toluene — 12.6 2-propanol — 7.6 Dichloromethane — 191.0 Ethyl acetate — 48.6 *n*-octanol — 6.2
Octanol/water partition coefficient (log K_{ow}) at 20°C	Log K_{ow} = 3.29
Dissociation constant (pK_a)	Does not dissociate.
Vapour pressure at 50°C	$< 0.1 \times 10^{-5}$ Pa
Relative density	1.343 g/mL
UV-visible absorption spectrum	λ_{max} at 212 nm and 263; no absorbance above 320 nm

ANALYTICAL METHODOLOGY			
Parameters	**Plant matrices**	**Plant matrices**	**Plant matrices**
Method ID	Method P91/151	Method AR 92-92(E)	Method MS 148.02
Type	Data gathering	Data gathering	Data gathering and enforcement
Analytes	Triticonazole and its associated hydroxy metabolites (RPA 406341, RPA 404886, RPA 406780)	Triticonazole	Triticonazole and metabolites RPA 404886 and RPA 406341

Parameters	Plant matrices	Plant matrices	Plant matrices
Instrumentation	Gas chromatograph equipped with a Mass Selective Detector (GC/MS)	Gas chromatograph equipped with a Thermionic Detector (GC/TID)	Liquid chromatograph with mass spectrometric (MS) or tandem mass spectrometric (MS/MS) detection.
LOQ	0.06 ppm for each analyte for plant material	0.01 ppm for grain 0.05 ppm for straw	0.01 ppm for grain (LC/MS) 0.04 ppm for forage and straw (LC/MS) 0.005 ppm for grain, forage and straw (LC/MS/MS)
Standard	External standard for retention time and detector response/calibration.	External standard for retention time and detector response/calibration.	External standard for retention time and detector response/calibration.
ILV	Developed for data gathering purposes. Therefore, ILV is not required.	Developed for data gathering purposes. Therefore ILV is not required.	ILV of the LC/MS and LC/MS/MS methods were successfully completed using wheat forage.
Extraction/ cleanup	Residues were extracted into acetone, filtered, evaporated and cleaned up using C18 and amino SPE.	Residues were extracted into acetone: water (4:1), filtered, re-extracted, evaporated and cleaned up using C18 and amino SPE.	Residues were extracted with water:acetone (3:1, v:v), centrifuged and re-extracted twice with water:acetone (10:90, v:v) prior to cleanup via SPE or liquid/liquid partitioning with dichloromethane.
Radiovalidation	Developed for data gathering purposes. Therefore radiovalidation is not required.	Developed for data gathering purposes. Therefore radiovalidation is not required.	As method MS1 48.02 was not radiovalidated using samples from the wheat metabolism study, the extraction efficiency of the method could not be determined.

Parameters	Animal matrices
Method ID	AR 104-94 (E)
Type	Data gathering and enforcement method
Analytes	Triticonazole
Instrumentation	Gas chromatograph equipped with an Electron Capture Detector (GC/ECD)
LOQ	0.05 ppm (eggs, beef and poultry tissues and fat) 0.01 ppm (milk)
Standard	External standard for retention time and detector response/calibration.
ILV	ILV of the GC/ECD method was successfully completed using beef, eggs, fat and milk.
Extraction/ cleanup	Residues were extracted with acetone or acetonitrile and cleaned up by solvent partitioning with hexane and C_{18} and/or amino SPE.
Radiovalidation	As method AR 104-94(E) was not radiovalidated using samples from the cattle and poultry metabolism studies, the extraction efficiency of the method could not be determined.

Parameters	Plant matrices	Plant matrices	Plant matrices
Multiresidue method	Residues of triticonazole in peas (seed and pod) and wheat (grain and straw) were adequately recovered using the GC/NPD European Multiresidue Analytical Method DFG S19. Residues of triticonazole in animal commodities were not subjected to a recognized multiresidue method.		

NATURE OF THE RESIDUE IN PLANTS – WINTER AND SPRING WHEAT, SPRING AND WINTER BARLEY				
	winter wheat	spring wheat	winter barley	spring barley
Radiolabel position	phenyl	triazole	phenyl	triazole
Test site	outdoor plots	outdoor plots	outdoor plots	outdoor plots
Treatment	seed	seed	seed	seed
Rate	180 g a.i./100 kg seed	190 g a.i./100 kg seed	240 g a.i./100 kg seed	300 g a.i./100 kg seed
PHI	240 days	134 days	240 days	134 days

The radioactivity was distributed to the aerial portions of the plants (straw, chaff and grain). Radioactivity was also detected in the top 10 cm of soil in the planting rows.

Metabolites identified		**Major metabolites (≥10% TRRs)**	**Minor metabolites (<10% TRRs)**
Radiolabel position		**phenyl**	**phenyl**
winter barley	grain	triticonazole, RPA 406341	
	chaff	RPA 404766 combined with RPA 406780, RPA 404886	triticonazole, RPA 406341
	straw	triticonazole	RPA 404766 combined with RPA 406780, RPA 404886, RPA 406341, RPA 406203
winter wheat	chaff	triticonazole, RPA 404886	RPA 406341
	straw	triticonazole, RPA 404886, RPA 406341	RPA 404766 combined with RPA 406780
Radiolabel position		**triazole**	**triazole**
spring barley	chaff	RPA 404886	triticonazole, RPA 404766 combined with RPA 406780
	straw	triticonazole, RPA 404886	RPA 404766
spring wheat	chaff	triticonazole, RPA 404766, RPA 404886	
	straw	triticonazole, RPA 404766, RPA 404886	

ROC	Triticonazole was readily metabolized in winter and spring wheat and barley. The metabolic profile in cereal crops suggests hydroxylation as the major pathway. None of the hydroxylated metabolites (RPA 404766, RPA 406780, RPA 404886, RPA 406341) are of toxicological concern and the unidentified polar metabolite A consists of a number of low molecular weight polar compounds which may have been incorporated into natural plant products. Therefore, the ROC is defined as the parent triticonazole.

CONFINED ROTATIONAL CROP STUDY – LETTUCE, RADISH, WHEAT

Radiolabel position	phenyl label
Test site	confined soil plots
Application rate and timing	286 g a.i./ha applied and incorporated into soil prior to planting of rotational crops

Crop	Triticonazole equivalents (ppm)		
	30-day tilling	149-day tilling	355-day tilling
Radish roots	0.231	0.049	0.043
Radish leaves	0.077	0.032	0.022
Lettuce leaves	0.048	0.015	0.033
Wheat grain	0.0029	0.0037	0.004
Wheat chaff	0.03	0.02	0.058
Wheat straw	0.16	0.17	0.11
ROC	Uptake of triticonazole into RACs of three representative crops was low. Triticonazole was the predominant extractable residue. Therefore, application of triticonazole at normal seed dressing rate would result in minimal uptake in rotational crops. The definition of the ROC remains as the parent, triticonazole.		

NATURE OF THE RESIDUE IN LAYING HEN

Species	Radiolabel	Dose Level	Length of Dosing	Sacrifice
Hen	[phenyl- ^{14}C-U] triticonazole	1 mg/kg 10 mg/kg	14 consecutive days	23.5 hours after last dose

85–107% of the administered dose was excreted in urine, feces; 0.31–0.42% remaining in tissues, organs and eggs.

Metabolites identified	**Major metabolites (≥10% TRRs)**		**Minor metabolites (<10% TRRs)**	
Dose level	**1 mg/kg**	**10 mg/kg**	**1 mg/kg**	**10 mg/kg**
liver	RPA 406972 (acid), RPA 404886, RPA 406341	RPA 406972 (acid), triticonazole, RPA 404886	RPA 406972 (acid), RPA 404766	

Metabolites identified	**Major metabolites (≥10% TRRs)**		**Minor metabolites (<10% TRRs)**	
Dose level	**1 mg/kg**	**10 mg/kg**	**1 mg/kg**	**10 mg/kg**
egg yolk	triticonazole, RPA 404886	triticonazole	RPA 406341	RPA 406972 (acid), RPA 404766, RPA 406780, RPA 404886, RPA 406341
egg white	—	triticonazole	—	RPA 406972 (acid), RPA 406780, RPA 404766, RPA 404886
ROC	At both dose levels, radioactivity was rapidly excreted. The parent compound, triticonazole was the predominant residue in eggs while triticonazole and the hydroxyl metabolites, RPA 406972 (acid) and RPA 404886 were the predominant residues in liver. TRRs in muscle, skin and fat were too low for metabolite identification/characterization. Therefore, the ROC is defined as the parent, triticonazole.			

NATURE OF THE RESIDUE IN RUMINANT				
Species	Radiolabel	Dose level	Length of dosing	Sacrifice
Dairy cattle	[phenyl- ^{14}C-U] triticonazole	1 mg/kg 10 mg/kg	7 consecutive days	23.5 h after last dose
80–85% of the administered dose was excreted in urine and feces; 0.2–0.3% remaining in tissues, organs and milk.				

Metabolites identified	**Major metabolites (≥10% TRRs)**		**Minor metabolites (<10% TRRs)**	
Dose level	**1 mg/kg**	**10 mg/kg**	**1 mg/kg**	**10 mg/kg**
kidney	—	RPA 404766 combined with RPA 404886, triticonazole	—	RPA 406341
liver		RPA 406780	RPA 404886, triticonazole, RPA 406341, RPA 406972 (acid)	RPA 406341, RPA 404766, triticonazole
ROC	At both dose levels, radioactivity was rapidly excreted. The hydroxyl metabolites RPA 404766 and 404886 as well as the parent compound were the predominant residues in kidney at the high dose. In liver the metabolite RPA 406780 was the predominant residue. TRRs in muscle and fat were too low for metabolite identification/characterization. Therefore, the ROC is defined as the parent, triticonazole.			

CROP FIELD TRIALS –WHEAT, BARLEY AND OATS
Trial site information: 1995 and 1996 (nine wheat trials, nine barley trials and six oat trials conducted in Ontario, Manitoba, Saskatchewan, Alberta and Ontario)

Commodity	Total Rate g a.i./100 kg seed	Post-emergence interval (days)	Residue levels (ppm)					
			n	Min.	Max.	HAFT	Mean/ Median	SD
wheat grain	10	77–116	12	<0.01	<0.01	0.01	0.01	0
wheat forage	10	30	12	<0.05	<0.06	0.05	0.05	0
barley grain	10	77–116	12	<0.01	<0.01	0.01	0.01	0
barley forage	10	30	12	<0.05	<0.06	0.05	0.05	0
wheat grain	35	77–116	6	<0.01	<0.01	0.01	0.01	0
wheat forage	35	30	6	<0.05	<0.06	0.05	0.05	0
wheat straw	35	77–116	4	<0.05	<0.06	0.05	0.05	0
barley grain	35	77–116	6	<0.01	<0.01	0.01	0.01	0
barley forage	35	30	6	<0.05	<0.06	0.05	0.05	0
barley straw	35	77–116	2	<0.05	<0.05	0.05	0.05	0
oat grain	35	77–116	12	<0.01	<0.01	0.01	0.01	0
oat forage	35	30	12	<0.05	<0.06	0.05	0.05	0
oat straw	35	77–116	4	<0.05	<0.05	0.05	0.05	0

RESIDUE DECLINE

As triticonazole is to be applied as a seed treatment, no residue decline studies were required.

MAXIMUM RESIDUE LIMITS

Crop	Canadian MRLs (ppm)
Wheat, barley and oat grain	0.01
Milk	0.01
Eggs	0.05
Poultry meat and meat byproducts	0.05
Meat and meat byproducts of cattle, goat, hogs, horses and sheep	0.05

FIELD ACCUMULATION IN ROTATIONAL CROPS

The results of the confined crop rotational study indicated that a field crop rotational study would not be required.

PROCESSED FOOD AND FEED

According to the supervised field trials, conducted in the major cereal growing regions of Canada, residues in wheat, barley and oat grain did not exceed the method LOQ (0.01 ppm) when treated at highly exaggerated rates. Therefore, no processing studies were required.

LIVESTOCK FEEDING
The maximum theoretical dietary burdens of triticonazole to beef, dairy cattle and poultry are 0.2, 0.4 and 0.03 ppm, respectively, based on diets consisting of forage, straw and grain containing maximum residues of 0.06 ppm (forage and straw) and 0.01 ppm (grain) as per the supervised field trials. The dairy cattle and poultry metabolism studies demonstrated that there were no residues of triticonazole detected at levels greater than 0.01 ppm in the milk and 0.05 ppm in meat and meat byproducts, when administered a diet representing 5–333× the maximum theoretical dietary burden. Because residues of triticonazole are unlikely to accumulate in milk, eggs, beef and poultry meat and meat byproducts, feeding studies were not required.

Table 2 Food residue chemistry overview of metabolism studies and risk assessment

PLANT STUDIES		
ROC for enforcement wheat, barley and oats	triticonazole	
ROC for risk assessment cereal grains	triticonazole	
Metabolic profile in diverse crops	The metabolic profile in cereal crops following seed treatment has been elucidated. The predominant pathway involves hydroxylation of the parent compound.	
ANIMAL STUDIES		
Animals	**Poultry**	**Ruminant**
ROC for enforcement	triticonazole	triticonazole
ROC for risk assessment	triticonazole	triticonazole
Metabolic profile in animals	The metabolism of triticonazole in poultry and ruminants involves hydroxylation of the parent compound followed by conjugation.	
Fat soluble residue	No	

DIETARY RISK FROM FOOD AND WATER			
Chronic non-cancer dietary risk ADI = 0.008 mg/kg bw/day	**POPULATION**	**ESTIMATED RISK (% of ADI)**	
		Food (STMR)	**Food + 10% drinking water**
	All infants (<1 year old)	1.3	11.3
	Children (1–6 years old)	3.5	13.5
	Children (7–12 years old)	2	12
	Females 13–50 years old	0.9	10.9
	Males 13–19 years old	1.4	11.4
	Males 20+ years old	1	11
	Seniors 55+ years old	0.8	10.8
	Total population	1.3	11.3
Acute dietary exposure Analysis, 95th percentile	**POPULATION**	**ESTIMATED RISK (% of ARfD)**	
		Food (STMR)	**Food + 10% drinking water**
ARfD = 0.017 mg/kg bw/day (females 13+)	**Females 13+ yrs**	2	12

Appendix III Environmental assessment

Table 1 Physical and chemical properties of the active ingredient relevant to the environment

Property	Value	Comments
Water solubility	8.4 mg/L at 20°C	Low solubility and solubility is independent of pH
Vapour pressure	$< 0.1 \times 10^{-5}$ Pa at 50°C	Non-volatile
Henry's Law constant	6.4×10^{7}	Not volatile from water and moist surfaces
log K_{ow}	3.29 at 20°C	Potential for bioconcentration/ bioaccumulation
pK_a	Does not dissociate	No dissociable functionality based on structure
UV–visible absorption	λmax at 212 and 263 nm; no absorbance above 320 nm	Low potential for phototransformation

Table 2 Adsorption coefficients for RPA 406341 and RPA 407922 in four soils and one sediment

Soil type	% OC	pH	RPA 406341			RPA 407922		
			K	$K_{oc\text{-}ads}$	Mobility[a]	K	$K_{oc\text{-}ads}$	Mobility[a]
Leland silt loam	0.5	6.5	0.82	163	moderate	3.88	775	low
Iola sandy loam	1.3	5.8	1.64	126	high	16.9	1305	low
Ongar loam	1.9	7	2.65	140	high	9.44	497	moderate
Royston clay loam	4.1	7.8	2.5	61	high	19.1	467	moderate
Ongar sandy clay loam (sediment)	2.6	8.2	3.31	127	high	10.6	407	moderate

a Based on the classification system of McCall et al. (1981).

Table 3 Classification of calculated GUS scores (Gustafson 1989)

GUS (Groundwater Ubiquity Score)	Probable attribute
> 2.8	Leacher
> 1.8 and < 2.8	Borderline leacher
< 1.8	Non-leacher

Table 4 Fate and behaviour in the terrestrial environment

Property	Test substance	Value	Comments
Abiotic transformation			
Hydrolysis	Triticonazole	stable at pH 5, pH 7, pH 9	Not a route of transformation in the environment
Biotransformation			
Biotransformation in aerobic soil	Triticonazole	DT_{50} 145–554 d	Moderately persistent to persistent Four major transformation products: RPA 406780, RPA 406341, RPA 407922 and RPA 404766
	RPA 406341	$t_{1/2}$ 165–330 d	Moderately persistent to persistent No major transformation product
	RPA 407922	DT_{50} 0.5–1.1 d	Non-persistent An unidentified polar major transformation product
Biotransformation in anaerobic soil	Triticonazole	no transformation	Very little biotransformation under anaerobic conditions Triticonazole is persistent
Mobility			
Adsorption/desorption in soil	Triticonazole	$K_{oc\text{-}ads}$ 184–812	Low to moderate mobility
	RPA 406341	$K_{oc\text{-}ads}$ 61–163	Moderate to high mobility
	RPA 407922	$K_{oc\text{-}ads}$ 407–1305	Low to moderate mobility
Soil leaching	Triticonazole	99% AR remained in soil column, except sandy soil where 70.5% AR in leachate	Leaching potential in sandy soil
Field studies			
Canadian field dissipation	Triticonazole	DT_{50} 144 d (bare soil)	moderately persistent under field conditions
American field dissipation	Triticonazole	DT_{50} 69–163 d (pre-plant incorporation)	moderately persistent under field conditions

Table 5 Fate and behaviour in the aquatic environment

Property	Test substance	Value	Comments
Abiotic transformation			
Hydrolysis	Triticonazole	stable to hydrolysis at pH 5, 7, 9	Not a route of transformation in the environment
Phototransformation in water	Triticonazole	DT_{50} = 4.9 d	Will transform to the *cis*-isomer in the photic zone

Table 6 Triticonazole in the diet (grain) of wild birds and mammals

Species	% of diet	EEC (mg a.i./kg dw)
Bobwhite quail	55	27.5
Mallard duck	70	35
Rat	20	10
Mouse	50	25

Table 7 Summary of effects on terrestrial organisms

Organism	Study type	Test substance	Endpoint value	Degree of toxicity[a]
Invertebrates				
Earthworm	Acute artificial soil	Triticonazole 95.9%	LC_{50} >1000 mg a.i./kg soil NOEC 1000 mg a.i./kg soil[b]	N/A
Birds				
Bobwhite quail	Gavage	Triticonazole, technical	LD_{50} > 2000 mg a.i./kg bw NOEC 2000 mg a.i./kg bw[b]	Practically non-toxic
	Dietary	Triticonazole, technical	LC_{50} > 5000 mg a.i./kg diet NOEC 1300 mg a.i./kg diet (bw)	
	Reproduction	Triticonazole, technical	parental NOEC 1000 mg a.i./kg[b]	N/A
			reproductive NOEC 250 mg a.i./kg diet (egg production and hatchling survival)	
Mallard duck	Gavage	Triticonazole, technical	LD_{50} > 2000 mg a.i./kg bw NOEC 1000 mg a.i./kg bw	Practically non-toxic
	Dietary	Triticonazole, technical	LC_{50} > 5000 mg a.i./kg diet NOEC 1300 mg a.i./kg diet (bw)	Practically non-toxic
	Reproduction	Triticonazole 90.52%	parent NOEC 1000 mg a.i./kg[b]	N/A
			reproductive NOEC 1000 mg a.i./kg diet[b]	
Wild mammals				
Rat	Gavage	Triticonazole, technical	LD_{50} > 2000 mg a.i./kg bw	Practically non-toxic
	Short-term (13-week)	Triticonazole, technical	no sublethal ♂ NOEC sublethal ♀ NOEC 250 mg a.i./kg diet sublethal ♀ LOEC 12 500 mg a.i./kg diet (generalized hair loss, ↓body-weight gain, ↓food efficiency, ↑♀ serum cholesterol, ↑liver weight, hepatocyte hypertrophy, fatty vacuolation, adrenocortical fatty vacuolation) lethal NOEC 12 500 mg a.i./kg diet	N/A

Organism	Study type	Test substance	Endpoint value	Degree of toxicity[a]
	Long-term (100-week)	Triticonazole, technical	NOEC 750 mg a.i./kg diet (↓♀ body-weight gain and food efficiency, multinucleated ♀ adrenal cells, chronic inflammation of ♀ adrenal, ♀ hepatocyte fatty vacuolation, ↑incidence of thyroid follicular cell adenomas) NOEC 5000 mg a.i./kg diet (mortality)	
	Reproduction	Triticonazole, technical	parental NOEC 750 mg a.i./kg diet (↑maternal deaths, ↓body weight, ↓body-weight gain, ↓food consumption, ↑liver weight and liver pathology, ↓♀adrenal weight, ♀ adrenal pathology)	
			offspring NOEC 750 mg a.i./kg diet (↓pup body weight, ↓viability index)	
			reproductive NOEC 750 mg a.i./kg diet (↓fertility and mating indices, ↑gestation interval, ↑ovary weight and vacuolation, ↑stillborn pups, ↓litter size, ↓live birth index)	
Mouse	Short-term (42-day)	Triticonazole, technical	NOEC 1500 mg a.i./kg diet (↑liver weight, liver histopathology) NOEC 5000 mg a.i./kg diet (mortality)	N/A
	Long-term (78-week)	Triticonazole, technical	NOEC 150 mg a.i./kg diet (↑liver weight, ♂ hepatocyte hypertrophy and fatty vacuolation, ↓♀ body-weight gain, ↓♂ food efficiency, ↑adrenal weight) NOEC 1500 mg a.i./kg diet (mortality)	

a Based on USEPA classification schemes
b No effects were observed at the highest dose

Table 8 Summary of effects on aquatic organisms

Organism	Study type	Test substance	Endpoint value	Degree of toxicity
Freshwater				
Daphnia magna	48-h static acute	Triticonazole, 99.5%	LC_{50} 9 mg a.i./L NOEC 3.2 mg a.i./L (immobilization)	Moderately toxic
	21-d static renewal reproduction	Triticonazole, 97.2%	NOEC 1.3 mg a.i./L LOEC 3.0 mg a.i./L (fecundity, mean total length)	N/A
Rainbow trout	96-h flow-through acute	Triticonazole, 97.2%	LC_{50} > 3.6 mg a.i./L NOEC 1.4 mg a.i./L (erratic swimming)	Not toxic at solubility limit
Bluegill sunfish	96-h flow-through acute	Triticonazole, 97.1%	LC_{50} > 8.9 mg a.i./L NOEC 8.9 mg a.i./L[a]	Not toxic at solubility limit
Fathead minnow	34-d flow-through early life stage	Triticonazole, 90.52%	NOEC 0.021 mg a.i./L LOEC 0.051 mg a.i./L (larval growth)	N/A

a Based on USEPA classification schemes

Table 9 Environmental risk classification scheme

Risk quotient (RQ)	Degree of risk
< 0.1	Negligible
≥ 0.1–1	Low
≥ 1–10	Moderate
≥ 10–100	High
≥ 100–1000	Very high
≥ 1000	Extremely high

Table 10 Summary of risk assessment to terrestrial organisms

Organism	Effect/ Exposure	NOEC/NOEL (mg a.i./kg diet/bw)	EEC (mg a.i./kg dw diet)	RQ	Risk	Mitigative measures
Bobwhite quail	Acute oral	2000	27.5	ND		Not required
	Dietary	1300		0.02	Negligible	
	Reproduction	250		0.11	Low	
Mallard duck	Acute oral	1000	35	ND		Not required
	Dietary	1300		0.03	Negligible	
	Reproduction	1000		0.04	Negligible	
Rat	Acute oral/dermal	200	10	ND		Not required
Rat	Dietary	250	10	0.04	Negligible	
Mouse	Chronic	150	25	0.17	Low	

ND: Not determined

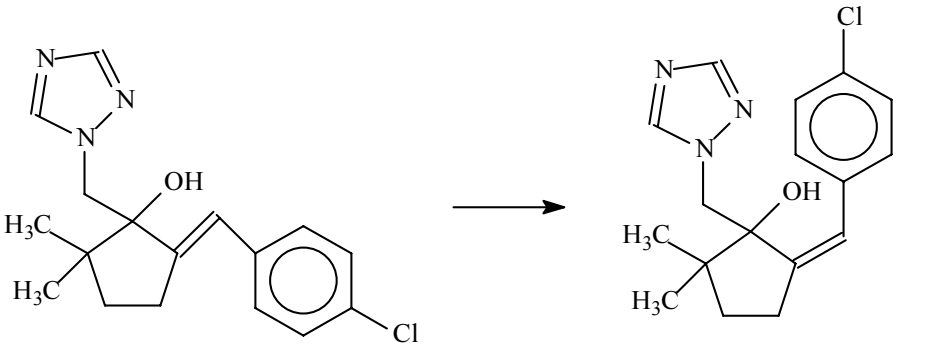
Table 11 Methods for environmental residue analysis

Matrix	Method ID	Analyte	Method	Spike level (mg/kg)	Mean % recovery	RSD (%)	LOQ (mg/kg)
Soil/sediment	AR 91-92	Triticonazole	GC-ECD	0.005 0.025 0.050	93–128	NR	0.01
	NR	RPA 406341	GC-ECD	0.005 0.010 0.050	86–115	13–22	0.02
		RPA 407922			80–94	13–28	0.01
		RPA 406780			64–96	22–25	0.01
Barley grain	AR 92-92 (E)	Triticonazole	GC-TID	0.010 0.050 0.100	106–110	NR	0.05
Barley straw, wheat straw				0.050 0.500	83–118	NR	0.01
Cereal straw, green plant	NR	Triticonazole	GC-MSD	0.04 0.08 0.20	23–44	NR	0.06
		RPA 406341			61–82	NR	
		RPA 406780			86–101	NR	
		RPA 406886			70–175	NR	

Matrix	Method ID	Analyte	Method	Spike level (mg/kg)	Mean % recovery	RSD (%)	LOQ (mg/kg)
Beef	AR 104-94 (E)	Triticonazole	GC-ECD	0.050 0.025	96–98	NR	0.05
Poultry					90–103	NR	
Eggs					77–94	NR	
Fat					103–108	NR	
Milk				0.010 0.050	90–93	NR	0.01

NR: Not reported

Figure 1 Proposed transformation pathway for photolysis in water



Triticonazole (*trans*-isomer) RPA 406203 (*cis*-isomer)

Figure 2 Proposed aerobic biotransformation pathway of photolysis in soil

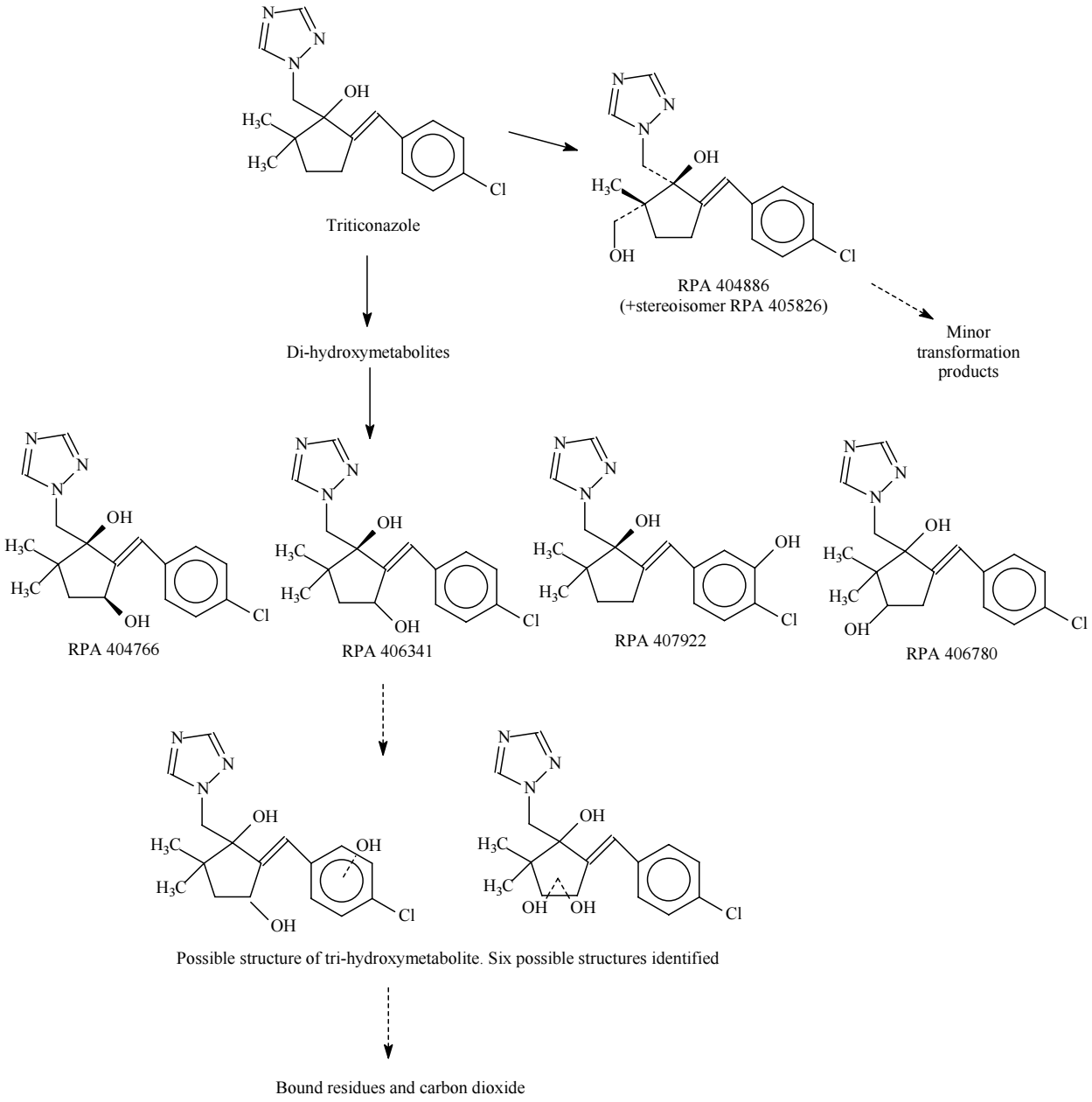
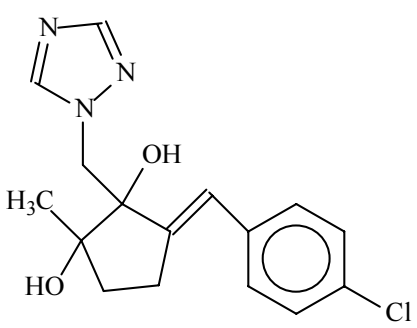
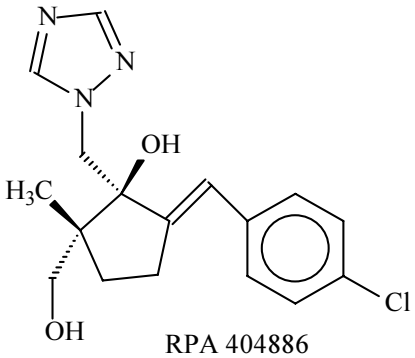


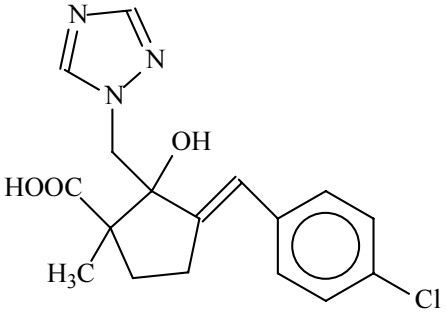
Figure 3 Metabolic products of triticonazole in fish



RPA 405826



RPA 404886



RPA 406972

Appendix IV Methods of analysis (OECD 4)

Table 1 Analytical methods for analysis of the active substance as manufactured (OECD IIA4.2.1)

Analyte	Method type	Linearity range	Mean recovery (%) (n)	RSD (%) (n)	Method
Triticonazole	HPLC	0.09–0.13 g/L	Not required	0.4	Accepted
Related impurities	HPLC	0.25–100 mg/L	101.8	0.2–16.2	Accepted

Table 2 Analytical methods for formulation analysis (OECD IIIA5.2.1)

Analyte	Method type	Linearity range (mg/mL)	Mean recovery (%) (n)	RSD (%) (n)	Method
Triticonazole	HPLC	0.01 – 0.03 r^2 = 0.99997	100.0 ± 0.3	±0.03 (n = 9)	Accepted
Thiram	HPLC	0.11– 0.30 r^2 = 0.99998	100.0 ± 0.4	±0.26 (n = 9)	Accepted

References

Goring, C.A.I., D.A. Laskowski, J.W. Hamaker and R.W. Meikle. 1975. Principles of pesticide degradation in soil. In: (Haque, R. and V.H. Freed, eds.) *Environmental dynamics of pesticides*. Plenum Press, New York, pp 135–172.

Gustafson, D.I. 1989. Groundwater ubiquity score: A simple method for assessing pesticide leachability. *Environmental Toxicology and Chemistry*. 8:339–357.

McCall J.P., D.A. Laskowski, R.L. Swann and H.J. Dishburger. 1981. Measurement of sorption coefficients of organic chemicals and their use in environmental fate analysis. *Proceedings*, Test protocols for environmental fate & movement of toxicants, Association of Official Environmental Chemists, 94th annual meeting, Washington, DC, USA, 21–22 October 1980, pp 89–109.

Urban, D. J. and N.J. Cook. 1986. Hazard Evaluation Division Standard Evaluation Procedure, *Ecological Risk Assessment*. USEPA 540/9–85–001.