Pest Management Regulatory Agency
Agence de réglementation de la lutte antiparasitaire

PRDD95-01

Proposed Regulatory Decision Document

Hexaconazole Wood Preservative
Hexaconazole (Passport®)

This Proposed Regulatory Decision Document (PRDD) outlines a regulatory option proposed for the active ingredient hexaconazole and provides background information on the scientific reviews and commentary that pertain to the proposal.

This document is part of the regulatory management process used by the Pest Management Regulatory Agency in making significant or complex registration decisions concerning pesticides.

Written comments should be forwarded within 60 days of the date of issue of this PRDD to:

Hexaconazole Working Group
Pest Management Regulatory Agency
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1.0 Introduction

The purpose of this document is to provide a summary of data on the new wood preservative active ingredient hexaconazole, and to request informed comments from key stakeholders on a proposed regulatory position for the technical active ingredient and its formulations. Hexaconazole is proposed for use in the lumber antisapstain area.

Passport® refers to a group of fungicide products developed for the protection of lumber by Zeneca Agro, a Canadian member of the Zeneca Inc. Group of England. Hexaconazole is the active ingredient in Passport® formulations. Hexaconazole, a triazole-type pesticide, was developed for use in agriculture and is currently sold in many countries under the trade name ANVIL. ANVIL is not yet registered in Canada for agricultural use. This document deals with proposed antimicrobial use patterns for hexaconazole.

Passport® formulations of hexaconazole have been specifically developed for the protection of those commercial softwood species of lumber that Canada ships to export markets throughout the world.

Freshly cut unseasoned lumber will suffer rapid attack by stain and mould, which results in unsightly discoloration and a significant reduction in product value. In some instances, decay fungi can become a problem during longer-term storage and in transit. In order to prevent such biodeterioration following manufacture, lumber must be chemically treated and/or kiln dried.

2.0 Pesticide Name and Properties

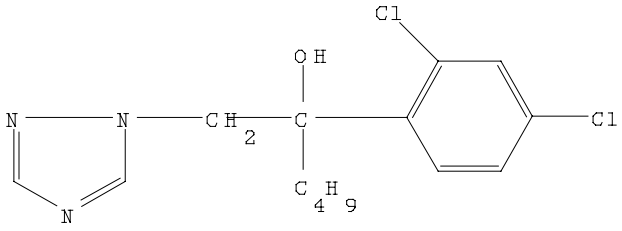
2.1 Pesticide Name

Common Name:	Hexaconazole
Chemical Name:	IUPAC: (RS)-2(2,4-dichlorophenyl) -1-(1H-1,2,4-triazol -1-yl)hexan 2-ol
Trade Names:	Anvil, Passport®
CAS Registry No.:	79983-71-4

2.2 Physical and Chemical Properties

Empirical Formula:	$C_{14}H_{17}Cl_2N_3O$
Molecular Weight:	314.2
Physical Appearance:	white odourless solid
Melting Point:	110-112˚C
Vapour Pressure:	2 X 10 kPa at 20˚C
Octanol/water Partition Coefficient:	3.9 at 20˚C (log K_{ow})

Structural Formula:



Solubility:	At 20˚C
Water	17 mg/L at pH 5.1 (Buffered water)
Methanol	246 g/L
Acetone	164 g/L
Dichloromethane	336 g/L
Toluene	59 g/L
Ethyl acetate	120 g/L
Hexane	0.8 g/L
Stability:	Hexaconazole is stable for at least 29 months at ambient temperature (15-25˚C)

2.3 Formulated Products

Product Name:	Passport® ED
Guarantee:	50 g/L of hexaconazole
Specific Gravity:	0.973
Viscosity:	350 cps
Flammability:	flash point above 30˚C
Storage Stability:	physically and chemically stable (3 years)

Product Name:	Passport® 50SC
Guarantee:	50 g/L of hexaconazole
Specific Gravity:	1.0534
Flammability:	N/A (water based)
Storage Stability:	not determined

Product Name:	Passport® 250SC
Guarantee:	250 g/L of hexaconazole
Specific gravity:	1.100
Flammability:	N/A (water based)
Storage Stability:	Physically and chemically stable (2 years)

3.0 Regulatory Proposal

The Pest Management Regulatory Agency (PMRA) is proposing to grant temporary registration of the technical active ingredient hexaconazole, for use in formulating wood preservatives that are registered under the *Pest Control Products Act.*

The PMRA is also proposing to grant temporary registration for three end-use hexaconazole-based formulations, for protecting wood from fungal organisms. They are Passport® 50SC, Passport® 250SC, and Passport® ED.

These temporary registrations would be contingent upon a commitment by Zeneca Agro, outlined in section 4.5 of this document, to produce some additional studies to develop a satisfactory risk assessment for the hexaconazole antimicrobial use pattern.

3.1 Regulatory Rationale

The proposal, if implemented, would utilize the existing regulatory mandate under Section 17 of the *Pest Control Products Regulations* (temporary registration for pest control products).

The Regulations state:

"The minister may, upon such terms and conditions, if any, as he may specify, register a control product for a period not exceeding one year where the applicant agrees to endeavour to produce additional scientific or technical information in relation to the control product."

The proposal for temporary registration provides for an ongoing regulatory control mechanism which is able to respond to new experience, and data as they are developed.

The proposal recognizes the largely complete and modern data base for hexaconazole and the fact that operator exposure data are unlikely to be developed without a temporary registration being granted.

The proposed registrations may provide an opportunity to maintain or improve Canada's international competitive position by ensuring a greater choice of products for the lumber industry sector.

3.2 Background to the Regulatory Proposal

The consideration of hexaconazole for registration must be put into historical perspective with other products used for sapstain control. In 1988, six chemicals were considered as alternatives to the use of chlorophenates and have been under review on an ongoing basis since that time. That review process includes temporary registrations, re-evaluation, data development and a

consultative decision-making process. Hexaconazole was **not** one of the six chemicals targeted for review by this process because the proposed use and data base (which compares favourably with the data bases developed for the six other chemicals) were submitted more recently.

The PMRA has committed to consultation with stakeholders prior to making a regulatory decision on hexaconazole.

4.0 Summary of Viewpoints and Positions

4.1 Health Assessment

Health evaluators in the PMRA have completed their evaluation of toxicological data for hexaconazole. The studies reviewed included acute toxicity of the technical active ingredient and its formulations. Reviews of toxicokinetics, short-term toxicity, chronic toxicity/carcinogenicity, genotoxicity, reproductive toxicity, teratogenicity and special studies were conducted for the technical active ingredient. An ADI (Acceptable Daily Intake) of 0.005 mg/kg bw was established for hexaconazole. Calculations were made on drinking water exposure based on the established ADI.

Health evaluators indicated that:

a) "The potential contamination of drinking water cannot be fully determined due to a lack of field data on leaching rates from stockpiles of treated lumber...".

b) "A risk assessment of hexaconazole for use on lumber cannot be conducted in the absence of an appropriate exposure study."

c) "It is not expected that the low level of dioxin contamination poses any potential hazard."

d) "The formulants used in the formulations were without toxicological significance."

4.2 Environment Assessment

Environment evaluators in the PMRA have completed a review of environmental data and study exemption rationales submitted in support of hexaconazole, its breakdown products and its formulations. The studies reviewed included physicochemical characteristics, phototransformation in soil, anaerobic biotransformation, aerobic soil biotransformation, and adsorption/desorption of hexaconazole in soils. Field dissipation studies for hexaconazole were conducted in Ontario and British Columbia. Soil and water

analytical procedures for hexaconazole, life cycle *Daphnia magna* (hexaconazole) and acute toxicity to rainbow trout (formulation Passport® 50SC) were assessed. A review and discussion of the chemical impurities, including dioxins and 2,3,7,8 tetracholorodibenzofuran (TCDF), were carried out. Study reviews on the major breakdown product, 1,2,4,-triazole, were conducted. They included soil column leaching, field soil dissipation, residue analysis, toxicity to earthworms, toxicity to fish, toxicity to *Daphnia magna*, and algae.

Specific concerns were identified for the following information gaps:

a) There is a lack of field data on the leaching rates from stockpiles of hexaconazole-treated wood, and on expected environmental concentrations in runoff water (storm water) and in adjacent water bodies.

b) There is a need for an analysis of leachate from lumber stockpiles for microcontaminants, including 2,3,7,8 -TCDF, in rainwater leachate, collected directly below the treated lumber.

c) There is an absence of specific information concerning toxicity to aquatic biota of Passport® ED formulation.

Environment evaluators indicated that hexaconazole and its major transformation product, 1,2,4-triazole, are expected to be persistent in the environment (in both soil and water/sediment systems).

4.3 Fisheries Assessment

Fisheries and Oceans Canada (DFO) has completed a review of data as it pertains to potential impact on fish, fish habitat and fishery resources. Their review included the following: an assessment of studies on four fresh water fish species; growth, survival and hatching success studies on the fathead minnow; acute and chronic *Daphnia magna* studies; bioconcentration studies for bluegill (^{14}C-labelled hexaconazole); 96-hour LC_{50} study for mysid shrimp; 48-hour LC_{50} for Pacific Oyster; and an algae toxicity study.

Fisheries and Oceans Canada's advisory statement to the PMRA read "It is unlikely that hexaconazole will pose a hazard to fish and fish habitat; therefore DFO is prepared to support temporary registration of hexaconazole and its end-use products, Passport® SC and Passport® ED, for the proposed use pattern in sapstain control."

DFO identified the following three information gaps that would require some resolution before that Department could support **full** registration status for hexaconazole-based products:

a) A study on the leaching of hexaconazole from stockpiles of hexaconazole treated lumber;

b) Development of an analytical method for determination of hexaconazole residues in fish;

c) Submission of any available data on the toxicity of the Passport® ED formulation to aquatic biota.

4.4 Value Assessment

Value evaluators in the PMRA completed the review of efficacy data submitted in support of hexaconazole-based products for lumber sapstain control. The review of data included an (in vitro) study on the technical active; field trials using conventional spray tests (portable spray unit) of Passport® SC formulations; on-site mill trials using conventional Passport® SC formulations; a spray trial conducted by Forintek Canada on a tank mix of hexaconazole/ thiabendazole; field dipping application trials using hexaconazole/thiabendazole (J.D. Irving Lumber Mill, New Brunswick); two mill shipping trials to Florida (via Panama) and Japan on hexaconazole/thiabendazole tank mix; field trials using hydraulic electrostatic spray of Passport® ED and Electrodyne application of Passport® ED formulation (Forintek Canada Corp); on-site field trials at lumber mills using hexaconazole/thiabendazole tank mix applied by a portable spray unit; a field shipping trial (Florida via Panama) on Passport® ED applied by electrodyne (MacMillan Bloedel).

Hexaconazole primarily controlled only two (moulds and wood decay fungi) of the three groups of fungal organisms usually associated with degradation of freshly sawn lumber. Control of the third group, wood staining fungi, ranged from poor to industrially acceptable, depending on the formulation and application method.

Passport® ED, a 5% oil-based formulation of hexaconazole designed specifically for electrostatic application, provided the best performance results of formulations containing only hexaconazole. Researchers with MacMillan Bloedel who conducted tests with the Passport® ED formulation suggested that its use at a mill may depend on “A means to reduce the solvent smell of the ED formulation” and development of a “Low volume spray application system which can survive the rigors of mill operation.”

The Passport® SC formulations may prove to be useful to industry for tank mixing purposes with other pesticides which might be registered in the future for that purpose. Currently there are no products registered for tank mixing with hexaconazole. Both Passport® SC formulations failed to give consistent performance levels for a range of wood species at the target deposition level.

It is probable that combinations of active ingredients will be necessary to broaden the control spectrum. Data were presented that compared the Passport® formulations to untreated controls and standard wood protectants. No field data were presented that allowed a comparison of the individual performance of hexaconazole with that of thiabendazole, the active chosen for the experimental tank mix.

The following conclusions were drawn from the data:

a) Hexaconazole is effective in controlling wood decay fungi and moulds on freshly sawn lumber when applied at a target deposition rate of between 30 and 40 micrograms/cm^2 of lumber surface.

b) Passport® ED formulation performed to industrially acceptable levels when applied to freshly sawn lumber by specialized electrostatic application technology.

c) Passport® 50SC (50 g/L) and Passport® 250SC (250 g/L) failed to consistently perform to industrially acceptable levels when applied by conventional dip or spray technology. In most instances, staining fungi were poorly controlled.

d) Experimental tank mixtures of Passport® in combination with thiabendazole consistently provided excellent performance and met industrially acceptable levels when applied by conventional techniques.

The PMRA has a responsibility under the *Pest Control Products Act* to assess the merit and value of pesticides. The merit of hexaconazole will be determined using the efficacy studies and the written comments of the user industry. A range of potential markets, based on the diversity of wood species, climatic conditions, product types, shipping and storage conditions and individual sawmill requirements, will be considered.

The British Columbia Council of Forest Industries (COFI) and individual manufacturers encourage industry self-reliance in assessing products for lumber manufacturer needs and client requirements. The PMRA supports this approach and a proposal to grant temporary registration to hexaconazole would provide some additional opportunities for an ongoing assessment of the merit of hexaconazole by the forest products industry.

4.5 Zeneca Agro

Zeneca Agro has responded to federal departments' concerns in the following manner:

a) Zeneca Agro has indicated that it is part of a consortium of nine companies addressing Canadian operator exposure for antisapstain uses and has committed to providing an adequate exposure study for their hexaconazole products. This commitment places Zeneca Agro and other registrants under an equal regulatory obligation.

b) Zeneca Agro has committed to produce field data on leaching rates of hexaconazole from stockpiles of treated lumber using PMRA protocols; furthermore, they will analyze the leachate for microcontaminants as requested.

c) Zeneca Agro has supplied PMRA with all available information on the toxicity of the Passport® ED formulation, including an acute toxicity study of rainbow trout for a similar formulation containing 10 g/L of hexaconazole.

d) Zeneca Agro has indicated that they have **no** further plans, at this time, to develop an analytical method for the determination of hexaconazole residues in fish.

e) Zeneca Agro has agreed to restrict efficacy claims for Passport® SC formulations only to the control of mould and decay fungi and to develop appropriate label statements to inform the user.

f) Zeneca Agro has requested, on the basis of the above commitments, a registration for Technical Hexaconazole and the end-use products Passport® ED, Passport® 50SC, and Passport® 250SC.

5.0 Health

5.l Chemical Description

Hexaconazole, empirical formula $C_{14}H_{17}Cl_2N_3O$, molecular weight 314.2, is a conazole fungicide. The technical product has a purity of 90%. Major impurities are triazol-4-yl isomer and methanol. Batch analyses have indicated some minor contamination of hexaconazole with dioxins and furans. In five batch analyses, total tetrachlorodibenzodioxin (TCDD) levels ranged from non-detectable to 2300 parts per trillion (ppt) and tetrachlorodibenzofuran (TCDF) levels ranged from 520 to 3300 ppt. Hexaconazole was not found to contain 2,3,7,8-TCDD, a dioxin of significant toxicological concern. The highest level of 2,3,7,8-TCDF detected (76 ppt) is toxicologically equivalent to a 2,3,7,8-TCDD level of 7.6 ppt or pg/g. It is not expected that the low level of dioxin contamination would pose any potential hazard.

5.2 Background

Hexaconazole is a new active ingredient (ai) from Zeneca Agro proposed for commercial control of decay, mould and sapstain on fresh-cut lumber, as an alternative to the chlorophenols. It is a protectant and eradicant against a broad range of fungi in which it is an inhibitor of ergosterol biosynthesis.

Zeneca Agro is currently seeking registration for the technical active and for the formulations Passport® 50SC (guarantee of 50 g/L), Passport® 250SC (guarantee of 250 g/L) and Passport® ED (guarantee of 50 g/L). The formulations are manufactured in England and shipped to Canada.

A complete toxicology data base was reviewed, but an occupational exposure study is still pending the applicant.

5.3 Evaluation

5.3.1 Product Chemistry

Technical hexaconazole has a purity of 90%. All major toxicity studies were conducted with technical hexaconazole of relevant purity. Formulation studies were conducted with Passport® 50SC (containing 5.27% hexaconazole), Passport® 250SC (containing 25.26% hexaconazole) and Passport® ED (containing 5.71% hexaconazole). The formulants used in the formulations were without toxicological significance.

5.3.2 Toxicology

a) Toxicokinetics - Technical

Hexaconazole was well absorbed and excreted after oral administration within the Alderly Park Wistar derived (Alpk:AP) rats 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 faeces 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. The initial

excretion was slightly slower in the high dose animals; however, no notable elimination differences were recorded between the dose groups after 72 hours.

Repeated oral administration (14 days) of 1 mg/kg bw/day 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 Alpk:AP 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 with 81% excreted in males compared to 41% in females (phenyl-labelled), and 75% excreted in males compared to 47% in females (triazole-labelled). The relative proportions of biliary metabolites was comparable between males and females. 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 faeces in both conjugated and unconjugated forms. The remainder was reabsorbed and eliminated via the urine. These urinary products 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.

In a dermal absorption study, male rats (Alpk:AP) were dosed with ^{14}C-phenyl-labelled hexaconazole as the end-use aqueous formulation (GFU399, 12SC) on a shaved area of the back at doses of 1.0, 0.1, 0.01 and 0.001 mg/cm^2. The 12SC formulation has a guarantee of 120 g/L and has basically the same constituents as the two SC formulations proposed for registration. 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 then sacrificed after the skin wash. Excreta, skin at the application site, blood and plasma, carcass, cage wash, swabs and site covers were analyzed for ^{14}C content to determine total dermal absorption. By 24 hours, 4.3%, 10.4%, 30.4% and 61.3% of the 1.0, 0.1, 0.01 and 0.001 mg/cm^2 doses, respectively, were absorbed. Since no estimate of dermal deposition in workers occupationally exposed is available, it is unknown which dose level most closely represents the dermal exposure expected by workers.

b) Acute Toxicity - Technical

By the oral route, hexaconazole was slightly toxic to Alpk:AP rats (male LD_{50} =2189 mg/kg bw, females LD_{50}=6071 mg/kg bw) and to Alpk mice (LD_{50} =557-1060 mg/kg bw). It was not acutely toxic to Alpk:AP rats via the dermal route (LD_{50}>2000 mg/kg bw). The technical product was non-irritating to New Zealand White (NZW) rabbit skin but slightly irritating to NZW rabbit eyes. It was considered a skin sensitizer in Dunkin Hartley guinea pigs via the Maximisation method. The gravimetric 4-hour inhalation toxicity (LC_{50}) of hexaconazole exceeded 5.9 mg/L in the Alpk:AP rat (nose-only exposure).

c) Acute Toxicity - Formulation

Passport® 50SC formulation was not acutely toxic to Alpk:AP rats via the oral route (LD_{50}>5000 mg/kg bw) and dermal route (LD_{50}>2000 mg/kg bw). It was a minimal skin irritant and mild eye irritant in NZW rabbits and did not produce a sensitization response in Dunkin Hartley guinea pigs via the Buehler method. A 4-hour inhalation study with a 12% SC (containing 12% technical hexaconazole and identical formulants as 50SC formulation) showed a gravimetric LC_{50} in excess of 4.16 mg/L in Alpk:AP rats (nose-only exposure).

Passport® 250SC formulation was not acutely toxic to Wistar rats via the oral route (LD_{50}>5000 mg/kg bw) and dermal route (LD_{50}>2000 mg/kg bw). The formulation was a mild skin and eye irritant in NZW rabbits and produced a mild sensitization response in Dunkin Hartley guinea pigs via the Buehler method. A data waiver was granted for the inhalation study due to the similarity in composition and end-use spray concentrations to a 12% SC formulation for which a study was provided (see above).

Passport® ED formulation was slightly toxic to Wistar rats via the oral route (LD_{50}>3500 mg/kg bw) and not acutely toxic via the dermal route (LD_{50}>2000 mg/kg bw). It was a severe skin irritant and mild eye irritant in NZW rabbits. It was a mild skin sensitizer in Dunkin Hartley guinea pigs via the Buehler method. The gravimetric 4-hour inhalation toxicity (LC_{50}) of Passport® ED exceeded 4.64 mg/L in the Wistar rat (nose-only exposure).

d) Short-Term Toxicity - Technical

A 90-day dietary study was conducted with hexaconazole in Alpk:AP rats with 20 rats/sex/group at dose levels of 0, 50, 500 and 5000 ppm. A No Observed Adverse Effect Level (NOAEL) was demonstrated at 50 ppm (equivalent to 2.5 mg/kg bw/day).

In both sexes at 5000 ppm, decreases were recorded in the following parameters: weight gain, haematocrit, clotting parameters, triglycerides and liver weights. Increases were recorded in lymphocytes, albumin and total protein. Males also had increased serum glutamic pyruvic transaminase (SGPT) levels and decreased glucose levels. The liver (fatty changes) and adrenal (cortical parenchymal vacuolation) were identified as target organs at histopathological examination.

At 500 ppm there were similar effects on weight gain, haematology, clinical chemistry, and pathology of the liver and adrenal. These effects were primarily restricted to male rats indicating that males appeared to be more sensitive. All animals, including those at 50 ppm, exhibited an increase in hepatic aminopyrine-N-demethylase (APDM) activity but this was considered an adaptive response to exposure.

In a 21-day dermal study with hexaconazole, five Alpk:AP rats/sex/group had 0, 100, 300 or 1000 mg/kg bw/day applied to intact shaved backs for 6 hours/day under occlusion. There were no significant treatment-related systemic effects and no significant irritation. The No Observed Effect Level (NOEL) was 1000 mg/kg bw/day.

In a 90-day oral study, Beagle dogs (four dogs/sex/group) received hexaconazole by capsule at dose levels of 0, 5, 25, 75 (later reduced to 50) or 125 mg/kg bw/day. Short-term administration (8 days) of 125 mg/kg bw/day was overtly toxic causing mortality, clinical signs (vomiting, hypoactivity, gait abnormalities and bloody faeces), weight loss, clinical chemistry findings (increased SGPT, SGOT [serum glutamic oxaloacetic

transaminase] and alkaline phosphatase), increases in liver weight and pathological changes of the liver (increased incidence of cytoplasmic lipid accumulation of parenchymal cells) and the heart (myocarditis). Dogs dosed with 75 mg/kg bw/day also showed toxicity through similar clinical signs, weight loss and reduced food consumption. Dose level reduction to 50 mg/kg bw/day at day 11 allowed for recovery from these observations. However at sacrifice, increased serum enzymes, decreased urea, calcium, albumin, cholesterol and triglycerides and hepatic pathology consistent with altered lipid metabolism were recorded. Hepatotoxicity, supported by pathology and clinical chemistry data (increased serum enzymes and decreased urea, albumin, cholesterol and triglycerides), was also evident in dogs dosed with 25 mg/kg bw/day. The NOEL for this study was 5 mg/kg bw/day.

In a one-year oral study, four Beagle dogs/sex/group received doses of 0, 2, 10 or 50 mg/kg bw/day of hexaconazole by capsule. Dose levels of 50 mg/kg bw/day resulted in a slight initial depression in weight gain (males only), increased platelets, depressed clinical chemistry values (albumin, total protein, calcium, cholesterol and triglycerides), increased enzyme activity (alkaline phosphatase and SGPT), increased liver and kidney weights and fatty accumulation in the liver. Dogs receiving 10 mg/kg bw/day exhibited increased platelets (females only), increased liver weights and fatty changes in the liver (males only). Overall, males showed a slightly higher sensitivity to hexaconazole than did female dogs. The NOEL was set at 2 mg/kg bw/day.

e) Chronic Toxicity/Carcinogenicity - Technical

In a two-year dietary study, C57BL CD-1/Alpk mice (50 mice/sex/group) received 0, 5, 40 or 200 ppm of hexaconazole. Concentrations of 200 ppm resulted in decreased body weight gain (males), reduced food intake (females) and haematological changes in erythrocyte parameters (increased haemoglobin, erythrocytes and haematocrit) in both sexes. The liver was the target organ with increased relative weight and fatty changes noted at pathology. Vacuolation of the renal tubular cortex was also noted in the high dose males. Slight elevations in the incidence of three tumours (hepatocellular adenoma and carcinoma and pituitary adenoma) in the 200 ppm males were considered incidental. Thus, hexaconazole was not

considered to be oncogenic in mice. The NOEL for chronic toxicity was set at 40 ppm equal to 4.7 mg/kg bw/day in males and 5.9 mg/kg bw/day in females.

In a two-year dietary study, Alpk:AP rats (52 rats/sex/group) received 0, 10, 100 or 1000 ppm of hexaconazole. An additional 12 rats/sex/group were sacrificed at 52 weeks. Male rats administered 1000 ppm hexaconazole showed the following: reduced weight gain and food intake, reduced triglyceride levels, increased alanine transaminase levels, transient increases in serum and urinary protein, increased APDM activity and increased liver weight (at interim and terminal sacrifice). At histopathology, fatty changes of the liver, hepatic hypertrophy, bile duct proliferation, fat vacuolation of the adrenal cortex and testicular atrophy were observed more frequently in the 1000 ppm males than in the controls.

High-dose females showed greater toxic effects on body weight gain and food intake than their male counterparts but less pathological evidence of toxicity. These animals also demonstrated decreased triglycerides, increased cholesterol, transient increases in urea and protein levels, increased APDM activity and increased organ weights at interim sacrifice (liver, adrenal and kidney) and terminal sacrifice (liver) compared to controls. Histopathological changes of the 1000 ppm females were limited to fatty changes of the liver relative to controls.

The 100 ppm male rats exhibited increased APDM activity and hepatic cytoplasmic vacuolation whereas females at this level displayed decreased weight gain and increased liver, adrenal and kidney weights at interim sacrifice.

A significant increase in benign Leydig cell tumours was recorded in the 1000 ppm males compared to the controls (Chi-square test $p=0.048$, trend test $p=0.007$, trend test adjusted for intergroup mortality $p=0.019$). The high dose incidence exceeded all historical control incidence save for one study conducted 6 years previously. The significance of these tumours is discussed in the Toxicological Summary.

No treatment-related effects were noted in the 10 ppm animals, thus the NOEL for chronic toxicity was set at 10 ppm (equal to 0.47 mg/kg bw/day in males and 0.61 mg/kg bw/day in females).

f) Genotoxicity - Technical

Hexaconazole did not demonstrate genotoxic potential in the following assays: Ames, in vitro forward mutation in L5178Y mouse lymphoma cells, mouse micronucleus, mouse dominant lethal, in vitro cytogenetics in human lymphocytes and unscheduled DNA synthesis in rat hepatocytes.

g) Reproductive Toxicity - Technical

In a two-generation reproduction study (two litters in the second generation), Alpk:AP rats (15 males and 30 females/group) were given dietary levels of 0, 20, 100 or 1000 ppm of hexaconazole for at least 11 weeks prior to mating. Levels of 1000 ppm produced clear evidence of parental toxicity. Reductions in body weight gain and increased liver weights were recorded in the F0 and F1 high dose animals compared to controls. An increase in histopathological changes of the adrenal and liver in these animals was generally limited to fatty changes in these tissues. No effect on reproductive performance was noted in the 1000 ppm animals.

In the parental animals receiving 100 ppm, histopathological changes in the liver and to a lesser extent, the adrenal, were recorded. These changes are consistent with the effects noted at the higher dose level and are thus considered treatment related. No parental toxicity was recorded at 20 ppm.

Toxicity was also demonstrated in the offspring with reductions in pup weight gain in the F1 and F2B 1000 ppm groups. Liver weights were significantly increased in all offspring at the 1000 ppm dose level compared to controls. Histopathological changes were evident in the 1000 ppm pups in the F1 generation (adrenal and liver) and F2 generation (liver) and consisted of fatty changes. An increase in fatty changes of the liver was also noted in the 100 ppm F1 and F2A litters. No treatment-related effects on offspring were noted at 20 ppm.

The NOEL for reproductive toxicity was set at the highest dose of 1000 ppm, equivalent to 50 mg/kg bw/day. The NOEL for general systemic toxicity was set at 20 ppm, equivalent to 1 mg/kg bw/day based on fatty changes of the liver (parental animals and offspring) and adrenal (parental animals).

h) Teratogenicity - Technical

Twenty-four mated female Alpk:AP rats/group received hexaconazole by gavage at dose levels of 0, 2.5, 25 or 250 mg/kg bw/day from day 7-16 (inclusive) of gestation. At 250 mg/kg bw/day, maternal animals exhibited clinical signs (piloerection and coat staining), reduced weight gain and food intake and an increased post-implantation loss attributable to an elevation in late intrauterine deaths. At the same dose level, fetuses displayed reduced body weights and increased visceral (pelvic dilation of the kidney and kinked ureter) and skeletal (delayed ossification) anomalies. No major treatment-related terata were evident at this dose level. At 25 mg/kg bw/day, skeletal anomalies (delayed ossification, extra 14th ribs) were evident in the fetuses compared to controls. No treatment-related effects were observed at 2.5 mg/kg bw/day. Thus, the NOEL's set for teratogenicity, maternal toxicity and fetotoxicity were 250, 25 and 2.5 mg/kg bw/day respectively.

Eighteen artificially inseminated female NZW rabbits/group received hexaconazole at doses of 0, 2.5, 12.5 or 50 mg/kg bw/day by gavage from day 7-19 (inclusive) of gestation. At the highest dose level, 50 mg/kg bw/day, no treatment-related effect was observed on the maternal animal or the fetus. The NOEL for maternal toxicity, fetotoxicity and teratogenicity was set at 50 mg/kg/day but it was questionable if the animals were sufficiently challenged with the dose levels tested.

In a range-finding study, ten artificially inseminated female NZW rabbits/group received hexaconazole at dose levels of 0, 200, 300 or 400 mg/kg bw/day by gavage from day 7-19 (inclusive) of gestation. The top two dose groups were terminated early due to severe toxicity (deaths, abortions and morbidity). Mortality, total litter resorptions and weight loss at 200 mg/kg bw/day also suggested excessive toxicity.

Twenty artificially inseminated female NZW rabbits/group received hexaconazole at dose levels of 0, 25, 50 or 100 mg/kg bw/day by gavage from day 7-19 (inclusive) of gestation. No maternal toxicity was evident at the highest dose level resulting in a NOEL of 100 mg/kg bw/day. A NOEL for fetotoxicity was set at 50 mg/kg bw/day based on the observation of holes in the parietal bone of the skull of fetuses in the high dose group (9/142 fetuses and 4/17 litters). The

incidence of this minor defect exceeded historical data (3/1669 fetuses and only one occurrence per study) and was considered to have resulted from an ossification delay. No major treatment-related terata were recorded in this study, therefore the NOEL for teratogenicity was set at the highest dose of 100 mg/kg bw/day.

i) Special Studies

A limited study was conducted to examine the effects of hexaconazole on the steroidogenic function of isolated Leydig cells. Leydig cell cultures from Alpk:AP rats were incubated with hexaconazole or ketoconazole (an imidazole drug) with or without stimulation with human chorionic gonadotrophin for 24 hours and analyzed for testosterone, progesterone and 17-OH progesterone. Both treatments resulted in decreased testosterone production compared to controls, with initial increased progesterone levels although cells were treated with much higher dose levels of hexaconazole (70X) than ketoconazole. Ketoconazole is known to cause Leydig cell hypertrophy through an inhibition of testosterone biosynthesis. The results of this study suggest a similar hypothesis for hexaconazole action in so far as steroid metabolism is affected by treatment.

j) Toxicology Summary

Technical and formulated hexaconazole were found to present a low acute hazard to laboratory animals by oral, dermal and inhalation routes of exposure. Irritation potential to the skin was variable with the technical being non-irritating and the formulations ranging from minimally irritating (Passport® 50SC) to severely irritating (Passport® ED). All formulations and technical product were mildly irritating to rabbit eyes. Skin sensitization potential was demonstrated with the technical product, Passport® 250SC and Passport® ED.

Hexaconazole is a member of the azole family of compounds which are known 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 (fatty changes). Given the role and origin of bile salts and the importance of the biliary pathway with hexaconazole, it is also noteworthy that high doses contributed to increased bile duct proliferation (in male rats). Similarly, the fat vacuolation observed in the adrenal cortex of animals treated

with high doses of hexaconazole may be a result of decreased hydroxylation and subsequent accumulation of cholesterol which has been observed with other azoles. The most sensitive species and study for this range of effects was the chronic rat study in which a NOEL of 10 ppm [equal to 0.47 mg/kg bw/day (males) and 0.61 mg/kg bw/day (females)] was noted.

No effect on reproductive performance was noted in rats receiving dietary doses up to 50 mg/kg bw/day. Likewise, no teratogenicity was observed in the rat (250 mg/kg bw/day) or rabbit (50 mg/kg bw/day). The lowest NOEL for fetotoxicity was in the rat at 2.5 mg/kg bw/day.

Inhibited steroid synthesis has also been documented with azoles. By inhibition of the hydroxylation of cholesterol, testosterone synthesis is also inhibited and it is this decrease that could account for the increased testicular atrophy noted in male rats receiving high doses of hexaconazole. A compensatory increased function of the Leydig cells to maintain functional testosterone levels could lead to the increased incidence of Leydig cell tumours observed in the high dose males in the rat oncogenicity study. The tumours were benign, non-life threatening and the response was marginal. Given that no positive evidence for mutagenicity was recorded and that the second species (mouse) did not exhibit any tumorigenic concerns, it is believed that the occurrence of Leydig cell tumours is dependant on abnormal gonadotrophic stimulation. Consequently, this is a “threshold response” and margins of safety based upon non-tumourigenic endpoints should be utilized.

5.3.3 Food Exposure

a) Acceptable Daily Intake (ADI)

An 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/day and a 100-fold safety factor. In addition, this ADI provides a margin of safety of 500 for the lowest NOEL for fetotoxicity in rats of 2.5 mg/kg bw/day. JMPR (1990) also set an ADI of 0.005 mg/kg bw.

b) Dietary Risk Assessment

Overall there is insufficient information available with respect to potential residues in food products resulting from the use of

treated wood in the construction of food-holding containers or storage facilities to permit comment on the safety of dietary exposure to such residues. In the absence of such data, a label statement against the use of hexaconazole- treated wood in the construction of food holding containers or food storage facilities is considered warranted. Additionally, a label statement warning against contact of treated sawdust and other wood with domestic animals or useful living plants is considered warranted.

5.3.4 Drinking Water Exposure and Risk Assessment

a) Based on the ADI of 0.005 mg/kg bw/day, an objective concentration can be calculated as approximately 22 µg/L, assuming an adult consumer with 10% allocation to drinking water. At this level, the intake of a bottle-fed infant would be approximately 60% of the ADI.

b) No monitoring data were found on residues of hexaconazole or its transformation product 1,2,4-triazole in surface water, drinking water and ground water.

c) Hexaconazole has a low water solubility (18 mg/L at 20°C) which does not vary with pH. Hexaconazole and its major transformation product 1,2,4-triazole is stable to photolysis in water and to phototransformation on soil. Both are relatively non volatile under field conditions. Hexaconazole has low mobility in soils while 1,2,4-triazole is highly mobile in soils. However, both are expected to be persistent in the environment (in both soil and water/sediment system). The high solubility in water (630,000 mg/L at 20°C)and low K_{ow} of 1,2,4-triazole indicate a limited potential for bioconcentration. In field studies in Ontario and British Columbia, hexaconazole was persistent in sandy and loam silt soil when applied to bare soils. It has negligible leaching potential in loam silt soil. In field studies the 1,2,4-triazole was also persistent (50% decline time in eight months) in silt loam soil when applied in the fall season and after 13.5 months, 60%, 31% and 7.5% of the residues were found in the top 37.5 cm section, 7.5 to 30 cm section and 30 to 60 cm section respectively. However, the potential contamination of drinking water cannot be fully determined at present because of the lack of field data on leaching rates from stockpiles of treated lumber and on environmental concentrations in run-off water and in adjacent surface water bodies.

5.3.5 Occupational Exposure

a) Qualitative Exposure Assessment

Three formulations of hexaconazole are being considered as part of the submission: Passport® 50SC, Passport® 250SC and Passport® ED. Passport® 50SC and 250SC would be applied with conventional equipment and Passport® ED would be applied with an Electrodyne technology which is not yet available in Canada. Passport® ED controls mould and decay fungi as well as sapstain. The SC formulations would be used to control mould and decay fungi and would be used mostly in the interior of British Columbia (B.C.). Passport® 50SC and 250SC are not effective for sapstain control and consequently would not be applied on lumber destined for export.

Prior to the late 1980's, chlorophenate compounds were used extensively in Canadian sawmills and planermills to control moulds and sapstain fungi on export lumber. Qualitative studies available for mostly chlorophenate compounds can be used to provide a comparative qualitative assessment of exposure.

Occupational exposure to chlorophenates was monitored and reported by B.C. Research, under contract for PMRA. Exposure to chlorophenates was monitored in various job categories within two mills by analyses of urine, dermal patches, gloves and air samples taken before, during and after a typical work day in B.C. sawmills and planermills. Urinalysis was based on spot sample collection only and could not be used quantitatively as an estimate of body dose.

The job categories receiving highest exposure to pentachlorophenol and tetrachlorophenol based on urinary excretion were graders, chainsorters, and dip tank carrier drivers in both the sawmills and planermills. Chlorophenates were detected on all dermal monitoring patches placed on the outside of clothing; under the outer layer of clothing of all participants; and on the skin of dip tank carrier drivers, chain pullers, and graders in both mills. Air concentrations were comparatively low; however, the highest levels were found in the cab of the dip tank carrier, sawmill grading area, and the area near sawmill spray boxes. Other studies reviewed by Teschke et al. (1992) also indicated that inhalation exposure to chlorophenates was relatively low. The interior of all gloves were contaminated, with heaviest contamination in those of the graders.

The trials demonstrated that chlorophenate compounds permeate normal work clothing and are absorbed by the skin. Analysis of urine showed highest levels of conjugated or free chlorophenates in workers whose job categories provided extended contact with treated lumber. Jobs which required short term, intermittent contact with the chemicals subsequently showed lower urinary concentrations. However, it was noted that individuals not involved in lumber treatment (i.e., office and lab staff at B.C. Research) also showed detectable low levels of chlorophenates in urine.

It was noteworthy that participating mill employees showed considerable reduction in exposure levels in a repeat study 10 months later. It appears that increased awareness of exposure from the monitoring study prompted the use of protective equipment and greater care in reducing exposure.

Teschke et al. (1992) indicated that in all studies which monitored exposure at a variety of jobs and locations throughout lumber mills, variability in exposure between individuals was great, with differences between the highest and lowest measured values being more than one order of magnitude in most studies and as high as three orders of magnitude in one study.

A survey of sawmills and shipping terminals where antisapstain products were used in B.C. in 1991 was conducted by Teschke et al. (1992) for the B.C. Multistakeholder Forum on Sapstain Control. This Forum includes lumbermill owners, worker unions and provincial regulators. Based on that survey, 67 sites used antisapstain chemicals in B.C. in 1991. The following seven types of treatment systems were in use: forklift diptank, forklift and elevator diptank, automated elevator diptank, sorting chain (trough) diptank, linear spraybox, crosschain (transverse) spraybox and carwash spraybox. The authors of the report grouped workers with the potential for exposure into the following groups: graders and lumber pullers who handle wet lumber; forklift drivers who dip lumber and elevator dip tank operators; maintenance workers who work on the treatment systems; jobs which require less frequent handling of wet wood, e.g., bin sorters; and workers who handle dry, treated lumber. The antisapstain applications take place on a continual basis throughout the year.

b) Quantitative Exposure Assessment

No quantitative exposure data exists for hexaconazole or its end-use formulations. However, a Scientific Advisory Panel on Sapstain Control developed Generic Guidelines for Assessing Worker Exposure to Antisapstain Chemicals in the Lumber Industry (Teschke et al. 1992) for the B.C. Multistakeholder Forum on Sapstain Control. Zeneca Agro, as part of a group of antisapstain registrants, has submitted a protocol for conducting a generic exposure study. The protocol has been reviewed and is currently being revised.

c) Risk Assessment

A risk assessment of hexaconazole for use on lumber can not be conducted in the absence of an appropriate exposure study. As the exposure of workers to these treatments would be chronic in nature, relevant toxicology studies may include the chronic oral studies and/or the short-term dermal study with an additional safety factor to compensate for the less than chronic exposure and possible increased absorption with the end-use product. The risk assessment would also have to consider the fetotoxicity observed at non-maternally toxic doses in the teratology studies. Further discussions with the registrant regarding the selection of the appropriate toxicological study for risk assessment will be pursued.

6.0 Environment

6.1 Summary

The PMRA's environmental review of hexaconazole is with reference to the proposed use of the technical for manufacturing use and of Passport® formulations for treatment of lumber against sapstain fungi.

Studies showed that hexaconazole was not susceptible to chemical hydrolysis or to phototransformation and was not likely to volatilize from water or moist soil. Microbial action was shown to be important in the transformation of hexaconazole in soils. Laboratory aerobic soil studies have shown 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 the fungicide will 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 the compound had negligible leaching potential and thus it is not expected to contaminate groundwater through leaching. Data on the extent of leaching of hexaconazole from stockpiles of treated lumber are currently unavailable.

Data indicated that the major transformation product 1,2,4-triazole is not susceptible to hydrolysis or phototransformation. Microbial action was shown to be important in the transformation of 1,2-4 triazole. Field studies showed that the transformation product was persistent in soil. A high water solubility and data from laboratory absorption and leaching studies indicated 1,2,4-triazole would be mobile. Field data, however, showed that, although there was some leaching of 1,2,4-triazole in the soil, 91% of the residues remained in the top 30 cm.

Hexaconazole had no major effect on soil microorganisms and was not toxic to earthworms and bees. It was toxic to *Daphnia magna* based on chronic toxicity studies. Studies on the transformation product 1,2,4-triazole showed that it was non-toxic to earthworms, and *Daphnia magna* but toxic to *Scenedesmus subspicatus*, a freshwater green alga.

The potential contamination of soils and aquatic systems cannot be determined at present due to lack of field data on leaching rates from stockpiles of treated lumber and on expected environmental concentrations in run-off water (storm water) and in adjacent water bodies. It is important that the study on wash-off from treated lumber be conducted since the potential hazard to aquatic organisms of hexaconazole or the microcontaminant 2,3,7,8-TCDF, will depend on the expected concentrations in water.

6.2 Environmental Chemistry and Fate of Hexaconazole

6.2.1 Physicochemical Characteristics

a) Water Solubility

Solubility of hexaconazole was 18 mg/L at 20°C and showed negligible variation in solubility with pH.

b) Vapour Pressure

The vapour pressure was 1.8×10^{-8} kPa (1.4×10^{-7} mm Hg) at 20°C. The pesticide would thus be considered relatively

nonvolatile under field conditions. Data on vapour pressure and water solubility indicate that hexaconazole is not likely to volatilize from water and moist soil.

c) Octanol-Water Partition Coefficient

The octanol-water partition coefficient (log K_{ow}) was 3.9 at 20°C. The K_{ow} value indicated a potential for uptake and accumulation of hexaconazole by biota.

d) Dissociation Constant

Dissociation (ionization) constant (pKa) was reported to be 2.3 ±0.5 at 25˚C.

6.2.2 Transformation

a) Hydrolysis

Chemical hydrolysis is not expected to be an important mode of transformation of hexaconazole in the environment as laboratory data indicated that hexaconazole was stable in sterile, buffered solutions of pH 5, 7 and 9 after 30 days incubation in the dark at 25°C.

b) Phototransformation

Results of a study showed that phototransformation of samples of [^{14}C]-labelled hexaconazole, in sterile aqueous solution was insignificant. The samples were exposed to radiation from a xenon arc burner that was filtered so as to approximate the spectral distribution of sunlight. Following irradiation for a period equivalent to a mean of 34 days of Florida summer sunlight, over 95% of the applied radioactivity in the irradiated samples (>97% in the dark controls), was identified and confirmed as hexaconazole.

Data from a laboratory study indicated that phototransformation is not expected to be a significant process for transformation of hexaconazole on soil. There was limited phototransformation of hexaconazole on soil surfaces as DT_{50} (50% decline time) by extrapolation, was 98 days equivalent Florida sunlight. Phototransformation products were each <10% of applied activity. There was no transformation observed in the dark samples.

The stability of hexaconazole to sunlight is as expected as absorption spectrum data showed that the peak absorption of U.V. radiation by hexaconazole was at a wavelength of 220 nm and radiation in the region of natural sunlight (>290 nm) was not absorbed.

c) Biotransformation

Results from laboratory aerobic soil studies (20°C) showed that hexaconazole was persistent in loamy sand soil as DT_{50} was about eight months, and at the end of the tests (10 months post-treatment), the parent compound accounted for slightly less than 50% of the applied radioactivity. Hexaconazole was moderately persistent in sandy loam (DT_{50} of about two months) and silty clay loam soils (DT_{50} of about three months). Microbial action was shown to be important in the transformation of hexaconazole in soils. Of the transformation products observed, 1,2,4-triazole was over 10% of applied radioactivity at 10 months post-treatment, in sandy loam and loamy sand soils but <10% in silty clay loam soil.

Laboratory data from a study, in which hexaconazole-treated sandy loam soil was aged for five weeks under aerobic conditions and then flooded, showed that hexaconazole was persistent in the flooded soil. At 40 weeks post-treatment, the parent compound accounted for >50% of applied radioactivity, and most of the decrease probably took place during the period of aerobic incubation, prior to flooding of the soil. The study showed that hexaconazole was persistent and that transformation of the compound in the flooded soil was minimal.

In laboratory aquatic aerobic sediment-water systems, hexaconazole was persistent and at four months post-treatment, constituted from about 45 to 50% of applied radioactivity.

The applicant requested a waiver on a study on an aquatic anaerobic biotransformation study with hexaconazole on the grounds that the study would add little to the understanding of hexaconazole's environmental fate. As data have shown that hexaconazole is persistent in anaerobic soil and would also be expected to persist in anaerobic aquatic sediment, the reviewer agreed to a waiver and PMRA's assessment is based on the expectation that hexaconazole will be persistent in anaerobic aquatic sediments.

6.2.3 Mobility (Laboratory Data)

a) Adsorption/desorption

Studies on soil adsorption/desorption indicated that according to the observed K_{oc} values (684 - 1625), hexaconazole is classified as having low mobility in soils. Results from desorption experiments showed that adsorption was not completely reversible.

b) Soil Thick Layer Chromatography

The potential mobility of hexaconazole in soils was assessed in a laboratory soil thick layer chromatography study. The results indicated that the leaching potential of hexaconazole is low.

c) Soil Column Leaching Study

Laboratory soil column leaching experiments with [^{14}C]-labelled hexaconazole have indicated that the leaching potential of hexaconazole and its transformation products in soils is limited. Leachates contained no hexaconazole and the transformation products present were each <10% of applied radioactivity.

6.2.4 Field Soil Dissipation Studies

Field soil dissipation studies were conducted on bare soil at two orchard sites in Ontario in which a 5% SC formulation of hexaconazole was applied three times at monthly intervals, 45 g a.i./ha at each application. The concentration observed in soil sampled immediately after the final application (in the fall) was considered as the 0 day level and DT_{50}s were estimated by the reviewer. The results showed that hexaconazole was persistent in sandy loam (DT_{50} about 10 months) and clay loam (DT_{50} about 5 months). Residues of hexaconazole remained in the top 0-5 cm soil depth and this indicated that hexaconazole has negligible leaching potential in the soils tested.

A field dissipation study was also conducted in British Columbia in which hexaconazole was applied to bare soil at 90 g a.i./ha. Results indicated that hexaconazole was persistent (DT_{50} about 5 months) in silt loam soil. About 13 months after treatment, the residue level in the soil was about 35% of that observed at 0 day. The data also indicated that hexaconazole had negligible leaching potential in the silt loam soil tested.

6.2.5 Leaching of Hexaconazole from Treated Lumber

The question about the extent of leaching of hexaconazole from stockpiles of treated lumber and on the concentrations of hexaconazole observed in run-off water (storm water) has not been addressed. The applicant has agreed to conduct a study to address this question following a method that was developed by the PMRA.

6.2.6 Analysis for Residues of Hexaconazole

a) Soil

The method described is suitable for the combined determination of residues of hexaconazole and transformation products with analysis by gas liquid chromatography. The limit of detection was reported to be 0.01-0.02 mg/kg. A separate method is used to determine concentrations of 1,2,4-triazole.

b) Water

The method is based on analysis by gas-liquid chromatography with a limit of detection reported to be 0.1 µg/L.

6.2.7 Environmental Chemistry and Fate of the Major Transformation Product 1,2,4-triazole

a) Physicochemical Characteristics

Information provided showed that 1,2,4-triazole has a high water solubility (630,000 mg/L at 20°C) and a low octanol/water partition coefficient. The low K_{ow} and the high water solubility indicate a limited potential for bioconcentration. The vapour pressure determination indicated that the volatility of 1,2,4-triazole could be intermediate to high depending on adsorption to soil and partitioning into water. However, Henry's Law Constant as calculated by the reviewer, showed that 1,2,4-triazole is not likely to volatilize from water or moist surfaces.

b) Hydrolysis

Data indicated that 1,2,4-triazole was stable at pH 5, pH 7 and pH 9 and, hence, chemical hydrolysis is not expected to be a major mode of transformation of 1,2,4-triazole in the environment.

c) Phototransformation

Information provided showed that phototransformation of 1,2,4-triazole in water by natural sunlight was not a significant process.

d) Aerobic Soil Biotransformation

Results from laboratory aerobic soil studies showed that 1,2,4-triazole was moderately persistent (50% decline time (DT_{50}) about 14 weeks) in silty loam soil. Results from the study showed that there was an increase in soil bound radioactivity during the test to about 60% of applied radioactivity at 24 weeks post-treatment. At 168 days post-treatment, 1,2,4-triazole accounted for about 37% of applied activity. In other aerobic soil studies with clay loam and coarse sandy loam, the amount of extractable 1,2,4-triazole declined to 2% and 15% of applied activity after 20 weeks post-treatment, in the clay loam and sandy loam, respectively. There was also an increase in soil bound radioactivity during the test and, at 20 weeks post-treatment, 48% and 68% of applied activity from clay loam and sandy loam, respectively, remained unextracted. Transformation products in the soil accounted for <10% of applied activity. Microbial action was shown to be important in the transformation of 1,2,4-triazole.

e) Adsorption/Desorption of 1,2,4-triazole

Laboratory studies with five soils indicated that adsorption of 1,2,4-triazole to soil was low and that 1,2,4-triazole would be classified as very highly mobile in soil. Results from desorption experiments indicated that there was substantial (40 to 50%) desorption of 1,2,4-triazole from the five soils but that it was not completely reversible.

f) Soil Column Leaching of 1,2,4-triazole

Results showed that 1,2,4-triazole was mobile as it leached through the columns and was found in the leachate. The leaching was particulary extensive in sandy soils (82 and 86% of applied) and less so in silt loam soils (<1 and 34% of applied).

g) Field Soil Dissipation of 1,2,4-triazole

Results from a field study with [^{14}C]-1,2,4-triazole in Pennsylvania showed that the compound was persistent (DT_{50} about eight months) in silt loam soil. The transformation product had been applied to the soil at 280 g/ha in the fall. Data indicated that there was some leaching of 1,2,4-triazole in the soil, although most of the residues remained in the top 30 cm. After 13.5 months, 60% of the residues detected were in the top 0-7.5 cm section of the soil profile, 31% were in the 7.5-30 cm section and 7.5% in the 30-60 cm section.

h) Analysis of 1,2,4-triazole Residues in Soil

The limit of detection was reported to be 0.01 mg/kg with analysis by HPLC.

6.3 Environmental Toxicology of Hexaconazole

6.3.1 Soil Microbial Systems

According to results from laboratory studies with lucerne-amended and unamended loamy sand and sandy loam soils, the impact of hexaconazole (at concentrations of 0.1 and 1.0 mg/kg) on soil respiration and soil nitrification was in most cases limited. Further, in most cases, hexaconazole had no major effect on numbers of fungi, bacteria and on total microorganism numbers. The exception was that, in lucerne-amended sandy loam soil treated at 1.0 mg/kg concentration, there was a significant reduction in carbon dioxide production during the test and in numbers of bacteria on the last day of incubation.

6.3.2 Terrestrial Invertebrates

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.

Results from a three-year field study indicated that hexaconazole had no significant adverse effect on total numbers or weight of earthworms. No single species appeared to be particularly susceptible to the hexaconazole treatments.

6.3.3 Aquatic Invertebrates

Data on the acute toxicity of technical hexaconazole to *Daphnia magna* (48-h EC_{50} 2.9 mg/L, based on measured concentrations) indicated that hexaconazole was moderately toxic (U.S. E.P.A. acute toxicity classification).

Chronic toxicity data have indicated that hexaconazole is toxic to *Daphnia magna*. The No Observed Effect Concentration (NOEC) was 0.25 mg/L as survival, growth and reproduction of *Daphnia magna* were affected by hexaconazole at nominal concentrations >0.25 mg/L, during the 21-day life cycle study. Results were reported in nominal concentrations of hexaconazole as the measured concentrations were 77 to 108% of the nominal values.

The toxicity to aquatic biota of Passport® ED, an oil-based formulation, is not known and as such the applicant should submit any available data to answer this question.

6.3.4 Environmental Toxicology of the Major Transformation Product 1,2,4-triazole

a) Toxicity of 1,2,4-triazole to Earthworms

Results from an earthworm (*Eisenia foetida*) acute toxicity study in an artificial soil indicated that 1,2,4-triazole was relatively non-toxic (14-day LC_{50} >1000 mg a.i./kg) to earthworms.

b) Toxicity of 1,2,4-triazole to Fish

Data on the acute toxicity of 1,2,4-triazole to rainbow trout (*Oncorhyncus mykiss*) indicated that it was practically non-toxic (96-h LC_{50} 533 mg/L).

c) Toxicity of 1,2,4-triazole to *Daphnia magna*

Acute toxicity data indicated that 1,2,4-triazole was practically non-toxic (24-h LC_{50} 900 mg/L) to *Daphnia magna*.

d) Toxicity of 1,2,4-triazole to Algae

Tests showed that 1,2,4-triazole was toxic to *Scenedesmus subspicatus*, a freshwater green alga. The 5-day EC_{50}, estimated by the reviewer and based on measured concentrations, was 1.5 mg/L.

6.4 Hexaconazole-Treated Wood Waste Disposal

Information on disposal (i.e., incineration/thermal decomposition) of hexaconazole-treated wood waste is not required at this time as it has not been finalized as a data requirement for registration of antisapstain pesticides. However, the PMRA recommends additional instructions be added to the label to warn users against unsafe disposal of waste materials including liquids, sludges and treated wood residues (e.g., trim ends, broken lumber, chips, sawdust, planer shavings and other wood residue resulting from processing and handling of wood following its treatment as well as wood waste or wood debris which has contacted antisapstain concentrate). Waste materials should not be burned under low-temperature conditions such as in a residential fireplace, stove or other open burning device, or open-fire pit as hazardous emissions may be released. Sludges and treated wood waste materials should be disposed of as hazardous or special waste in accordance with provincial guidelines or regulations, where appropriate.

6.5 Dioxins and Furans in Hexaconazole Technical Material

The PMRA is concerned about the presence of 2,3,7,8-TCDF (up to 76 pg/g [ppt]) in technical hexaconazole. Dioxins and furans with chlorines in the 2, 3, 7 and 8 positions are of concern in view of their acute and chronic toxicity to mammals, birds, aquatic invertebrates and fish. However, based on the proposed use of hexaconazole, potential exposure to the environment and nontarget organisms is expected to be reduced substantially when the technical (90%) is diluted to form the 5% and 25% formulated products, which are then diluted further to 2% when spray solutions are prepared. Nevertheless, confirmation of this is required and the applicant should check for 2,3,7,8-TCDF in rainwater leachate collected directly below the treated lumber during the study to determine concentrations of hexaconazole in storm water run-off from treated lumber. The applicant should use a method of analysis for 2,3,7,8-TCDF that is sensitive at the parts per quadrillion (parts per 10^{15}) level. For a sample of storm water of 1 L, the level of quantification is 5 pg/L (ppq).

6.6 Evaluation

Data have indicated that hexaconazole and its major transformation product 1,2,4-triazole are expected to be persistent in the environment (in both soil and water/sediment systems). The potential contamination of soils and aquatic systems cannot be determined at present due to lack of field data on leaching rates from stockpiles of treated lumber and on expected environmental concentrations in run-off water (storm water) and in adjacent water bodies. It is important that the study on wash-off from treated lumber be conducted since the potential hazard of hexaconazole to aquatic organisms will depend on the expected concentration in water. The applicant has agreed to conduct the wash-off study during a period of temporary registration and to follow a

method that was developed by the PMRA. A determination should be made for 2,3,7,8-TCDF in the rainwater leachate collected directly below the treated lumber and the analytical method used should be sensitive at ppq level.

As was indicated by the Department of Fisheries and Oceans in their review of hexaconazole, the toxicity to aquatic biota of Passport® ED, an oil-based formulation, is not known and, as such, the applicant should submit any available data to answer this question.

7.0 Fisheries and Oceans Canada

7.1 Fish

Hexaconazole has a moderate acute toxicity to fish as indicated by results from flow-through studies in which the technical product was tested on four freshwater species - rainbow trout (*Oncorhynchus mykiss*, formerly *Salmo gairdneri*), bluegill sunfish (*Lepomis macrochirus*), mirror carp (*Cyprinus carpio*) and sheepshead minnow (*Cyprinodon variegatus*); 96-hour LC_{50}s reported for these species are >6.7, 5.1, 5.94, and 5.4 mg a.i./L, respectively. Symptoms of toxicity generally include loss of equilibrium, quiescence, darkening of body colour and abnormal respiratory activity; reported 96-hour No-Observed-Effect-Levels (NOELs) are <0.97, 1.92 and 1.7 mg/L for trout, carp and sheepshead, respectively, but none has been reported for bluegill.

Survival and growth in fathead minnow (*Pimephales promelas*) larvae are significantly (P=0.05) affected by hexaconazole concentrations greater than 1.2 and 0.6 mg/L, respectively. Hatching success in this same species is unaffected at hexaconazole concentrations up to 2.5 mg/L (highest concentration tested).

The major transformation product, 1,2,4-triazole, is practically non-toxic to rainbow trout as indicated by 96-hour LC_{50}s of 532 mg a.i./L.

Formulated hexaconazole has a moderate acute toxicity to fish as indicated by results from the testing of Passport® SC and Passport® EC formulations on rainbow trout; 96-hour LC_{50}s of 2 and 7.2 mg a.i./L have been determined as well as a NOEL of 0.45 mg a.i./L (Passport® SC only). Toxicity of the Passport® ED formulation to aquatic biota has not been confirmed[1].

The octanol:water partitioning coefficient (log K_{ow}) of hexaconazole is 3.9, indicating a potential for bioconcentration and testing has confirmed that concentration in fish tissues can be substantial. Flow-through exposure of

[1] The applicant has indicated that toxicity testing of this formulation is not planned.

bluegill sunfish to ^{14}C-chlorophenyl-labelled- and ^{14}C-triazolyl-labelled hexaconazole resulted in a ^{14}C-concentration plateau being reached in all sampled tissues by the first day of exposure. Bioconcentration factors (BCFs) were 107 in whole fish, 45 in muscle and 778 in viscera, indicating a tendency for residues to accumulate in viscera. The process is reversible, with depuration of >95% of the residues occurring within three days and radioactivity in all tissues approaching background levels within 14 days.

7.2 Fish Habitat

Hexaconazole technical has a moderate acute toxicity to aquatic invertebrates which serve as food for fish. A 48-hour EC_{50} of 2.9 mg a.i./L has been determined during acute testing of *Daphnia magna* and, although a NOEL has not been reported, the lowest exposure concentration of 0.6 mg a.i./L resulted in 1.1% mortality.

Chronic testing of *D. magna*, using hexaconazole technical, indicates that growth and reproduction in this species are significantly (P=0.05) affected by hexaconazole concentrations of 0.50 mg/L or greater; a 21-day EC_{50} of 0.51 mg/L and a 21-day NOEL of 0.25 mg/L have been determined.

Moderate acute toxicity is confirmed by tests using other invertebrate species. For example, a 96-hour LC_{50} of 1.8 mg/L and a NOEL of 1.0 mg/L have been reported for mysid shrimp (*Mysidopsis bahia*) and a 48-hour LC_{50} of 5.8 mg/L and a NOEL of 3.4 mg/L have been reported for Pacific oyster larvae (*Crassostrea gigas*) when exposed to hexaconazole technical.

The toxicity of hexaconazole end-use formulations to aquatic invertebrates is not known.

Growth inhibition occurs in the green alga, *Selenastrum capricornutum*, when exposed to hexaconazole technical at concentrations greater than 0.56 mg/L (NOEL); a 96-hour EC_{50} of 1.7 mg a.i./L has been reported.

The transformation product, 1,2,4-triazole, is practically non-toxic to *D. magna* as indicated by a 24-hour EC_{50} of 747 mg/L but greater toxicity to *S. capricornutum* is indicated by a 5-day EC_{50} of <6.3 mg/L.

7.3 Movement into and Transformation in Aquatic Environments

Hexaconazole is not likely to enter aquatic ecosystems by leaching through soil or by soil run-off, but storm water run-off of that chemical from treated lumber remains a potential source for entry into nearby aquatic systems. However, the

significance of hexaconazole leaching from treated wood, as a result of rainfall events, cannot be determined at this time because wash-off testing has not been conducted[2].

In aquatic systems, the hexaconazole molecule is resistant to hydrolytic and photolytic transformations and will partition from the aqueous phase to suspended particulate material and to sediment. Aerobic transformation, in the aquatic environment, has not been tested but the route of transformation and the pattern of degradation in sediment is expected to be similar to the process as it occurs in aerobic soil; similar persistence (i.e., several months) is therefore expected. The role of aquatic anaerobic transformation in the fate of hexaconazole is not known, but submitted information indicates that hexaconazole and its major transformation products will partition to sediments and will persist.

7.4 Analytical Methods

Although methods with satisfactory detection limits are available for the analytical determination of hexaconazole residues in water and in sediment, a procedure for residue determination in fish tissue is not available[3]. Hexaconazole has a potential for accumulation in aquatic biota and, although testing has indicated that 95% of residues in fish would likely be cleared from the tissues within three days, the nature of the antisapstain use-pattern is such that the potential for chronic exposure may not allow full depuration to occur, with the result that high tissue levels may be maintained. Without the methodology to measure hexaconazole residues in fish tissues, such accumulation cannot be monitored.

7.5 Impact Assessment

Hexaconazole, as a technical product or as Passport® SC or EC end-use formulations, is moderately toxic to fish and to organisms which serve as food for fish. Toxicity of this compound to aquatic plants is also acceptable, although its major transformation product (which is practically non-toxic to fish and aquatic invertebrates) is moderately-to-highly toxic to algae. In addition, toxicity of the Passport® ED end-use formulation to aquatic biota has not been confirmed.

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[2] The applicant has agreed to conduct wash-off testing during a period of temporary registration.

[3] The applicant has indicated that development of such methodology is not planned.

In order to assess the hazard of hexaconazole to fish and fish habitat, information on the potential exposure of aquatic organisms to this chemical is required. It is expected that this information will be available when hexaconazole wash-off testing has been completed.

8.0 Regulatory Management Process

The PMRA uses a regulatory management process for making significant or complex registration decisions concerning pesticides. This approach considers both the scientific and public policy aspects of the risks and values associated with pesticide use.

The determination of the potential value component of the proposed use of hexaconazole for wood protection and wood preservation can only be estimated. However, in a public policy context, the potential value component merits comments from other parties, including users, by whom it will ultimately be judged.

Potential risks can be measured scientifically and assessed by experts. The risk component also merits comments from other parties, including environmental agencies, the lumber manufacturing industry, other levels of government, the public and users.

Written comments may be forwarded within 60 days from the issue date of this document to:

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