Proposed Regulatory Decision Document PRDD99-05

Hexaconazole

The active ingredient hexaconazole and the end-use product Proseed fungicide seed treatment, for control of diseases of wheat and barley, are proposed for registration under Section 13 of the Pest Control Products Regulations.

The Pest Management Regulatory Agency (PMRA) has completed its assessment of hexaconazole and Proseed, based on hexaconazole, for control of certain diseases of wheat and barley. The active ingredient has been previously proposed for registration in Canada, see Proposed Regulatory Decision Document PRDD95-01, Hexaconazole Wood Preservative (Passport), August 18, 1995.

The current document provides a summary of data reviewed with respect to seed-treatment use and the rationale for the proposed Section 13 registration of Proseed fungicide and hexaconazole technical.

The PMRA will accept written comments on this proposal up to 45 days from the date of publication of this document.

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Publications Coordinator
Pest Management Regulatory Agency
Health Canada
2250 Riverside Drive
A.L. 6606D1
Ottawa, Ontario
K1A 0K9

Internet: pmra_publications@hc-sc.gc.ca
www.hc-sc.gc.ca
Facsimile: (613) 736-3798
Information Service:
1-800-267-6315 or (613) 736-3799

Foreword

This regulatory document proposes registration of Proseed (hexaconazole) fungicide seed treatment for control of certain diseases of wheat and barley, and details the supporting scientific rationale. The active ingredient, hexaconazole, is a triazole fungicide. Proseed may be applied as a seed treatment at very low use rates (1.5 g active ingredient [a.i.]/100 kg seed).

Hexaconazole contains low levels of contaminants that are Track 1 substances as defined in the federal government's Toxic Substances Management Policy (TSMP). In 1995, the PMRA published PRDD95-01, focussed on reviews of the technical and wood- preservative uses of hexaconazole. As part of the public response to this document, concerns were raised around potential release of Track 1 substances, which have been slated for virtual elimination. A risk assessment for the wood-preservative use showed that potential release of the contaminants would be below levels that could be measured. Due to other issues with this use pattern, however, the review of the wood-use products is ongoing.

The current document summarizes the review of the cereal seed-treatment use of hexaconazole, including assessment of risk resulting from contaminants in accordance with The Pest Management Regulatory Agency's Strategy for Implementing the Toxic Substances Management Policy (TSMP) (Regulatory Directive Dir99-03). The proposed registration will be the first agricultural use for hexaconazole in North America.

Table of Contents

1.0 The active substances, its properties, uses, proposed classification and labelling

1.1 Identity of the active substance and preparations containing it

Active substance:	hexaconazole
Function:	fungicide
Chemical names International Union of Pure and Applied Chemistry:	(RS)-2-(2,4-dichlorophenyl)-1-(1H-1,2,4-triazol-1-yl)hexan-2-ol
Chemical Abstracts Service (CAS):	"-butyl-"-(2,4-dichlorophenyl)-1H-1,2,4-triazole-1-ethanol
CAS Registry Number：	79983-71-4
Nominal purity of active:	90%

Identity of relevant impurities of toxicological, environmental and/or other significance:

This product contains low levels of a group of compounds identified as Track 1 substances in the TSMP.

Five samples were analysed for polychlorodibenzodioxins and polychlorodibenzofurans. Total tetrachlorodibenzodioxin (TCDD) levels ranged from non-detectable to 2300 parts per trillion (ppt), total tetrachlorodibenzofuran (TCDF) levels ranged from 520 to 3300 ppt, and octachlorofuran was found in one sample at 270 ppt. Of these totals, however, no dioxins and only two furans had 2,3,7,8 substitution. It is the isomers chlorinated at the 2,3,7,8 positions that are considered toxicologically significant and are listed as Track 1 substances.

Track 1 substances found in hexaconazole were 2,3,7,8-TCDF in three out of the five samples and octachlorofuran in one sample. In these analyses, a limit of detection (LOD) was established for each individual isomer in each individual sample. Almost all of the LODs fell between 5 and 20 ppt. The highest level found was 76 ppt of 2,3,7,8-TCDF in one sample. This is toxicologically equivalent to 7.6 ppt of 2,3,7,8-TCDD. The octachlorofuran was found at 270 ppt, which is toxicologically equivalent to 0.027 ppt of 2,3,7,8-TCDD and, thus, does not contribute appreciably to the total contaminant of toxicological concern. For interpretation

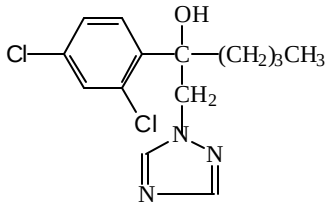
of these results with respect to human and environmental health, refer to Sections 4.2, 5.2.6, 6.4.3 and 8.0.

The level of microcontaminants found in the technical material was near to the LOD of the method of analysis. The end-use product Proseed contains only 0.56% technical and, therefore, the level of microcontaminants would most likely be too low for detection.

Molecular Formula: $C_{14}H_{17}Cl_2N_3O$

Molecular Mass: 314.2

Structural Formula:



(racemate)

1.2 Physical and chemical properties of active substance

Table 1.1 **Technical product: Hexaconazole** Properties of technical material, except where marked PAI (Pure Active Ingredient).

Property	Result	Comments
Colour and physical state	Light brown solid	
Odour	None	
Melting point/range	110–112/C	
Boiling point/range	Not applicable	
Density	1.29 g/mL at 25/C	
Vapour pressure	1.4×10^{-7} mm Hg (at 20/C)	Non-volatile. Low potential for residues to decrease as a result of volatilization.
Henry's law constant	1/H = 7.48 × 106 K = 3.5×10^{-4} Pa m^3 $mole^{1}$	Non-volatile from moist soil or a water surface.
UV/visible spectrum for PAI	8 (nm) , ($M^{-1}cm^{-1}$) 220 10 280 263 197 270 222 279 159	Indicates stability to sunlight. Peak absorption of UV radiation was at 220 nm and radiation in the region of natural sunlight (>290) was not absorbed.

Property	Result	Comments
Solubility in water at 25/C	17 mg a.i./L at pH 5.1 18 mg a.i./L at pH 6.5	Low solubility in water.
Solubility in organic solvents at 20/C	Solvent — Solubility (g/L) Methanol 246.0 Acetone 164.0 Dichloromet 336.0 Toluene 59.0 Ethyl acetate 120.0 Hexane 0.8	Soluble in organic solvents, especially more polar solvents.
n-Octanol/water partition coefficient (K_{ow})	Log K_{ow} = 3.9 (at 20°C)	Indicates potential for uptake and accumulation by biota.
Dissociation constant	pKa = 2.3 ± 0.5 at 25/C (The value is the same as 1,2,4-triazole)	Dissociates and exists as negatively charged ion at environmentally relevant pH values (pH 5–pH 9).
Oxidizing properties	Not an oxidizing or reducing agent.	
Storage stability	Stable under ambient conditions for 29 months or over.	

Table 1.2 End-use product: Proseed fungicide seed treatment

Property	Result
Colour	Red
Odour	Moderate solvent odour
Physical state	Liquid
Formulation type	Suspension
Guarantee	0.5%, nominal
Container material and description	Plastic
Density	1.051 g/mL at 25/C
pH of 1% dispersion in water at 20/C	Not available
Storage stability	Stable for at least one year
Explodability	Not explosive

1.3 Details of uses and further information

Hexaconazole is registered as a foliar-applied fungicide for cereals, vegetables and fruit (primarily orchards) in Europe and elsewhere. It is not registered in the United States (U.S.). The active ingredient was first submitted for registration in Canada in 1988 with respect to wood- preservative use. In 1995, the PMRA published PRDD95-01, focussed on reviews of the technical and wood- preservative uses of hexaconazole. As part of the public response to this document, concerns were raised around potential release of Track 1 substances, which have been slated for virtual elimination. A risk assessment for this use showed that potential release of the contaminants from hexaconazole would be below levels that could be measured. Due to other issues with this use pattern, however, the review of the wood-use products is ongoing. If accepted, the proposed agricultural use will represent the first registration of hexaconazole in Canada.

Hexaconazole is a triazole fungicide. This group of compounds is generally systemic in plants, and interferes with sterol biosynthesis necessary for proper functioning of fungal membranes in the pathogen. Proseed, the product proposed for registration, is a flowable suspension containing 0.5% hexaconazole.

Proseed is a seed treatment for use on cereals to control loose smut of wheat, true loose smut and covered smut of barley, and to suppress common root rot of wheat. Proseed may be applied at 75 mL/25 kg seed (1.5 g hexaconazole/100 kg seed) in either commercial seed-treatment plants or on-farm treating equipment. Product and seed should be above 0°C at time of treatment, and storage of treated seed is not recommended.

2.0 Methods of analysis

2.1 Methods for analysis of the active substance as manufactured

Gas chromatography (GC) methods using a flame ionization detector were used for the determination of the active substance and significant impurities (content $ 0.1%) in the technical product. Microcontaminants were determined by GC/mass spectrometry methods. The methods have been shown to have satisfactory specificity, linearity, precision and accuracy.

2.2 Method for formulation analysis

A GC method using a flame ionization detector was submitted for the determination of active in Proseed fungicide seed treatment. The method was shown to have satisfactory specificity, linearity, precision and accuracy.

2.3 Methods for residue analysis

2.3.1 Multiresidue methods for residue analysis

Not applicable to this use pattern.

2.3.2 Methods for residue analysis of plants and plant products

The residue of concern (ROC) for wheat raw agricultural commodities (RACs) was defined from the wheat metabolism study as hexaconazole.

For wheat commodities, the gas-liquid chromatography (GLC) method (Standard Operating Procedure No. RAM/238/01) measured residues of hexaconazole in straw and grain. Quantification was performed with GLC using a thermionic nitrogen specific detector. The LOD was 0.01 parts per million (ppm) for grain and 0.05 ppm for straw. The method was validated by spiking grain samples with hexaconazole and diclobutrazol (internal standard) at levels of 0.01–0.5 ppm, and by spiking straw samples with hexaconazole and diclobutrazol (internal standard) at levels of 0.05–1.0 ppm. The average recoveries were 82% in grain and 84–87% in straw.

2.3.3 Methods for residue analysis of food of animal origin

No analytical method was submitted for livestock. Based on residue studies on spring wheat and spring barley, residues of hexaconazole are unlikely to be detectable in the grain, straw and forage samples grown from treated seeds (<0.01 ppm for grain and <0.05 ppm for straw/forage). When animals are fed with the RACs grown from treated seeds, no residues of hexaconazole in livestock commodities are expected to be detected (<0.002 ppm). An analytical method for the analysis of food of animal origin, therefore, is not required.

3.0 Impact on human and animal health

3.1 Effects having relevance to human and animal health arising from exposure to the active substance or to impurities in the active substance or to their transformation products

3.1.1 Absorption, distribution, metabolism and excretion

Refer to Table 3.1.

3.1.2 Acute toxicity—formulation

The formulated product, Proseed, was considered of low toxicity via the oral, dermal and inhalation routes to rats. It was practically non-irritating to the eye and a slight irritant to the skin of rabbits. A limited study concluded that it was not a dermal sensitizer in guinea pigs but, as the active ingredient in this formulation is a dermal sensitizer and the study had deficiencies, it would be prudent to label this product accordingly.

3.1.3–3.1.6 Toxicity

Refer to Table 3.1 of this document and Section 5.3.2 of PRDD95-01.

3.1.7 Overall toxicological summary—technical

The toxicological data base for the active ingredient, hexaconazole, was considered complete by the PMRA. The data base included toxicokinetics, acute, short-term, chronic, reproduction, teratology and genotoxicity studies.

Technical hexaconazole is a member of the azole family of compounds, which are known to induce liver toxicity and to inhibit cytochrome P450 monooxygenase and subsequent hydroxylation of steroids and fatty acids. It is, therefore, not unexpected that hexaconazole has an effect on lipid metabolism, which is manifested in altered clinical chemistry and hepatic pathology (hepatocytic lipid). Increased testicular atrophy and increased incidence of Leydig-cell tumours were observed in high-dose male rats. This was considered a threshold response dependent on abnormal gonadotrophic stimulation. High-dose males also had bile-duct proliferation and fat vacuolation in the adrenal cortex. The most sensitive species and study for this range of effects was the chronic rat-dietary study with a no observed effect level (NOEL) of 0.47 mg/kg body weight (bw)/day (d) in males and 0.61 mg/kg bw/d in females. There were no adverse effects on reproductive performance, or evidence of teratogenicity or mutagenicity in the submitted studies. Fetotoxicity in the form of delayed ossification, however, occurred in the rat and rabbit teratology studies in the absence of maternal toxicity. The lowest NOEL for fetotoxicity was 2.5 mg/kg bw/d in the rat teratology study.

Table 3.1 Summary of the toxicity studies with hexaconazole

Absorption, distribution, metabolism and excretion

Active Ingredient

Hexaconazole was well absorbed and excreted by the rat with quantitative differences in excretion between sexes. Males exhibited greater faecal elimination than females, in whom urinary elimination was foremost. Following a single oral dose of 1 mg/kg bw or 200 mg/kg bw of ^{14}C-phenyl-labelled hexaconazole, the majority of radioactivity was excreted in the urine and feces within 72 hours. Negligible amounts of hexaconazole were found in the exhaled air and tissues/carcass following 72 hours. The adrenal, liver and bile duct were the sites of significant radioactivity during the first 24 hours post-dosing. Overall, the patterns of distribution and excretion were comparable between the high and low doses.

Repeated administration (14 days) of 1 mg/kg bw/d of hexaconazole to Alpk:AP rats did not appear to affect the distribution, biotransformation or excretion of the product compared to the administration of a single dose. There did not appear to be any long-term retention of hexaconazole.

Using doses of 100 or 200 mg/kg bw of ^{14}C-phenyl- or ^{14}C-triazine-labelled hexaconazole, quantitative but not qualitative differences were noted in the biotransformation of hexaconazole between male and female rats. Most metabolism resulted in oxidation products of the n-butyl chain including the acid, hydroxy, keto and hydroxyketo forms of hexaconazole. No metabolism of the dichlorophenyl ring was recorded; however, there was some cleavage of the triazole portion.

Biliary elimination, although important in both sexes, was especially important in males (twice that of females). The relative proportions of biliary metabolites were eliminated mostly as glucuronide conjugates, primarily as 5-hydroxy hexaconazole and hydroxy-keto hexaconazole. Half of the biliary radioactivity was excreted in the feces in both conjugated and deconjugated forms. The remainder was reabsorbed and eliminated via the urine. These urinary metabolites consisted mainly of hydroxy-keto hexaconazole, hexaconazole, a conjugate of 5-hydroxy hexaconazole and triazole. Triazole is presumed to be derived from one or both of the two major biliary metabolites. In addition, a minor biotransformation pathway of hexaconazole yielded hexaconazole acid as an exclusive urinary metabolite.

Formulation

In a dermal-absorption study, male rats were dosed with ^{14}C-phenyl-labelled hexaconazole as the end-use aqueous formulation on a shaved area of the back at doses of 1.0, 0.1. 0.01 and 0.001 mg/cm^2. By 10 hours, 4.2%, 7.4%, 14.6% and 47.6% of the respective doses had been absorbed.

Study	Species/strain	LD_{50} mg/kg bw	Target organ /significant effects
Acute studies—technical			
Oral	Rat, Alpk SPF, 5/sex/group	Males: 2189 mg/kg bw Females: 6071 mg/kg bw	Clinical observations at doses $1093 mg/kg bw consisted of piloerection, dehydration, urinary incontinence, upward curvature of the spine, hypothermia and facial staining. LOW TOXICITY
Oral	Mouse, Alpk SPF, 5/sex/group	Lethal dose 50% (LD_{50}) cannot be calculated, range is 557– 1060 mg/kg bw	Clinical observations consisted of piloerection, upward curvature of the spine, decreased activity, hypothermia, dehydration, reduced righting reflex and ptosis. SLIGHT TO MODERATE TOXICITY

Dermal	Rat, Alpk SPF, 5/sex/group	>2000 mg/kg bw	Clinical observations consisted of urinary incontinence, upward curvature of the spine and facial staining. LOW TOXICITY
Inhalation	Rat, Alpk SPF, 5/sex/group	Lethal concentration 50% (LC_{50}) >5.9 mg/L	Clinical signs consisted of salivation, respiratory abnormalities, piloerection, hunched posture and incontinence. LOW TOXICITY
Skin irritation	Rabbits, New Zealand white (NZW), 6 males, 0.5 g dose	No erythema or edema	NON-IRRITATING
Eye irritation	Rabbits NZW, 9 males (3 had eyes rinsed), 0.1 g dose	Maximum average score (MAS) = 8.5 (unrinsed group)	SLIGHTLY IRRITATING
Skin sensitization	Guinea pig, Dunkin Hartley, female, Maximisation method	Incidence in test group greater than in naive control group	POTENTIAL SKIN SENSITIZER
Acute studies—formulation (Proseed)			
Oral	Rat, SPF Alpk:APfSD, 5/sex/dose	>5000 mg/kg bw	No clinical signs of toxicity. LOW TOXICITY
Dermal	Rat, SPF Alpk:APfSD, 5/sex/dose	>2000 mg/kg bw	No clinical signs of toxicity. LOW TOXICITY
Inhalation	Rat, SPF Alpk:APfSD, 5/sex/dose	LC_{50} > 4.9 mg/L of formulation and 0.16 mg/L of active ingredient	LOW TOXICITY

Study	Species/strain	LD 50 mg/kg bw	Target organ /significant effects
Skin irritation	Rabbit, NZW, 6 females, special study that included histology		SLIGHTLY IRRITATING
Eye irritation	Rabbit, NZW, 6 females	MAS = 0.7	NON-IRRITATING
Skin sensitization	Guinea pigs, Hsd/Poc:DH, Buehler method, special study that included histology	Difficult to interpret. Considered positive based on active ingredient.	POTENTIAL SKIN SENSITIZER
Study	**Species/strain**	**NOEL/NOAEL* mg/kg bw**	**Target organ/significant effects**
Short term			
21-day dermal	Rat, Alpk:AP, 5/sex/dose, 0, 100, 300, 1000	NOEL = 1000	None, no irritation.
90-day dietary	Rat, Alpk:AP, 20/sex/dose, 0, 2.5, 25, 250	NOAEL = 2.5	25 mg/kg bw: Increased aminopyrine-N-demethylase (APDM), decreased weight gain, decreased haematocrit, decreased triglycerides, increased liver weights, increased liver and adrenal pathology. 250 mg/kg bw: Same as above with a dose related increase. Target organs: Liver and adrenal, males more sensitive.
90-day oral (capsule)	Dog, beagle, 4/sex/dose, 0, 5, 25, 50/75, 125	NOEL = 5	25 mg/kg bw: Increased serum glutamate pyruvate transaminase (SGPT), alkaline phosphatase (ALP), decreased urea, albumin, cholesterol, triglycerides, increased hepatocytic lipid. 50/75 mg/kg bw: As above plus clinical signs, weight loss, increased absolute and relative liver weights, myocarditis. 125 mg/kg bw: As above plus mortality, increased serum glutamate oxaloacetate transaminase (SGOT). Target Organ: Liver

Study	Species/strain	NOEL/NOAEL* mg/kg bw	Target organ/significant effects
One-year (capsule)	Dog, beagle, 4/sex/dose, 0, 2, 10, 50	NOEL = 2	10 mg/kg bw: Increased platelets, increased liver weights, hepatocytic lipid. 50 mg/kg bw: As above plus decreased weight gain, decreased albumin, protein, calcium, cholesterol, triglycerides, increased ALP, increased SGPT, increased kidney weights, increased hepatocytic lipid, increased hemosiderin in Kupffer cells. Target organ: Liver
Chronic toxicity/oncogenicity			
Two-year dietary	Rat, Alp:AP 52/sex/dose, 12 interim sacrifice, 0, 0.47, 5, 50	NOEL = 0.47	5 mg/kg bw: Increased APDM, hepatocytic cytoplasmic vacuolation, decreased body-weight gain, increased liver, adrenal, kidney weights. 50 mg/kg bw: As above plus increased liver, adrenal, kidney weights, decreased triglycerides, increased SGOT, increased SGPT, increased APDM, increased hepatocytic hypertrophy, centrilobular fat deposition, bile-duct proliferation and spongiosis, fatty vacuolation of adrenal cortex, tubular atrophy of testis, Leydig cell tumours. Target organ: Liver
Two-year dietary	Mouse, CD-1, 50/sex/group, 0, 0.6, 4.7, 23.5	NOEL = 4.7	23.5 mg/kg bw: Decreased body-weight gain, decreased red blood cells, increased liver weight, hepatocytic fatty changes, vacuolation of renal tubular cortex. Target organ: Liver

Study	Species/strain	NOEL/NOAEL* mg/kg bw	Target organ/significant effects
Reproduction/developmental toxicity			
Multi-generation reproduction	Rat, Alpk:AP, 15 males, 30 females, 0, 1, 5, 50	NOEL = 1 general toxicity NOEL = 50 reproductive toxicity	5 mg/kg bw: Parents: hepatocytic cytoplasmic vacuolation and lipid, adrenal cytoplasmic vacuolation. Offspring: hepatocytic lipid. 50 mg/kg bw: As above and Parents: decreased body-weight gain and food consumption, increased relative liver weight, hepatocytic hypertrophy. Offspring: decreased pup body weight, hepatocytic cytoplasmic vacuolation, adrenal cytoplasmic vacuolation. NO EFFECTS ON REPRODUCTIVE PARAMETERS AT ANY DOSE TESTED
Teratology	Rat, Alpk:AP, 24 dams/group, 0, 2.5, 25, 250	NOEL: fetal = 2.5 maternal = 25	25 mg/kg bw/d: Fetal effects: increased skeletal anomalies (7th cervical transverse process partly ossified, extra 14th rib). 250 mg/kg bw/d: Fetal effects: as above and decreased body weights, increased pelvic dilatation, kinked ureter, extra 7th cervical rib, decreased ossification of sternebrae, cervical vertebrae. Dams: Increased clinical signs (piloerection, coat staining), decreased body-weight gain, increased post-implantation loss. NO TERATOGENIC EFFECTS AT ANY DOSE TESTED
Teratology	Rabbit, NZW, 20 dams/group 0, 25, 50, 100	NOEL: fetal = 50 maternal = 100	100 mg/kg bw: Holes in parietal of skull. NO TERATOGENIC EFFECTS AT ANY DOSE TESTED
MUTAGENICITY			
Ames, mouse lymphoma, mouse micronucleus, mouse dominant lethal, human lymphocytes, unscheduled deoxyribonucleic (DNA) synthesis			NEGATIVE

* No observed adverse effect level

3.2 Determination of acceptable daily intake

An acceptable daily intake (ADI) for hexaconazole can be established at 0.005 mg/kg bw based on the NOEL from the chronic rat study of 0.5 mg/kg bw/d and a 100-fold safety factor. This ADI provides a margin of exposure of 500 for the lowest NOEL for fetotoxicity in rats of 2.5 mg/kg bw/d and a MOE of 1000 for the NOEL of 5 mg/kg bw/d for testicular effects in the chronic rat study. The Joint Meeting on Pesticide Residues (JMPR), 1990, also set an ADI of 0.005 mg/kg bw/d.

3.3 Acute reference dose

An acute reference dose (ARfD) was established for hexaconazole based on the NOEL of 2.5 mg/kg bw/d set in the rat teratology study, based on fetotoxicity in the absence of maternal toxicity. A 300-fold MOE was used to ensure protection for the increased sensitivity of the fetus. The ARfD for hexaconazole is set at 0.008 mg/kg bw/d.

3.4 Toxicology end-point selection for occupational and bystander risk assessment

Occupational exposure to hexaconazole is expected to be predominantly via the dermal route. Commercial seed treaters would be intermittently exposed over two to three months per year. Workers planting commercially-treated seed would be exposed for up to several days per year. Similarly, on-farm seed treaters would be exposed for up to several days per year.

Given the short-term nature of the occupational exposure, short-term toxicology studies were identified as the most relevant for use in the occupational risk assessment. As fetotoxicity was identified as the endpoint of concern in the toxicological database, studies examining this endpoint were selected for risk assessment purposes.

The two-generation rat reproduction study with a NOEL of 1 mg/kg bw/d was selected for the assessment of occupational risk assessment as it had the lowest NOEL of the relevant studies (reproduction and teratology studies); it augments the evaluation of the fetotoxicity identified in the teratology studies by assessing viability, growth and the ability to thrive and reproduce through two generations; and it identified the same spectrum of effects observed in other studies in the database.

Selection of a toxicology endpoint for bystanders was not considered applicable to the proposed use pattern.

3.5 Drinking water limit

Addressed in Section 4.2.

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

3.6.1 Operator exposure assessment

Dermal absorption

In an in vivo dermal-absorption study, male rats were dosed with ^{14}C-phenyl-labelled hexaconazole as an end-use aqueous formulation at doses of 1.0, 0.1, 0.01 and 0.001 mg a.i./cm^2. (The test material was similar to PROSEED with respect to formulants and formulation type.) The animals were exposed for 0.5, 1, 2, 4, 10 and 24 hours before washing the skin site. A blood sample was taken and the animals were then sacrificed after the skin wash. Excreta, skin at the application site, blood and plasma, carcass, cage wash, swabs and site covers were analysed for ^{14}C content to determine total dermal absorption. The 10-hour exposure period corresponds most closely with the anticipated length of daily worker exposure. By 10 hours, 4.2%, 7.4%, 14.6% and 47.6% of the 1.0, 0.1, 0.01 and 0.001 mg a.i./cm^2 doses, respectively, had been absorbed. As the lowest dose, 0.001 mg a.i./cm^2, corresponds most closely with the anticipated field exposure, it was considered appropriate to adjust dermal deposition values by 47.6%.

Commercial seed treatment

Seed-treatment facilities can vary in production capacities, processes and manpower requirements depending on the size of the facility, but most plants use similar types of equipment. Gustafson or Gustafson-like seed treaters, which have a closed mixing system, are the predominant type of equipment used in Canada. The large, medium and small facilities can treat about 65 000 kg seed/d, 43 700 kg seed/d or 8700 kg seed/d, respectively. Job functions include mixing/loading, bagging, clean up and repair. Seed treatment can occur over several months of the year, depending on the geographic region and seed type. Proseed would typically be used, intermittently, two to three months per year.

A study conducted with a surrogate chemical was submitted to support the commercial seed-treatment use. In the study, 13 commercial seed-treatment workers were monitored at four seed-treatment plants in the United Kingdom on separate days in September 1993. The surrogate seed-treatment product was Baytan (active ingredient triadimenol). Workers carried out typical activities, which included one or more of calibration of the coating equipment, mixing/loading of the product, bagging of treated seed, clean up of equipment and forklift operation. Dermal (including hands) and inhalation monitoring were conducted. The study was considered an acceptable surrogate study. The major difference between the Baytan exposure study conditions and the proposed Proseed use pattern is the difference in application rates. Given this difference in use rates and some limitations in the study design, it was considered appropriate to derive an upper bound estimate of exposure from the study (i.e., 1.29 mg/kg a.i. handled). Dermal exposure was the predominant route of exposure, with exposure from the inhalation route considered negligible.

To determine systemic exposure, the following equation, with adjustments for unit conversion, was used:

$$\text{Exposure} = \frac{\text{exposure (mg a.i./kg)} \times \text{application rate (mg a.i./kg seed)} \times \text{seed treated (kg)} \times \%\text{dermal absorption}}{\text{body weight}}$$

As 65 000 kg seed may typically be treated in a day at a large facility at an application rate of 15 mg a.i./kg seed, systemic exposure to a 70-kg worker wearing one layer of clothing and gloves (assuming dermal absorption of 47.6%) would be 0.0086 mg a.i./kg bw/d. (For a 60-kg female worker, systemic exposure would be 0.010 mg/kg bw/d.)

For the commercial seed treaters (wearing one layer of clothing and gloves), the NOEL of 1 mg/kg bw/d and systemic exposure of 0.010 mg a.i./kg bw/d yields an MOE of 100. This MOE is considered adequate.

On-farm seed treatment

Seed treatment would occur in the spring and late summer. A variety of treatment methods can be used for on-farm treatment of seed, including drill boxes, augers and newer technology such as "treat-on-the-go" seeders. Drill boxes, in which the product would be manually poured over the seed and manually mixed with a paddle until a uniform colour is achieved, are no longer widely used. Augers are common and can involve various set-ups including a tank mounted to the auger; a direct connection to a product container; a connection to the auger via a pump and drum; or use of an auger with a pump and spray nozzle. New technology includes seeders with a built-in holding tank for the formulation (i.e., the product would be applied to the seed in a closed application chamber as the seed moves through the air flow on the seeder, such as the "treat on-the-go" seeder). There is varying potential for dermal and inhalation exposure during operation of these types of equipment. Generally, exposure would be expected to be highest with drill boxes and lowest with the closed application systems. For all methods, exposure would also occur during equipment clean up and repair activities, and handling of unused treated seed. Seed is deposited directly in the seed furrow, 3–5 cm below the soil surface. The maximum hectarage that a farmer could sow in a typical day, with concurrent treatment, would be approximately 40 ha (i.e., 4400 kg barley seed). This task could occur over several days, depending on the hectarage to be sowed.

Based on the studies summarized above, a quantitative estimate of exposure could not be derived for on-farm seed treatment using Proseed. Given the low application rate and the lesser amount of seed that can be treated and sowed in a day using on-farm equipment, however, occupational exposure to individuals is not expected to exceed exposure estimates for commercial seed treaters or planters (refer to Section 3.6.3) and MOEs are expected to be adequate.

Additional considerations

For the risk assessments it should be noted that the increased sensitivity of the fetus observed in the teratology studies is accommodated by the extra 2.5-fold MOE with the use of the lower NOEL of 1 mg/kg bw/d from the reproduction study.

There is also an adequate MOE for the abnormal gonadotrophic stimulation (benign Leydig cell tumours, testicular atrophy) observed at 50 mg/kg bw/d. The NOEL for these effects was 4.7 mg/kg bw/d, providing an MOE of 470 for commercial seed treaters and 293 for workers planting treated seed. It is recognized that some elements of the assessment are considered conservative (e.g., some use of upper bound values in the exposure assessment, assumption of equivalent dermal absorption of liquid formulation and dried residues). For commercial seed-treatment workers and on-farm seed-treatment workers, wearing coveralls over normal work clothes would decrease dermal exposure. Further, for workers planting treated seed, exposure to the bare hands was the predominant route of exposure (contributing in excess of 85% to the total exposure) and wearing gloves would significantly reduce dermal exposure, thereby, increasing the MOE several fold. The MOEs are considered adequate (>500).

3.6.2 Bystanders

Not applicable to the proposed use pattern.

3.6.3 Workers planting treated seed

A study conducted with a surrogate chemical was submitted to support the commercial seed-treatment use. In the study, 13 workers were monitored throughout a typical workday, including transportation to and from the fields, loading seed, planting and any clean up and repair activities. The surrogate seed-treatment product was Baytan (active ingredient triadimenol). Dermal (including hands) and inhalation monitoring were conducted. The study was considered an acceptable surrogate study.

The average amount of treated seed that workers handled in the surrogate study, and the rate at which the seed was treated, were both less than for the proposed Proseed use pattern. In Canada, an average of 11 000 kg of seed would be planted during a typical workday. In addition, the application rate proposed for Proseed is low (i.e., 15 mg a.i./kg seed) and it was considered appropriate to normalize the results on a per-kilogram-of-active-ingredient-handled basis. Dermal exposure was the predominant route of exposure; inhalation exposure was considered negligible.

To determine systemic exposure, the following equation, with adjustments for unit conversion, was used:

$$\text{Exposure} = \frac{\text{exposure (mg a.i./kg)} \times \text{application rate (mg a.i./kg seed)} \times \text{seed treated (kg)} \times \%\text{dermal absorption}}{\text{body weight}}$$

Using the normalized exposure unit of 12.8 mg a.i./kg a.i. handled, and an application rate of 15 mg a.i./kg seed, systemic exposure to a 70-kg worker wearing one layer of clothing and no gloves (assuming dermal absorption of 47.6%) would be 0.014 mg/kg bw/d. (For a 60-kg female worker, systemic exposure would be 0.016 mg/kg bw/d.) Exposure to the bare hands accounted for greater than 85% of the total exposure.

For workers planting treated seed (wearing one layer of clothing and no gloves), the NOEL of 1.0 mg/kg bw/d and systemic exposure of 0.016 mg/kg bw/d yields an MOE of 63. As exposure to the bare hands was the predominant route of exposure (i.e., contributing in excess of 85% to the total exposure), wearing gloves would significantly reduce dermal exposure, and the resulting MOE would be expected to be adequate (>100).

The information under "Additional Considerations" in Section 3.6.1 is also applicable to planting treated seed.

4.0 Residues

4.1 Definition of the residues relevant to maximum residue limits

4.1.1 Definition of the residues in wheat and barley relevant to maximum residue limits

Wheat metabolism study
Wheat plants were treated with ^{14}C-labelled hexaconazole at growth stage 30 (250 g a.i./ha), flag leaf emergence (125 g a.i./ha) and after ear emergence (125 g a.i./ha), for a total application rate of 500 g a.i./ha. Wheat was harvested 45 days after the last spray and separated into grain, straw and chaff for analysis.

Residue levels of hexaconazole in grain and straw were 0.002 ppm (0.7% of the total radioactive residues [TRRs]), and 0.1 ppm (10% of the TRRs), respectively. The nature of the radioactive residues in the chaff was similar to that found in the straw, with the (±)-2-(2,4-dichlorophenyl)-1-(1H-1,2,4-triazol-1-yl)hexan-2,5-diol metabolite (2,5-diol) being the major radioactive component.

The ROC is considered to be the parent pesticide hexaconazole.

Confined crop rotation study
A summary of the confined crop rotation study on wheat was submitted. Spring wheat seeds were planted 30 days after soil was treated with about 450 g a.i./ha of ^{14}C-labelled hexaconazole. Immature forage samples (60 days after planting), mature grain and straw samples were analysed for residues of hexaconazole. The results indicated that the metabolic profiles in wheat from soil and foliage treatment were similar.

The parent hexaconazole was not detected in grain. The major metabolites found in grain were triazolyl alanine (TA) and triazole acetic acid (TAA). The major metabolites found in forage in decreasing order were the 2,5-diol, the parent hexaconazole, TAA and TA.

Storage stability

Frozen samples were stored up to 10 months prior to analysis. Hexaconazole residues in grain and straw samples have been shown to be stable for 12 months under this storage condition.

4.1.2 Definition of the residues in food of animal origin relevant to maximum residue limits

A goat metabolism study (JMPR review [1990]) indicated that at a feeding level of 15 ppm for four consecutive days, most of the administered ^{14}C-hexaconazole dose was excreted via urine and feces. The maximum TRRs were found in liver (0.48 ppm) and muscle tissues (#0.05 ppm) 16 hours after the last dose. No parent hexaconazole was found in either meat or milk (<0.005 ppm). Although the log K_{ow} is 3.9, indicating a potential for uptake and bioaccumulation, the residue level of hexaconazole in tissues or milk is not reflective of this.

Residue levels in treated wheat commodities were under the limit of quantitation (LOQ) in grain (LOQ < 0.01 ppm), and straw and forage (LOQ < 0.05 ppm). The TRRs in edible commodities of lactating goat were <0.0016 ppm when extrapolated from the 300× feeding level to the potential 1× feeding level.

4.2 Residues relevant to consumer safety

Trials were carried out on spring wheat and spring barley each in Ontario, Manitoba, Saskatchewan and Alberta. The seeds were treated with hexaconazole according to the proposed label rate (0.375 g a.i./25 kg seed) before seeding. The forage, grain and straw samples were collected at a preharvest interval of 48–94 days, and 100–118 days, respectively. Residues of hexaconazole in grain, straw and forage grown from treated seeds were all less than the LOQs (0.01 ppm for grain, 0.05 ppm for straw/forage).

The wheat metabolism study identified 2,5-diol as the major metabolite in wheat straw (0.4 ppm). No other measurable residues of metabolites were detected (LOQ < 0.02 ppm) in the forage and straw samples.

The major metabolites detected in grain were TA (#0.09) and TAA (0.07 ppm). Residues of traizolyl alanine will be covered under the existing maximum residue limit (MRL), 2 ppm, established for all food crops in Canada.

The potential exposure of consumers to hexaconazole residues through dietary intake is very low. At the proposed seed-treatment application rate of 0.375 g a.i./25 kg seeds, residues of hexaconazole are not expected to occur in cereal grain grown from treated seeds at levels greater than 0.01 ppm.

A chronic dietary risk assessment was conducted using the Dietary Exposure Evaluation Model™ (DEEM™) Software to estimate the dietary exposure to residues of hexaconazole from existing and proposed uses. The assessment was conducted using the 1994-1996 Continuing Survey of Food Intake for Individuals, and the proposed MRLs on plant and animal comoodities. The highest potential daily intake (PDI)/ADI percentage (+10% for drinking water) was for children one to six years of age, calculated to be approximately 20%. The PDI for the remainder of the population subgroups, including infants, children, and seniors, represented on average 14% of the ADI.

Microcontaminants of toxicological concern were reported in batch analyses of hexaconazole technical at levels from non-detectable (LOQ) to 76 ppt (2,3,7,8-TCDF). This is toxicologically equivalent to 7.6 ppt of 2,3,7,8-TCDD. The calculated PDI for this level was no greater than 0.3% of the tolerable daily intake of 10 pg/kg bw for 2,3,7,8-TCDD set by World Health Organization. A chronic dietary risk assessment indicated that these low concentrations of 2,3,7,8-TCDF are not expected to cause a dietary health risk to humans, including infants and children.

4.3 Residue relevant to worker safety

Addressed in Section 3.6.3.

4.4 Proposed maximum residue limits and compliance with existing maximum residue limits

4.4.1 Compliance with existing maximum residue limits

Codex recommended an MRL of 0.1 ppm in wheat grain. The proposed cereal seed-treatment use for hexaconazole is unlikely to result in residues in progeny seeds exceeding the 0.1 ppm level.

There is no tolerance in the U.S. for hexaconazole in grain at this time; therefore, a potential exists for a trade irritant to arise should hexaconazole residues be found in Canadian grain for export. The submitted residue data suggest, however, that in commercial practice, a trade irritant is unlikely to result from treatment of cereal seed according to the Proseed label.

4.4.2 Proposed maximum residue limits

On the basis of the results of supervised trials carried out in Canada, when cereal seeds are treated with hexaconazole according to the proposed label directions, the residues of hexaconazole in progeny cereal grain will not be expected to exceed 0.01 ppm. Codex recommended an MRL of 0.1 ppm in wheat grain and 0.5 ppm on wheat straw and fodder. In the spirit of harmonization, an MRL of 0.1 ppm for cereal grain has been proposed.

Since the anticipated residue levels in treated cereal commodities were under the LOD (<0.01 ppm for grain and <0.05 ppm for straw/forage), an animal feeding study was not required. Maximum residue limits would not be needed for meat, milk and eggs. The residues of hexaconazole in meat, milk and eggs from animals fed with commodities grown from treated seeds, however, will be covered under the subsection B15.002 (1), (i.e., #0.1 ppm) of the Food and Drugs Regulations.

5.0 Fate and behaviour in the environment

Hexaconazole was not susceptible to chemical hydrolysis or to phototransformation, and was not likely to volatilize from water or moist soil. Microbial action was important in the transformation of hexaconazole in soils. Laboratory aerobic soil studies demonstrated that hexaconazole was persistent in loamy sand soil and moderately persistent in sandy loam and silty clay loam soils. A major transformation product observed was 1,2,4-triazole. Laboratory studies also showed that hexaconazole was persistent in anaerobic soil and in aquatic aerobic water-sediment systems. In addition, it was concluded that hexaconazole would be persistent in aquatic anaerobic systems. Canadian field data on dissipation in soil showed that hexaconazole was persistent. Laboratory soil adsorption and leaching studies and field soil dissipation studies indicated that hexaconazole had negligible leaching potential and is not expected to contaminate groundwater through leaching.

5.1 Physicochemical properties

Refer to PRDD95-01, Section 6.2.1

5.2 Fate and behaviour in soil

5.2.1 Phototransformation on soil

Laboratory data indicated that phototransformation is not expected to be a significant process for the transformation of hexaconazole in soil, as reported previously in Section 6.2.2 (b) of PRDD95-01.

5.2.2 Aerobic soil biotransformation

Results from laboratory aerobic soil studies (20°C) showed that hexaconazole was persistent (decline time 50% [DT_{50}] of about eight months) in loamy sand soil, moderately persistent (DT_{50} of about two months) in sandy loam, and moderately persistent (DT_{50} of about three months) in silty clay loam soils. Of the transformation products observed, 1,2,4-triazole was detected at concentrations over 10% of applied radioactivity in sandy loam and loamy sand soils, but at concentrations of less than 10% in silty clay loam soil (see Section 6.2.2 (c), PRDD95-01).

5.2.3 Anaerobic soil biotransformation

Hexaconazole was persistent (DT_{50} greater than nine months) and transformation of the compound was minimal in flooded sandy loam soil (see Section 6.2.2 (c), PRDD95-01).

5.2.4 Field soil dissipation studies

Field dissipation studies were initiated in Manitoba (Almissippi fine sand [sandy loam or loamy sand from the black soil zone]) and Alberta (brown soil zone [sandy clay loam]). Hexaconazole was applied to non-cropped soil as ANVIL, at a rate of 90 g a.i./ha. The reviewer classified the DT_{50} to be between 45 and 180 days for the Manitoba site and greater than 180 days for the Alberta site. A DT_{90} was not reached in any of the plots within 742 days. Hexaconazole, therefore, was moderately persistent in Almissippi fine sand (sandy loam soils in Manitoba) and persistent in sandy clay loam (Alberta soils).

The applicant submitted a waiver request in lieu of dissipation studies conducted in the Canadian Prairies for the major transformation product (1,2,4-triazole). The waiver request was granted for the following reasons. Previous laboratory studies indicated that 1,2,4-triazole can constitute up to 30% of the residue, but this is further degraded to carbon dioxide. In field dissipation studies in the U.S., even though 1,2,4-triazole was persistent, the detectable concentration was low and most of the compound did not migrate below 30 cm. The applicant indicated that the level of 1,2,4-triazole from a dissipation study at the seed-treatment application rate would be below the current LOD. The transformation product, 1,2,4-triazole, is non-toxic to earthworms, rainbow trout and *Daphnia magna*, but it is toxic to freshwater green algae. If the use pattern changes or the application rate increases, the PMRA would recommend that 1,2,4-triazole residues be measured in a prairie field dissipation study.

In Ontario, hexaconazole was persistent in sandy loam (DT_{50} approximately 10 months) and moderately persistent in clay loam (DT_{50} of about 5 months) (see Section 6.2.4, PRDD95-01).

In a field dissipation study conducted in British Columbia, hexaconazole was moderately persistent (DT_{50} of about five months) in silt loam soil (see Section 6.2.4, PRDD95-01).

5.2.5 Mobility

5.2.5.1 Soil adsorption/desorption studies

Based on soil adsorption/desorption studies, hexaconazole is classified as having low mobility in soils (see Section 6.2.3 (a), PRDD95-01).

5.2.5.2 Soil-column leaching

Laboratory soil-column leaching experiments with hexaconazole have indicated that the leaching potential of hexaconazole and its transformation products in soils is limited (see Section 6.2.3 (c), PRDD95-01).

5.2.5.3 Soil thick-layer chromatography

The results of a laboratory soil thick-layer chromatography study indicated that the leaching potential of hexaconazole is low (see Section 6.2.3 (b), PRDD95-01).

5.2.5.4 Field leaching data

In Manitoba (Almissippi fine sand [sandy loam or loamy sand from the black soil zone]) and Alberta (brown soil zone [sandy clay loam]), hexaconazole did not move below the 10-cm level and, therefore, would be of limited soil mobility.

In Ontario (sandy loam and clay loam) and British Columbia (silt loam) soils, hexaconazole had negligible leaching potential (see Section 6.2.4, PRDD95-01).

5.2.6 Expected environmental concentrations in soil

Hexaconazole and Proseed formulation

For the Proseed fungicide seed treatment application rate of 1.5 g a.i./100 kg seed, equivalent to 3.03 g a.i./ha, the expected environmental concentration (EEC) would be 0.0067 mg a.i./kg in soil of 3-cm depth and 0.0013 mg a.i./kg in soil of 15-cm depth (Table 5.1). Expressed in terms of product, the EEC would be 1.347 and 0.269 mg Proseed/kg in soil of 3- and 15-cm depths, respectively (Table 5.1).

Table 5.1 The maximum expected environmental concentrations for hexaconazole and Proseed in soil and water, following seed treatment at the Canadian maximum label rate of 3.03 kg a.i./ha.

Environmental Compartment	Depth (cm)	Density	EEC	
			Technical hexaconazole	Proseed formulation
Soil	15	1.5 g/cm^3	0.0013 mg a.i./kg	0.269 mg Proseed/kg
Soil	3	1.5 g/cm^3	0.0067 mg a.i./kg	1.347 mg Proseed/kg
Soil (after 20 years of accumulation based on 40% carryover)	3	1.5 g/cm^3	0.0112 mg a.i./kg	—
Pond water (following runoff event) [a]	30	1.0 g/mL	0.0005 mg a.i./L	0.101 mg Proseed/L
Pond water (after 20 years based on 0% carryover)	30	1.0 g/mL	0.0005 mg a.i./L	—
EEC for human drinking water [b]	246	1.0 g/mL	0.000 38–0.0076 mg a.i./L	0.0758–1.515 mg Proseed/L

[a] EEC based on a 100-ha watershed, 1-ha pond (30 cm deep) and 0.5 % runoff of pesticide.
[b] EEC based on a 4000-m^3 dugout (246 cm deep), 100–2000-ha watershed and 0.5 % runoff of pesticide.

Microcontaminants

Batch analyses of technical hexaconazole have indicated some minor contamination with dioxins and furans. The highest level of 2,3,7,8-TCDF detected was 76 ppt, or a toxic equivalent quantity (TEQ) of 7.6 ppt (pg/g) of 2,3,7,8-TCDD, which was used in the environmental loading calculations (see Section 6.4.3). The other dioxin and furan congeners were found in much lower concentrations. When all the congeners were expressed in terms of the TEQ, the concentrations ranged from 0.027 to 7.6 ppt.

5.3 Fate and behaviour in aquatic systems

5.3.1 Hydrolysis

As determined from laboratory data, chemical hydrolysis is not expected to be an important mode of transformation of hexaconazole in the environment (see Section 6.2.2 (a), PRDD95-01).

5.3.2 Phototransformation in water

Phototransformation of hexaconazole in sterile aqueous solution was insignificant (see Section 6.2.2 (b), PRDD95-01).

5.3.3 Aquatic aerobic biotransformation

In laboratory aquatic aerobic sediment-water systems, hexaconazole was moderately persistent (see Section 6.2.2 (c), PRDD95-01).

5.3.4 Aquatic anaerobic biotransformation

The applicant requested a waiver for aquatic anaerobic biotransformation with hexaconazole. Because hexaconazole is persistent in anaerobic soil and would also be expected to persist in anaerobic aquatic sediment, the environmental assessment by the PMRA was based on the expectation that hexaconazole will be persistent in anaerobic aquatic sediments (see Section 6.2.2 (c), PRDD95-01).

5.3.5 Expected environmental concentration in surface water

Based on a 100-ha watershed and 0.5% runoff, 0.0005 mg a.i./L or 0.101 mg Proseed/L could enter shallow water bodies and small ponds (1 ha) that are 30 cm deep. Based on a 4000-m^3 dugout (246 cm deep), 100- to 2000-ha watershed and 0.5 % runoff of pesticide, the EEC for human drinking water would be 0.000 38–0.0076 mg a.i./L or 0.0758– 1.515 mg Proseed/L (Table 5.1). Runoff calculations were based on the pesticide being applied directly to the soil and then soil incorporated. Runoff concentrations based on treated seed planted in the soil might be different and may be lower.

5.4 Fate and behaviour in air

The vapour pressure was 1.8×10^{-8} kPa (1.4×10^{-7} mm Hg) at 20°C, which indicates that hexaconazole would be considered relatively non-volatile under field conditions. Henry's law constant was 3.5×10^{-9} atm m^3 mol^{-1} (3.5×10^{-4} Pa m^3 mol^{-1}), which indicates that hexaconazole is not likely to volatilize from water and moist soil. There is minimal potential, therefore, for hexaconazole to contaminate the atmosphere.

6.0 Effects on non-target species

A summary of the toxic effects of hexaconazole on non-target organisms is presented in Table 6.1. Hexaconazole had no major effect on soil micro-organisms and was not toxic to earthworms and bees. Hexaconazole was practically non-toxic to birds and had moderate acute toxicity to fish and aquatic invertebrates. Chronic toxicity data have indicated that hexaconazole is toxic to *Daphnia magna*, a freshwater invertebrate. Hexaconazole bioconcentrated in fish, but the process was reversible. Bioaccumulation, therefore, is not expected to be a major environmental problem.

Table 6.1 Summary of the results of toxicity studies with hexaconazole on non-target terrestrial and aquatic organisms. These data, except the toxicity to birds, were previously presented in PRDD95-01.

Species and study type	LD_{50}, LC_{50} or EC_{50}*	NOEL or NOEC**
Rainbow trout (*Oncorhyncus mykiss*)	96-hr LC_{50} > 6.7 mg a.i./L	96-hr NOEL < 0.97 mg a.i./L
Bluegill sunfish (*Lepomis macrochirus*)	96-hr LC_{50} = 5.1 mg a.i./L	Not available
Aquatic invertebrate (*Daphnia magna*)	48-hr EC_{50} = 2.9 mg a.i./L	Not available
Algae (*Selenastrum capricornutum*)	96-hr EC_{50} = 1.5 mg a.i./L	96-hr NOEL = 0.56 mg a.i./L
Mallard duck (*Anas platyrhynchos*) (Acute toxicity)	14-d LD_{50} > 4060 mg a.i./kg	14-d NOEL = 4060 mg a.i./kg
Bobwhite quail (*Colinus virginianus*) (Dietary toxicity)	15-d LC_{50} = 5145 mg a.i./kg	15-d NOEC of 1320 mg/kg
Mallard duck (*Anas platyrhynchos*) (Dietary toxicity)	15-d LC_{50} = 10642 mg a.i./kg	15-d NOEL (mortality) = 3710 mg a.i./kg 15-d NOEL (liver abnormalities) <825 mg/kg
Soil invertebrate, earthworm (*Eisenia foetida*)	Field study at 1 kg a.i./ha had no significant effects	

* Environmental concentration 50%
** No observed effect concentration

6.1 Effects on terrestrial non-target species

6.1.1 Wild birds

The 14-day acute oral NOEL was 4060 mg a.i./kg and the LD_{50} was greater than 4060 mg a.i./kg for the effect of hexaconazole on mallard ducks (Table 6.1). In this acute oral study, mean food consumption in the control group during the test period was 0.077 kg dry weight of diet per bird per day. The most sensitive endpoint for dietary exposure in mallard ducks was obtained for liver abnormalities with a NOEC of <825 mg/kg (Table 6.1).

For bobwhite quail, the dietary NOEC was 1320 mg/kg, based on reduced mean body weight and reduced food consumption. The dietary LC_{50} was 5145 mg a.i./kg (Table 6.1). Hexaconazole, therefore, is practically non-toxic to birds.

6.1.2 Wild mammals

Technical hexaconazole was slightly to moderately toxic to mice via oral exposure, but of low toxicity to rats exposed orally and dermally. The Proseed formulation was of low oral acute toxicity to rats (see Section 3.1.3).

6.1.3 Bees

Data from contact toxicity tests indicated that hexaconazole is relatively nontoxic to bees. Results from oral toxicity tests are questionable as all the concentrations tested were well above the water solubility of hexaconazole (see Section 6.3.2, PRDD95-01). Because Proseed is a seed treatment, there should be no exposure to bees.

6.1.4 Arthropod predators and parasites

The acute contact toxicity of a 5% SC formulation of hexaconazole to predatory mites (*Panonychus ulmi*) was estimated. The 24- and 48-hr LC_{50} values were 190 mg a.i./L and the NOEC for mortality was <50 mg a.i./L.

The acute contact effects of formulated hexaconazole (4.8 % weight per weight [w/w]) on two polyphagous predatory arthropods, the ground beetle, *Pterostichus cupreus*, and the wolf spider, *Paradosa* spp., were determined in a laboratory study. A soluble grain formulation (4.8% hexaconazole) was tested at a rate of 250 g a.i./ha, which is 82 times below the recommended rate for Proseed. Six days after direct overspray, only 5% mortality was observed in both species.

6.1.5 Earthworms

Results from a three-year field study indicated that formulated hexaconazole (5.5% w/w) at 1 kg a.i./ha had no significant adverse effect on total numbers or weight of earthworms (see Section 6.3.2, PRDD95-01).

6.1.6 Soil micro-organisms

According to results from laboratory studies with loamy sand and sandy loam soils, the impact of formulated hexaconazole (5% w/w) on soil respiration, soil nitrification, the number of fungi and bacteria, and on total micro-organism numbers was in most cases limited (see Section 6.3.1, PRDD95-01).

6.1.7 Terrestrial vascular plants

No data were submitted for the effect of hexaconazole on non-target terrestrial plants. Because of the limited exposure to non-target terrestrial plants, these data are not required for the proposed use pattern (seed treatment).

6.2 Effects on non-target aquatic species

Data from these sections are not required for the proposed use pattern (seed treatment); however, the following data on hexaconazole were available from the review of the proposed wood- preservative products.

6.2.1 Fish bioconcentration study

Bioconcentration factors in bluegill sunfish were 107 in whole fish, 45 in muscle and 778 in viscera, indicating a tendency for residues to accumulate in viscera. This process was reversible (see Section 7.1, PRDD95-01); therefore, bioaccumulation is not expected to be a major environmental problem.

6.2.2 Aquatic invertebrates

Data on the acute toxicity of technical hexaconazole to *Daphnia magna, Mysidopsis bahia* and *Crassostrea gigas* indicated that hexaconazole was moderately toxic. Chronic toxicity data have indicated that hexaconazole is toxic to *Daphnia magna* growth and reproduction (see Sections 6.3.3 and 7.2, PRDD95-01).

6.2.3 Fish

As based on acute toxicity studies, hexaconazole is moderately toxic to fish (see Section 7.1, PRDD95-01).

6.2.4 Algae

Growth inhibition occurred in the green alga, *Selenastrum capricornutum* (see Section 7.2, PRDD95-01).

6.2.5 Aquatic vascular plants

No toxicity data were submitted for the effect of hexaconazole on non-target aquatic vascular plants. These data are not required for the proposed use pattern (seed treatment).

6.3 Effects on biological methods of sewage treatment

These studies are not required by PMRA.

6.4 Environmental risk assessment

6.4.1 Terrestrial organisms

Wild Birds

Because Proseed is a seed treatment, there is a possible risk that the treated seeds might be eaten by birds. Many species of waterbirds, marsh birds, game birds, songbirds, and small mammals feed on the seeds of wheat, barley and oats. The 14-day acute oral NOEL was 4060 mg a.i./kg for mallard ducks (see Section 6.1.1 and Table 6.1). In their natural environment, mallard ducks consume 70% grains. If all the grain consumed consisted of treated seed with an EEC of 15 mg hexaconazole per kg seed, the bird would have to feed for 5020 days before reaching the reported NOEL for acute effects. The risk to wild birds via acute oral exposure, therefore, would be negligible.

The most sensitive endpoint for dietary exposure in mallard ducks was obtained for liver abnormalities with a NOEC of <825 mg/kg (see Section 6.1.1 and Table 6.1). Assuming that the 70% grain ingested by the birds would consist of treated seed, the safety factor for liver abnormalities would be 78.6. For bobwhite quail, the dietary NOEC was 1320 mg/kg, based on reduced mean body weight and reduced food consumption (see Section 6.1.1 and Table 6.1) In their natural environment, bobwhite quail consume 55% grains. Assuming that the 55% grain ingested by the birds would consist of treated seed, the safety factor for body weight would be 160. The risk to wild birds through dietary exposure, therefore, would be minimal.

Wild mammals

It is possible that the seeds treated with Proseed might be eaten by wild mammals. Rats and mice can obtain 20% and 50% of their diet from grains and seeds, respectively. Based on an acute oral toxicity greater than 2000 mg a.i./kg bw (see Section 3.1.3), rats would have to consume a large quantity of seed treated with Proseed before an acute effect would be observed. The EEC in diet of rats is estimated to be 3 mg a.i./kg dry weight. Similarly, the EEC in diet of mice is calculated to be 7.50 mg a.i./kg dry weight, which is much less than the oral acute LD_{50} for mouse (557–1060 mg a.i./kg bw). The risk to small wild mammals, therefore, would be minimal, based on acute toxicity. A multi-generation reproduction study on rats showed no effects on reproductive parameters at any dose tested. A two-year dietary study on rats showed a decrease in triglycerides and atrophy of testis, but only at the highest dose (50 mg/kg bw) tested. Results from this study are not applicable to small wild mammals in the field, since it is not likely that they would be exposed to a daily diet containing hexaconazole for a two-year period. It is expected that treated seeds on the ground would be available for only a limited period of time after planting.

Honeybee
Not required for this use pattern (seed treatment).

Earthworm
For the seed treatment, the EEC would be 0.0067 mg a.i./kg in soil of 3-cm depth and 0.0013 mg a.i./kg in soil of 15-cm depth (Table 5.1). Hexaconazole at 1 kg a.i./ha in a field study had no significant effect on earthworms. At 1 kg a.i./ha, the EEC in 3 and 15 cm of soil would be 2.2 and 0.44 mg a.i./kg, which is much higher than the EEC in soil from the proposed use of Proseed. Earthworms, therefore, should be protected by a safety factor of several orders of magnitude. In addition, the risk to earthworms over the long term is also minimal. The EEC in soil after 20 years was estimated to be only 0.0112 mg a.i./kg (Table 5.1).

6.4.2 Aquatic organisms

Based on estimated runoff, hexaconazole at a concentration of 0.0005 mg a.i./L could enter shallow water bodies and small ponds (see Section 5.3.5 and Table 5.1). Based on the species tested, the most sensitive aquatic species to the toxic effects of hexaconazole is the freshwater alga, *Selenastrum capricornutum* (Table 6.1). Based on a 96-hour EC_{50} of 1.7 mg/L and a 96-hour NOEL of 0.56 mg/L, there would be safety factors of 300 and over. Runoff calculations were based on the pesticide being applied directly to the soil and then soil incorporated. Runoff concentrations based on Proseed treated seed planted in the soil may be lower. The risk to *Selenastrum capricornutum* over the long term is also limited. There is no increase in the EEC in water after 20 years (Table 5.1).

6.4.3 Microcontaminants

As indicated in Section 1.0, the Track 1 substance detected with the highest level in technical hexaconazole was 2,3,7,8-TCDF (at 76 ppt). The other dioxin and furan congeners were found in much lower concentrations. When all the congeners were expressed in terms of the TEQ, the concentrations ranged from 0.027 to 7.6 ppt. The environmental risk assessment was, therefore, based on 2,3,7,8-TCDF.

The environmental risk assessment considered 1) the EEC of 2,3,7,8-TCDF as a result of seed treatment with Proseed fungicide; 2) a comparison of release rates from other sources of emission and the projected release rate of furan from seed treatment with Proseed, which is dependent on the rate and frequency of application of Proseed and the maximum area seeded; 3) the toxic equivalency factor; 4) the persistence in the environment and its toxicity to non-target organisms; and 5) the provision to the PMRA of routine microcontaminant environmental monitoring data as conditions of registration.

The estimation of the maximum annual loading of furans in Canada from Proseed seed treatment was based on the assumption that seed for all the target crops were treated with hexaconazole at the maximum label rate. The maximum area that could be seeded with

Proseed-treated seed would be over 18 million ha. Based on an application rate of 3.03 g hexaconazole/ha, the loading of 2,3,7,8-TCDF would be 4.21×10^{-3} g/yr. The concentration of 2,3,7,8-TCDF in soil from Proseed-treated seed would be 5.12×10^{-13} mg/kg soil, and the concentration in 30 cm of water would be 3.84×10^{-14} mg/L.

The annual loading of 2,3,7,8-TCDF from seed treatment with hexaconazole, when expressed in terms of dioxins and furans, is calculated to be 4.21×10^{-4} g TEQ/yr (4.21×10^{-3} g/yr × 0.1 TEQ). The release of 2,3,7,8-tetrachlorodibenzofuran to the environment from the addition of hexaconazole is low when compared with releases from other sources. The projected total release in 1999 from other sources is 377 g TEQ.

Since toxicity values for 2,3,7,8-TCDF were not available, toxicity values for 2,3,7,8-TCDD were used based on the system of International Toxicity Equivalency Factors (I-TEF) (NATO, 1988). An I-TEF of 0.1 was used in assessing the risk posed by 2,3,7,8-TCDF.

The potential of 2,3,7,8-TCDF to pose a risk to fish from runoff from Proseed treated fields was assessed and a NOAEL of 11.0 pg/L was estimated for rainbow trout swim-up fry. Using the EEC of 3.84×10^{-14} mg 2,3,7,8-TCDF/L in water, there would be a 287 000-times safety factor protecting rainbow trout from the adverse effects.

Such low levels of 2,3,7,8-TCDF would not be measurable in the environment, even considering their persistence and after years of use, and, therefore, would not significantly increase the environmental loading of this compound. Thus, post-registration environmental monitoring of soil and water would not provide any useful data, since the concentrations of the microcontaminants would not be measurable. It should also be noted that the applicant used the best available technology to maintain low levels of this microcontaminant. Considering all these factors, the presence of 2,3,7,8-tetrachlorodibenzofuran, even though persistent, bioaccumulative and toxic, in hexaconazole technical active ingredient at concentrations of 76 ppt is not expected to pose unacceptable risk to the Canadian environment when Proseed Fungicide Seed Treatment is used at the proposed label rates.

6.5 Environmental risk mitigation

Based on the toxicity of hexaconazole to aquatic organisms, there is potential concern that hexaconazole can impact non-target organisms. Buffer-zone limits for the protection of aquatic and terrestrial non-target areas are not required for seed treatment. Cereal growers, however, should ensure that the hexaconazole treated seed is not planted on steep slopes above sensitive wetland habitats. The rows of treated seed should be planted at right angles to the gradient to minimize soil erosion and reduce seed loss. Growers should ensure maximum soil incorporation of the treated seed.

The following label statement is required:

ENVIRONMENTAL HAZARDS: This product is toxic to aquatic species. Do not contaminate ponds, lakes, streams or wetlands with rinsate, or when disposing of equipment wash waters. To prevent movement of treated seed and product into adjacent water bodies, use good management practices on sloped land and ensure proper soil incorporation of treated seed at planting.

7.0 Efficacy data and information

7.1 Effectiveness

7.1.1 Intended uses

Proseed is a seed-treatment fungicide proposed for wheat, barley and oats. Proseed may be applied at 75 mL/25 kg seed (1.5 g hexaconazole/100 kg seed) in either commercial seed-treatment plants or on-farm treating equipment. Product and seed should be above 0°C at time of treatment and storage of treated seed is not recommended.

Efficacy of hexaconazole for control of various cereal diseases was assessed in numerous field trials. Proseed and an earlier experimental formulation of similar composition were used in these trials. Four of the proposed disease claims were supported by adequate data (see bolded text, Table 7.1). The remainder of claims were not accepted due to insufficient valid trials.

Table 7.1 Proposed disease control claims for Proseed applied at 75 mL/25 kg seed.

Crop	Diseases controlled	Early season control only
Wheat	**Loose smut** ***Ustilago tritici*** Common bunt *Tilletia caries*, *Tilletia foetida*	**Common root rot** ***Cochliobolus sativus*** Seedling blight *Fusarium* sp. Septoria leaf blotch *Septoria tritici*, *S. nodorum* Powdery mildew *Erysiphe graminis*, f. sp. *tritici*
Barley	**True loose smut** ***Ustilago nuda*** False loose smut (semiloose smut, brown loose smut, black loose smut) *Ustilago nigra* **Covered smut** ***Ustilago hordei***	Leaf stripe *Pyrenophora graminea* Net blotch *Drechslera teres* Common root rot *Cochliobolus sativus* Seedling blight *Fusarium* sp.
Oat	Loose smut *Ustilago avenae* Covered smut *Ustilago kolleri*	Common root rot *Cochliobolus sativus* Septoria leaf blotch and black stem (speckled leaf blotch) *Septoria avenae* f. sp. *avenae*

7.1.2 Mode of action

Hexaconazole belongs to the triazole group of fungicides, which act by inhibiting sterol demethylation. This results in impaired fungal membrane function and death of hyphae of the pathogen.

7.1.3 Crops

Proseed is acceptable for use on wheat and barley.

7.1.4 Effectiveness against disease

7.1.4.1 Effectiveness against wheat loose smut *(Ustilago tritici)*

Loose smut is a seedborne disease affecting spring and winter wheat. A number of protectant and systemic seed treatments are currently registered for this disease (i.e., carbathiin, thiram, triadimenol, tebuconazole, difenoconazole). In the present submission, eighteen trials were submitted from Ontario, Manitoba and Alberta. Hexaconazole was applied at rates from 1.2 to 2.5 g a.i./100 kg seed. Loose smut in the untreated check ranged from 3 to 18% incidence of smutted heads. At the proposed rate (1.5 g), hexaconazole provided greater than 91% control, and typically 100% control, in these trials.

The proposed claim of control of wheat loose smut is supported.

7.1.4.2 Effectiveness against wheat common root rot (*Cochliobolus sativus, Bipolaris sorokiniana*)

Common root rot is a soilborne disease of spring and winter wheat, and is most significant on the Prairies. It is partly managed by use of resistant cultivars and seed treatments (i.e., carbathiin, thiram, maneb, difenoconazole). Although the disease can result in whiteheads (sterile or reduced grain), the most distinctive symptom is a dark brown lesion on the subcrown internode. Four studies with hexaconazole were submitted from Saskatchewan, at sites with 14–53% incidence of check plants with severe lesions. Hexaconazole was assessed at the proposed rate (1.5 g) in two trials and provided an average of 70% control (reduction in disease incidence). The remaining trials also showed a reduction in disease; however, these were done with a higher rate. These data suggest that a claim of disease *suppression* is appropriate for results expected with the recommended rate. Suppression is defined here as consistent control at a level that is not optimal but is still of commercial benefit. The disease data were collected late in the season (after soft-dough stage); therefore, the proposed label limitation to early season control is not necessary.

The proposed claim, revised to “suppression of common root rot”, is supported.

7.1.4.3 Effectiveness against barley loose smut *(Ustilago nuda)*

Barley loose smut is similar in biology to wheat loose smut, and can be managed by use of resistant cultivars and seed treatments (i.e., carbathiin, thiram, triadimenol, tebuconazole). Five studies on hexaconazole were submitted from Manitoba and Alberta. Disease levels in the check were 4–25% incidence of smutted heads. Hexaconazole was applied at 1.0–2.5 g a.i./100 kg seed. When applied at the proposed rate of 1.5 g a.i./100 kg seed, hexaconazole was very effective (100% control) against loose smut. Lower rates were equally effective, but only in three of five trials.

The proposed claim of control of barley loose smut is supported.

7.1.4.4 Effectiveness against barley covered smut (*Ustilago hordei*)

Barley covered smut affects grain by contamination of seed at harvest, and subsequently causes seedling infection at germination. It is managed by use of resistant cultivars and seed treatments (i.e., carbathiin, thiram, maneb, triadimenol). Six studies were submitted from Alberta and Ontario. Hexaconazole was assessed at 1.0–2.0 g a.i./100 kg seed. At the proposed rate (1.5 g) hexaconazole was very effective in controlling covered smut (100% control) in five of six trials. Although disease levels were generally low, there was adequate disease pressure (3–18% smut in the check) in three of these trials.

The claim of control of barley covered smut is supported.

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

There are no available reports of commercial scale resistance to hexaconazole. This active ingredient, however, is chemically related to other triazole fungicides currently registered for use on cereals in Canada (i.e., triadimenol, tebuconazole, difenoconazole, propiconazole). Some cross-resistance within this group has been demonstrated in laboratory tests of the barley and wheat powdery mildew pathogens (*Erysiphe graminis*), which are capable of frequent genetic change. Based on this example, there is some potential for those pathogens noted on the Proseed label to develop resistance to hexaconazole. Although standard resistant-management statements are not yet established in Canada, for good agricultural practice, general recommendations on alternating triazole-based products with fungicides having a different site of action should be added to the Proseed label. For example:

> For resistance management, note that Proseed contains a triazole fungicide. Some loss of disease control may occur over time if hexaconazole or other fungicides in this group are used repeatedly or consecutively in successive years on the same fields, due to development of resistant strains of pathogens. It is recommended that fungicides with a different mode of action be alternated in the disease control program. Contact your local extension agent or crop advisor for further information on resistance management in your area.

7.3 Effects on yield of treated plants or plant products in terms of quantity and/or quality

7.3.1 Effects on quality of plant products

Hexaconazole provides control or suppression of plant diseases that affect quality of grain (i.e., smuts and common root rot). If not controlled, these diseases can result in downgrading due to reduced kernel size or fungal contamination. In addition, the quality of grain for seed use will be improved by treatment due to reduction in seedborne contaminants.

7.3.2 Effects on transformation products

Effect on processed grain (e.g., flour) was not assessed. Generally improved quality may be expected due to use of hexaconazole (see Section 7.3.1).

7.3.3 Effects on yield of treated plants

Yield variables (plant count, tiller number, thousand kernel weights, bushel weights or yield per hectare) were assessed in the majority of field trials. Positive yield effects with hexaconazole can be expected where a yield-limiting disease is present and other determinants such as water, temperature and soil fertility are favourable.

7.4 Phytotoxicity to target plants

Among field-trial reports, phytotoxicity was specifically addressed in 13 trials, and crop-tolerance observations were frequently recorded in the remaining efficacy trials. In a few reports, reduced emergence was noted, but this was most likely due to environmental conditions. Crop tolerance as measured by emergence, vigour and head counts in wheat and barley was good in most reports, using hexaconazole rates up to 10 g/100 kg seed.

7.5 Observations on undesirable or unintended side effects (non-target effects)

No non-target effects are expected from a seed treatment.

7.5.1 Impact on seed viability

In laboratory studies with wheat and barley, germination was not negatively affected after treatment with hexaconazole at up to 2.0 g a.i./100 kg seed and storage for up to 28 months. The label does not, however, recommend storage of treated seed because of a general decline in cereal seed viability after prolonged storage under commercial conditions.

7.5.2 Impact on beneficial and other non-target organisms

Currently, no biological seed treatments for cereals are registered in Canada, and the impact of hexaconazole on beneficial micro-organisms has been not evaluated from an efficacy aspect. Environmental laboratory studies showed, however, that hexaconazole had a minimal effect on soil properties and microbial populations (see Section 6.1.6).

7.6 Conclusions

Proseed, applied at 75 mL product per 25 kg seed, will provide control of loose smut on wheat and barley, control of covered smut of barley, and suppression of common root rot on wheat. Protectant seed treatments and use of resistant varieties have become the main methods used to limit the effect of soil and seedborne diseases. Proseed is not considered critical for control of the labelled diseases on wheat and barley, due to availability of alternative products. Proseed, however, provides another fungicide option for cereal growers, one that has the advantage of a very low rate of active, thus, potentially reducing pesticide loading.

8.0 Overall Conclusions

Proseed, the agricultural product proposed for registration, is a flowable suspension containing 0.5% hexaconazole. Proseed is an effective seed treatment for use on cereals to control loose smut of wheat, true loose smut and covered smut of barley, and to suppress common root rot of wheat. Proseed may be applied at 75 mL/25 kg seed (1.5 g hexaconazole/100 kg seed) in either commercial seed-treatment plants or on-farm treating equipment. Proseed provides another fungicide option for cereal growers, one that has the advantage of a very low application rate of active ingredient.

Hexaconazole was of low acute toxicity by the oral, dermal and inhalation routes to rats and slightly to moderately toxic by the oral route to mice. It was non-irritating to rabbit skin, slightly irritating to rabbit eyes and was considered a potential dermal sensitizer in guinea pigs.

Hexaconazole has an effect on lipid metabolism, which is manifested in altered clinical chemistry and hepatic pathology (hepatocytic lipid). Increased testicular atrophy and increased incidence of Leydig cell tumours were observed in high-dose male rats. This was considered a threshold response dependent on abnormal gonadotrophic stimulation. High-dose males also had bile-duct proliferation and fat vacuolation in the adrenal cortex. The most sensitive species and study for this range of effects was the chronic rat-dietary study, with a NOEL of 0.47 mg/kg bw/d in males and 0.61 mg/kg bw/d in females. There were no adverse effects on reproductive performance, or evidence of teratogenicity or mutagenicity in the submitted studies. Fetotoxicity in the form of delayed ossification, however, occurred in the rat and rabbit teratology studies in the absence of maternal toxicity.

The rat reproduction study was selected as the most relevant for occupational risk assessment for all the proposed use scenarios. The MOEs for all commercial seed-treatment workers, on-farm seed treaters and those planting treated seed were determined to be acceptable, provided recommendations regarding personal protective clothing are adopted.

An ADI for hexaconazole of 0.005 mg/kg bw is recommended, based on the NOEL from the chronic rat study of 0.5 mg/kg bw/d and a 100-fold safety factor. An ARfD was set for hexaconazole using the NOEL of 2.5 mg/kg bw/d based on fetotoxicity in the absence of maternal toxicity observed in the rat teratology study and a 300-fold MOE.

The risk assessments for both occupational and food exposure have provided additional MOEs for the toxicology endpoints of concern identified in the rat, which were selective fetotoxicity, testicular atrophy and Leydig cell tumours.

The plant metabolism study indicated that the major metabolites in grain were triazole TA and TAA. The residue of hexaconazole in grain consisted of 0.002 ppm (0.7% of the TRRs). The (2,5-diol) metabolite was the major component in the straw. Plant metabolism studies indicated that there were no significant novel wheat plant metabolites when compared to goat or rat metabolic profiles.

The animal metabolism studies showed that the ^{14}C-hexaconazole dose fed in the diet was excreted mainly via feces and urine. Residue levels in cereal commodities grown from treated seeds were under the LOQs; therefore, no animal feeding study was submitted. Maximum residue limits would not be needed for meat, milk and eggs. The residues of hexaconazole in meat, milk and egg, however, will be covered under 0.1 ppm of the general Regulations B.15.002(1).

Results of the supervised residue trials conducted in four provinces in Canada indicated that when spring wheat and spring barley grown from seeds were treated with hexaconazole according to the proposed label rate, residues of hexaconazole were less than the LOQs (0.01 ppm for grain, 0.05 ppm for straw/forage). No measurable residues of metabolites were detected in the forage and straw samples (<0.02 ppm). Residues of triazolyl alanine were #0.09 ppm in untreated and treated spring wheat and barley grain. The residues of triazolyl alanine will be covered under the existing MRL (2 ppm) established for all food crops in Canada.

The PMRA proposes an MRL of 0.1 ppm for wheat and barley grains to harmonize with the Codex MRL. There is no tolerance in the U.S. for hexaconazole in grain at this time; therefore, a potential exists for a trade irritant to arise should hexaconazole residues be found in Canadian grain for export. The submitted residue data suggest, however, that in commercial practice, a trade irritant is unlikely to result from treatment of cereal seed according to the Proseed label.

Potential exposure to hexaconazole in the diet was determined not to result in any health concerns for human subpopulations, including infants and children. The PDIs for all human subpopulations, including infants and children, are all below 20 % of the ADI.

Hexaconazole was not susceptible to chemical hydrolysis or to phototransformation, and was not likely to volatilize from water or moist soil. Microbial action was important in the transformation of hexaconazole in soils. Laboratory aerobic soil studies demonstrated that hexaconazole was persistent in loamy sand soil and moderately persistent in sandy loam and silty clay loam soils. A major transformation product observed was 1,2,4-triazole. Laboratory studies also showed that hexaconazole was persistent in anaerobic soil and moderately persistent in aquatic aerobic water-sediment systems. In addition, it was concluded that hexaconazole would be persistent in aquatic anaerobic systems. Canadian field data on dissipation in soil showed that hexaconazole was moderately persistent to persistent. Laboratory soil adsorption and leaching studies and field soil dissipation studies indicated that hexaconazole had negligible leaching potential and is not expected to contaminate groundwater through leaching.

Hexaconazole had no major effect on soil micro-organisms and was not toxic to earthworms and bees. Hexaconazole was practically non-toxic to birds and had moderate acute toxicity to fish and aquatic invertebrates. Chronic toxicity data have indicated that hexaconazole is toxic to *Daphnia magna*, a freshwater invertebrate. Hexaconazole bioconcentrated in fish, but the process was reversible. Bioaccumulation, therefore, is not expected to be a major environmental problem.

Label amendments

Consistent with the above conclusions, the following revisions have been made to the Proseed label:

Product Information includes only claims for control of wheat loose smut, suppression of wheat common root rot, control of barley true loose smut and control of barley covered smut.

Directions for Use includes:

> For resistance management, note that Proseed contains a triazole fungicide. Some loss of disease control may occur over time if hexaconazole or other fungicides in this group are used repeatedly or consecutively in successive years on the same fields, due to development of resistant strains of pathogens. It is recommended that fungicides with a different mode of action be alternated in the disease control program. Contact your local extension agent or crop advisor for further information on resistance management in your area.

“Potential Skin Sensitizer” was added to the front panel

Use Restrictions includes:

> All bags containing treated seed must be labelled or tagged as follows: "This seed has been treated with Proseed fungicide that contains hexaconazole. Wear a long sleeved shirt and long pants and protective gloves when handling treated seed."

Precautions section includes:

> Commercial Seed Treatment: Treat in a well-ventilated area. Wear coveralls over a long-sleeve shirt and long pants, chemical-resistant gloves and a dust mask or respirator fitted to exclude dust.
>
> Planting Treated Seed: Wear long-sleeved shirt and long pants and protective gloves.
>
> On-Farm Seed Treatment: Wear coveralls over a long-sleeve shirt and long pants and chemical-resistant gloves. In addition, wear a dust mask or respirator fitted to exclude dust if there is manual mixing while treating the seed.

ENVIRONMENTAL HAZARDS section was expanded to:

> This product is toxic to aquatic species. Do not contaminate ponds, lakes, streams or wetlands with rinsate, or when disposing of equipment wash waters. To prevent movement of treated seed and product into adjacent water bodies, use good management practices on sloped land and ensure proper soil incorporation of treated seed at planting.

Toxic Substances Management Policy considerations

Active ingredient

During the review of hexaconazole, the persistence and bioaccumulation potential of this active ingredient were considered. The PMRA found evidence of persistence in the environment, but data from studies on fish and residue levels of hexaconazole in rat and goat tissues, including milk, showed that bioaccumulation was limited. On this basis, the PMRA concluded that hexaconazole does not meet the bioaccumulation criteria for Track 1 classification under the TSMP [1].

Contaminants

Microcontaminants (2,3,7,8-TCDF and octachlorofuran) were reported in batch analyses of hexaconazole technical. The highest level found for these Track 1 contaminants was 76 ppt of 2,3,7,8-TCDF, which is toxicologically equivalent to 7.6 ppt of 2,3,7,8-TCDD. The octachlorofuran was found at 270 ppt, which is toxicologically equivalent to 0.027 ppt of

[1] Regulatory Directive Dir99-03, *The Pest Management Regulatory Agency's Strategy for Implementing the Toxic Substances Management Policy (TSMP)*, March 12, 1999

2,3,7,8-TCDD and, thus, does not contribute appreciably to the total contaminant of toxicological concern.

Overall, the level of these substances is sufficiently low that it would be difficult to monitor any effect of changes to the manufacturing process on the level of contamination. It is unlikely, therefore, that substantial reductions in contaminant level could be achieved by altering the manufacturing method, and the current technical can be considered best available technology.

These low concentrations of 2,3,7,8-TCDF found in hexaconazole technical are not expected to pose a significant dietary health risk to humans and they do not represent a significant risk to health of workers in seed-treatment facilities or when using treated seeds.

The environmental level of 2,3,7,8-TCDF resulting from the proposed use is expected to be far below the current level of detection in soil and the resulting soil levels, even after many years of application, are not expected to present an unacceptable risk to the environment. Post-registration environmental monitoring of soil and water would not provide any useful data since the concentrations of the microcontaminants in these media would not be measurable.

It was concluded that with respect to the proposed use pattern for Proseed, hexaconazole meets the criteria suggested in Dir99-03 for managing a new product containing Track 1 microcontaminants, i.e., the Track 1 substance 2,3,7,8-TCDF can be considered virtually eliminated in this context because:

- the level of 2,3,7,8-TCDD equivalent is very low;
- this level is considered to be as low as can be achieved by best available technology in the manufacture of the technical; and
- the use of Proseed in accordance with the proposed label is not expected to present unacceptable risks to either human health or the environment.

The proposed registration of hexaconazole and Proseed seed treatment is, therefore, consistent with the PMRA's strategy for implementing the TSMP.

Proposed Decision

It is proposed that full registration be granted for hexaconazole technical and Proseed seed-treatment fungicide.

The registrant will be required to submit, on a yearly basis, microcontaminant analytical data from representative batches of the technical grade active ingredient to ensure that the levels remain consistent with the requirements of the TSMP.

At the renewal of this registration, after a period of five years, the product will be subject to a review of any new information relevant to health and environmental risks, batch analyses and availability of alternatives.

List of Abbreviations

a.i.	active ingredient
ADI	acceptable daily intake
ALP	alkaline phosphatase
APDM	aminopyrine-N-demethylase
ARfD	acute reference dose
bw	body weight
CAS	Chemical Abstracts Service
d	day
DEEM™	Dietary Exposure Evaluation Model™
DT_{50}	decline time 50%
DT_{90}	decline time 90%
EC_{50}	environmental concentration 50%
EEC	expected environmental concentration
GC	gas chromatography
GLC	gas-liquid chromatography
I-TEF	International Toxicity Equivalency Factors
K_{ow}	n-Octanol/water coefficient
LC_{50}	lethal concentration 50%
LD_{50}	lethal dose 50%
LOD	limit of detection
LOQ	limit of quantitation
MAS	maximum average score
MOE	margin of exposure
MRL	maximum residue limit
NOAEL	no observed adverse effect level
NOEC	no observed effect concentration
NOEL	no observed effect level
NZW	New Zealand white
PAI	pure active ingredient
PDI	potential daily intake
PMRA	Pest Management Regulatory Agency
ppm	parts per million
ppt	parts per trillion
RAC	raw agricultural commodity
ROC	residue of concern
SGOT	serum glutamate oxaloacetate transaminase
SGPT	serum glutamate pyruvate transaminase
TA	triazolyl alanine
TAA	triazole acetic acid
TCDD	tetrachlorodibenzodioxin
TCDF	tetrachlorodibenzofuran
TEQ	toxic equivalent quantity

TRR	total radioactive residues
TSMP	Toxic Substances Management Policy
U.S.	United States
w/w	weight per weight