Agence de réglementation de la lutte antiparasitaire
Pest Management Regulatory Agency

Regulatory Decision Document RDD2000-04

Hexaconazole Fungicide (Proseed)

Hexaconazole and the formulated product Proseed (*Pest Control Products Act* registration number PCP 25892), which contains hexaconazole as the active ingredient and is used for the control of seedborne and soilborne diseases of wheat and barley in Canada, are eligible for full registration pursuant to Section 13 of the Pest Control Products (PCP) Regulations.

This Decision Document outlines the Pest Management Regulatory Agency's (PMRA) regulatory decision-making process concerning the use of hexaconazole (Proseed) agricultural fungicide on wheat and barley seed.

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

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/pmra-arla/
Information Service:
1-800-267-6315 or (613) 736-3799
Facsimile: (613) 736-3798

1.0 Introduction

This Decision Document outlines the Pest Management Regulatory Agency's (PMRA) regulatory decision-making process concerning the use of hexaconazole (Proseed) fungicide seed treatment for wheat and barley.

2.0 Background

The PMRA carried out an assessment of available information in accordance with Section 9 of the Pest Control Products (PCP) Regulations. The assessment found that there was sufficient information, pursuant to Section 18.b, to allow a determination of the safety, merit, and value of hexaconazole and Proseed (manufactured by Zeneca Agro). The PMRA concluded that the use of Proseed in accordance with the label accompanying the product has merit and value consistent with Section 18.c of the PCP Regulations and does not entail an unacceptable risk of harm pursuant to Section 18.d.

In Proposed Regulatory Decision Document PRDD99-05 it was proposed that Proseed be registered for use in the control of seedborne and soilborne diseases of wheat and barley. Comments received by the PMRA concerning PRDD99-05 are give in Appendix 1.

3.0 Regulatory Decision

Based on the considerations outlined above, the use of Proseed on wheat and barley seed is eligible for full registration, pursuant to Section 13 of the Pest Control Products (PCP) Regulations.

List of Abbreviations

ADI	allowable daily intake
a.i.	active ingredient
bw	body weight
CEPA	*Canadian Environmental Protection Act*
DIR	Regulatory Directive
EEC	estimated environmental concentration
EPA	Environmental Protection Agency
FQPA	*Food Quality Protection Act*
K_{ow}	octanol–water partition coefficient
LOD	limit of detection
LOQ	limit of quantification
ng	nanograms
NOAEL	no observable adverse effect level
NOEL	no observed effect level
PCP	Pest Control Products
PDI	potential daily intake
pg	picogram
PMRA	Pest Management Regulatory Agency
ppt	parts per trillion
PRDD	Proposed Regulatory Decision Document
PSL	Priority Substances List
TDI	tolerable daily intake
TEF	toxic equivalent factor
TEQ	toxic equivalent
TSMP	Toxic Substances Management Policy
VE	virtual elimination
WHO	World Health Organization

Appendix I Comments and Responses

Comments were received by the PMRA concerning the Proposed Regulatory Decision Document PRDD99-05 *Hexaconazole* published on October 27, 1999. The comments were from government and public interest groups and related to the principles and application of the Toxic Substances Management Policy (TSMP) and assessment methodology for health and environmental aspects of hexaconazole. In following the PMRA's commitment to implement the federal TSMP, the PMRA review included consideration of Track 1 substances found as contaminants in the technical product (i.e., Proseed). The PMRA has consolidated and summarized the comments received and provides responses to the comments in the following sections.

1.0 TSMP Track 1 Microcontaminants

1.1 Comments on PRDD99-05 Sections 1.1, 4.2, 5.2.6, 6.4.3, and 8.0

1. *We object in principle to registration of any pesticide which is or contains Track 1 substances. We disagree that the presence of "very low" levels of 2,3,7,8-TCDF is consistent with requirements of the* Canadian Environmental Protection Act *(CEPA) and TSMP.*

2. *It is unclear whether the TEQ used in the assessment is in fact the total TEQ or is based only on the 2,3,7,8-TCDF. In addition, it appears that the assessment was limited to isomers, chlorinated at the 2,3,7,8 positions, which are listed as Track 1 substances. A full assessment of the effect of all microcontaminants was not conducted.*

   The TEQ of 0.1 ppt used to convert 2,3,7,8-TCDF into toxicologically equivalent concentrations of 2,3,7,8-TCDD is not relevant to birds, as the World Health Organization (WHO 19XX)[1] *has agreed on a TEQ of 1.0 ppt for birds.*

3. *Hexaconazole contains three dioxins, for which the U.S. Environmental Protection Agency (EPA) has set a level of concern for foods at 1 ppt. The WHO has lowered its "tolerable daily intake" (TDI) standard for dioxin from 10 pg/kg body weight (bw) to 1–4 pg/kg bw. Canada's TDI has not changed and is currently 2–10 times the WHO limit.*

4. *There is no assessment of the risks [of Track 1 substances] posed to wild birds, even though the risk of exposure is probably greater than that for humans and fish, the two receptors for which an assessment was conducted, since birds consume the treated seeds.*

[1] WHO. 19XX. XXXXX. Environ. Health Perspect. 106(12): 775–792.

1.2 Responses

1. In 1995, the federal TSMP set the goal of "virtual elimination" (VE) from the environment of Track 1 substances. The TSMP defined VE to mean "the lowest concentration of a substance that can be accurately detected and quantified using sensitive but routine analytical methods." The implementation strategies of Environment Canada's *Implementation Strategy for Existing Substances* (December 1996) and the PMRA Regulatory Directive DIR99-03 have relied on this definition and use the limit of quantification (LOQ) as a measure of having achieved VE. This definition of VE has also been adopted in the CEPA Bill C-32 (Part 5, 65), which defines VE as "reduction of the quantity or concentration of a substance in the release into the environment below the level of quantitation." The registration of new pesticides with Track1 contaminants below the LOQ is therefore consistent with the TSMP, the implementation strategy of Environment Canada, and the CEPA.

   Regulatory Directive DIR99-03 details the PMRA strategy for implementation of the federal TSMP and specifies that a new pest control product containing a Track 1 substance as a microcontaminant may be registered "where the Track 1 substance has been virtually eliminated." Additionally, the following conditions of registration must be met: (a) the level of microcontaminant in the product must be very low, i.e., below the LOQ; (b) the registrant must demonstrate that the level of microcontaminant in the product is as low as can be achieved by the application of the best available technology from a manufacturing perspective; and (c) the use of the product in accordance with the label must not represent unacceptable risks.

   The potential levels of 2,3,7,8-TCDF in different environmental media, as cited in the PRDD, are below the level of quantification and thus meet the TSMP goal of "virtual elimination." Based on an application rate of 3.03 g hexaconazole/ha, 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 cmof water would be 3.84×10^{-14} mg/L. These predicted concentrations are several orders of magnitude below current LOQs for these environmental media. The registrant has also demonstrated that the level of microcontaminant in the product is as low as can be achieved by application of the best available manufacturing technology. The PMRA review has concluded that the use of this product in accordance with the label will not result in unacceptable risks to health and the environment. Therefore, all conditions of DIR99-03 for registration of a new pesticide with Track 1 contaminants have been met for the proposed seed treatment use of hexaconazole.

2. 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 amount of contaminant of toxicological concern. Since no other Track 1 substances were found in the batch containing 76 ppt TCDF, the TEQ level of 7.6 ppt used in the calculations corresponds to the sum of the TEQs in the highest batch. The total TEQs for all other batches were lower or not detected.

Analyses of five samples of hexaconazole revealed no dioxins with 2,3,7,8 substitution. Two furans with 2,3,7,8 substitution were detected. It is the isomers chlorinated at the 2,3,7,8 positions that are considered toxicologically significant and, according to the TSMP, are listed as Track 1 substances. The other isomers contribute comparatively little to the toxicity of a complex mixture.

We agree that the toxic equivalent factor (TEF) of 0.1 for 2,3,7,8-TCDF is not applicable to birds and has been changed to 1.0. Even with this increased TEF the risk to birds related to 2,3,7,8-TCDF remains acceptable.

3. The level of concern set by the U.S. EPA is only for dioxins and furans which display chlorine substitution in the 2,3,7, and 8 positions. The analysis of hexaconazole found two furan isomers with 2,3,7,8 substitution, but no 2,3,7,8-substituted dioxins were detected. Based on the lower TDI of 1 pg/kg bw set by the WHO, the dietary risk for all subpopulations including infants and children is still very low. The calculated potential daily intake (PDI) for various age groups was no greater than 0.4% of the 1 pg/kg bw TDI set by the WHO.

   The PDI was calculated based on the maximum concentration of microcontaminants on treated seeds (not for animal or human consumption) which was higher than that on the progeny seeds. The PDI for the grains grown from treated seeds would be even lower.

4. Based on an application rate of 3 mL of formulation per kg of seed and a maximum seeding rate of 202 kg/ha for wheat, the application rate is 3.03 g hexaconazole/ha. This is equivalent to 2.303×10^{-10} g of 2,3,7,8-TCDF/ha, i.e., 23 pg of 2,3,7,8-TCDF on 202 kg of treated seed will be spread out on 1 ha of land. At this level of dilution, an acute or chronic effect on seed-eating birds is not expected, even if all the treated seeds are lying exposed on the surface. This is supported by the information cited in the Environment Canada PSL document on dioxins and furans, which indicated that based on intake of 2,3,7,8-TCDD in daily food, the semichronic no-effect level for birds is 2100 ng of 2,3,7,8-TCDD/kg bw.

2.0 Human Health: Toxicology and Food Residues

2.1 Comments on PRDD99-05 Section 3.1

5. *It is possible that hexaconazole, like its contaminants the dioxins, are endocrine-disrupting chemicals. These are most toxic to the fetus: fetotoxicity was observed in studies of rats and rabbits in the absence of maternal toxicity. Dioxins and endocrine-disrupting chemicals interfere with hormonal systems and cause disorders of the reproductive system. The signs of abnormal gonadotrophic stimulation (i.e., increased testicular atrophy and increased incidence of Leydig cell tumours observed in the high-dose rats) and the abnormalities of reproductive organ development observed in the teratology study could be due to endocrine disruption from this chemical.*

6. *It is puzzling why the teratology columns contain the highlighted words "No Teratogenic Effects At Any Dose Tested" when teratogenic effects were clearly observed and noted.*

7. *The toxicology data base did include a teratology study, but as usual no functional end points were assessed in the offspring. In addition, there was no immunotoxicity study, nor a developmental neurotoxicity study.*

8. *Under the provisions of the 1996* Food Quality Protection Act (FQPA), *"an additional tenfold margin of safety for the chemical residue and other sources of exposure shall be applied for infants and children to take into account potential pre- and post-natal toxicity and completeness of the data with respect to exposure and toxicity to infants and children." Given that increased sensitivity to the fetus was shown in the reproductive toxicity tests, an additional safety factor, or a least a data base uncertainty factor, would have been applied under FQPA reevaluations. Since important developmental toxicity tests are unavailable, and because one of the prime effects of dioxins is on the immune system, this could be a factor of 10 which would change the allowable daily dose (ADI) to 0.0005 mg/kg bw.*

9. *Why was this product not registered in the United States?*

2.2 Responses

5. As noted in the toxicology summary, hexaconazole is a member of the azole class of chemicals which are known to induce liver toxicity and to inhibit cytochrome P450 monooxygenase and subsequent hydroxylation of steroids and fatty acids. The nature and sequence of effects observed in animal toxicity studies are consistent with what is known about this class of chemicals. It is believed that liver toxicity plays an important role in the effects observed in the testes. In the study of chronic toxicity in rats, as the severity of the observed liver toxicity increased, adverse effects were observed on lipid metabolism. At progressively

higher doses, the alterations in lipid metabolism lead to changes in testicular function (possibly mediated through alterations in steroid levels), ultimately leading to the observation of Leydig cell tumours. Hence, these signs of abnormal gonadotropic stimulation observed at the high dose of the rat chronic toxicity study are the result of a cascade of effects initially triggered by effects on the liver at much lower dose levels. One principle that is inherent in the hazard assessment is consideration of the dose–response relationship. In performing a risk assessment, appropriate safety factors are applied to the relevant no observed effect level (NOEL) from the toxicology data base. In the case of hexaconazole, the application of safety factors against the NOEL for the liver effects provides an extra level of protection or "buffer" to the testicular effects observed at higher doses. This approach provides reasonable assurance that anticipated exposure levels resulting from the use of hexaconazole would be orders of magnitude below those which that elicited any adverse effects on the endocrine system.

As a point of clarification, there were no abnormalities of reproductive organ development observed in the teratology or reproductive toxicology studies.

6. Hexaconazole is not a teratogen. The effects in offspring observed in the teratology studies were considered variations or delays in development and not malformations (terata). In evaluating developmental toxicity studies, the PMRA makes a clear distinction between the variations and malformations for regulatory purposes and regulates chemicals that demonstrate malformations much more aggressively than those which elicit variations. This approach is consistent internationally. Developmental variations or delays occur frequently in untreated animals. Generally, they are considered reversible, are highly dependent on dose in treated groups, and do not affect fetal survival, development, or function. Malformations are rare, irreversible structural changes that are likely to adversely affect fetal survival, development, or function.

7. In the studies which form a toxicological data base, there are numerous parameters that provide evidence for potential effects on organ systems such as the neurological and immunological systems. For example, chemicals that affect the immune system generally affect immune organ pathology (lymph nodes, spleen, bone marrow), haematology parameters (white blood cell counts, differentials), and the ability to resist infection or neoplastic events. Such parameters are examined in the toxicology data base involving several animal species and including lifetime exposures. Similarly, the toxicology data are closely assessed for effects on the neurological system. If the evidence suggests that these and other organ systems might be affected, additional information is requested to further this investigation. Upon examination of the toxicological data base for hexaconazole, it was concluded that there were no indications of adverse effects on other organ systems and hence further studies and information were not required.

8. PMRA's approach for ensuring safety to infants and children is consistent with that of the U.S. EPA. Like the U.S. EPA, the PMRA applies additional uncertainty factors when warranted by the results observed in the data base. The increased sensitivity of the fetus and the observations suggesting adverse effects on the endocrine system were flagged as warranting additional attention. These issues were addressed in the PRDD. To set the ADI, the PMRA used the lowest no observable adverse effect level (NOAEL) from the study of chronic toxicity in rats rather than a higher NOAEL from the teratology study with the end point of concern. By doing this, a 500-fold safety margin was built into the risk assessment for the observed fetal variations. This also resulted in a 1000-fold safety margin for the observed testicular effects. These are considered acceptable.

9. Hexaconazole has not been assessed for use as a fungicide seed treatment for barley and wheat in the United States. At the time of making their submission, the company (Zeneca Agro) chose to apply for registration in Canada only.

3.0 Drinking Water

3.1 Comments on PRDD99-05 Sections 4.2 and 5.3.5

10. The drinking water limit has not been adequately addressed in Section 4.2. The PDI is not defined and there is no clear explanation as to what " +10% drinking water" means.

11. No information was provided regarding the disposal or fate of the fungicide after the treatment process. The potential contamination of drinking water via wastewater cannot be fully determined at present …. The document contained no monitoring data on residues of hexaconazole or its transformation product 1,2,4-triazole in surface water, drinking water, and groundwater.

12. In Section 5.3.5, a factor which may require clarification is the use of 0.5% as an estimated value for runoff. Is the estimated runoff based on data or a model? *Animals could be drinking from streams and ponds contaminated by runoff. The possibility of uptake and accumulation in animals should be assessed, and residue analysis data should be collected for food of animal origin.*

13. 1,2,4-Triazole was found to be persistent in loamy soil and moderately persistent in other soils. Although the compound did not migrate deep into the soil, there is a possibility of runoff into creeks and streams, with an accumulation in water over time.

3.2 Responses

10. The PDI is calculated from the amount of residue that remains on each food when the pesticide is used according to the proposed label and the intake of that food in the diet. PDIs are calculated for various Canadian subpopulations and age groups.

In general, a dietary risk assessment is calculated based on the PDI for foods plus an estimated 10% of the ADI allotted to water, the latter being an exaggerated estimation. In the case of hexaconazole, the estimated environmental concentration (EEC) for human drinking water is #0.0076 mg active ingredient (a.i.)/L. When a dietary risk assessment is calculated using the EEC value for drinking water, the PDI for foods plus drinking water for various subgroups, including infants, children, and seniors, is <19% of the ADI.

11. The potential contamination of drinking water via wastewater will be minimal. Based on the proposed method of seed treatment, there will be minimal production of wastewater. Unused pesticide material will be saved and reused later to treat more seeds, and therefore the issue of disposal will not arise.

12. The runoff factor of 0.5% was based on data obtained in field studies by Wauchope (1978)[2]. According to the data, a 0.5% runoff value should be used for soil-incorporated pesticides. As indicated in the PRDD, runoff calculations were based on the pesticide being applied directly to the soil and then incorporated into the soil. It is recognized that runoff from treated seed planted in the soil might be different.

    A log K_{ow} value of 3.9 indicates a potential for bioaccumulation, where K_{ow} is the octanol–water partition coefficient. However, as indicated in the PRDD, data from studies on fish and residue levels of hexaconazole in rat and goat tissue and milk showed that bioaccumulation was limited.

    Residues of hexaconazole were not detected in wheat grain, straw, or forage. Thus, the concern about uptake and accumulation in food animals consuming feed or water is not warranted.

13. It is estimated that at the seed-treatment application rate of Proseed, the concentration of the transformation product 1,2,4-triazole in the soil will be below the level of detection (0.01 mg/kg). Thus, the potential for runoff of substantial amounts of 1,2,4-triazole residues would be minimal.

4.0 Occupational Exposure

4.1 Comment on PRDD 99-05 Section 3.6.1

14. Although nearly all occupational exposure is expected to be via the dermal route, almost all of the toxicological studies were performed for exposure via the oral route. The dermal absorption data generated in the rat using 14C-hexaconazole were used to correct for dermal occupational exposure. Differences in rat versus

[2] Wauchope, R.D. 1978. The pesticide content of surface water draining from agricultural fields — a review. J. Environ. Qual. 7(4): 459–472.

human dermal absorption are not specifically accounted for in occupational risk assessment.

4.2 Response

14. Dermal absorption studies where the compound is applied to human skin *in vivo* provide the most relevant information for human exposure and risk assessment. However, toxicity and ethics preclude the use of humans for such studies. Therefore, animal studies typically are performed to assess dermal absorption. Based on comparative data, rat skin has consistently been shown to be more permeable to topically applied compounds than human skin. Therefore dermal absorption studies with rat skin would overestimate dermal absorption in humans and provide a conservative (i.e., higher) estimate of absorbed dose in humans.

5.0 Environmental Toxicology and Fate

5.1 Comments on PRDD99-05 Forward and Sections 6.0, 6.4.1, 7.6, and 8.0

15. There is no mention … of the standard reproduction studies conducted with the bobwhite quail and the mallard duck. We believe this issue needs to be addressed because treated seeds represent a high-exposure situation for birds which usually coincides with the timing of reproduction …. Given the effects seen with two [previously reviewed] fungicides of the same chemical family, we strongly believe the same attention should be given to the potential reproductive effects on birds of hexaconazole.

16. Statements such as "Proseed may be applied as a seed treatment at very low use rates (1.5 g a.i./100 kg seed)" and " … has the advantage of a very low rate of activity, thus potentially reducing pesticide loading" may imply that the use of a substance is safe or safer than a substance used at a higher rate. The important point is that a product is used at a rate that is biologically active, and as such it is irrelevant if this rate is "low" or "high." What matters is the biological activity of the product, not the total loading in and of itself.

17. EC_{50} is referred to as an "Environmental Concentration 50%;" EC_{50} is in fact a "median effective concentration."

5.2 Responses

15. At the time of the review of hexaconazole, avian reproduction studies were not part of the data requirements for this use pattern. However, the PMRA has since revised the data requirements and now has included these studies in its list of those required for all outdoor use patterns. Avian reproduction studies on bobwhite quail and mallard duck for hexaconazole were requested from the applicant. The PMRA reviewed these studies and found that if all treated seed was exposed on the soil surface and the birds ate the treated seed at a maximum

feeding rate (4.17% of mallard body weight per day and 8.94% of bobwhite body weight per day), there would be adequate margins of safety for reproductive effects. These margins were ×24 for mallard duck and ×4.3 for bobwhite quail. It is concluded that the use of hexaconazole as seed treatment for wheat and barley will not be a risk to wild birds such as mallard duck and bobwhite quail.

16. Relative to other fungicides currently used in Canada for the same purpose, Proseed provides similar disease control using less active ingredient. However, we agree that it is the biological activity of the product that matters.

17. Agree.