Proposed Registration Decision PRD2010-08

# Prothioconazole

*(publié aussi en français)*

**19 May 2010**

This document is published by the Health Canada Pest Management Regulatory Agency. For further information, please contact:

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HC Pub: 100163

ISBN: 978-1-100-15550-0 978-1-100-15551-7
Catalogue number: H113-9/2010-8E H113-9/2010-8E-PDF

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# Overview

## Proposed Registration Decision for Prothioconazole

Health Canada's Pest Management Regulatory Agency (PMRA), under the authority of the *Pest Control Products Act* and Regulations, is proposing full registration for the sale and use of Prothioconazole Technical Fungicide and Proline 480 SC Foliar Fungicide, containing the technical grade active ingredient prothioconazole, for the control or suppression of Ascomycetes, Basidiomycetes and Deuteromycetes diseases on chickpeas, lentils, canola, rapeseed, Oriental mustard, wheat and barley.

Prothioconazole Technical Fungicide (Registration Number 28358) and Proline 480 SC Foliar Fungicide (Registration Number 28359) are conditionally registered in Canada. The detailed review for prothioconazole and Proline 480 SC Foliar Fungicide can be found in Regulatory Note REG2007-03 *Prothioconazole.* The current applications were submitted to convert Prothioconazole Technical Fungicide and Proline 480 SC Foliar Fungicide from conditional registration to full registration.

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

This Overview describes the key points of the evaluation, while the Science Evaluation provides detailed technical information on the human health, environmental and value assessments of prothioconazole and Proline 480 SC Foliar Fungicide.

## What Does Health Canada Consider When Making a Registration Decision?

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

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

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

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

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

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

## What Is Prothioconazole?

The active ingredient prothioconazole and the associated end-use product Proline 480 SC Foliar Fungicide is a systemic fungicide from the Group 3 Fungicides, specifically within the demethylation inhibitor (DMI) class of sterol biosynthesis inhibitors (SBI) fungicides. Proline 480 SC Foliar Fungicide is a foliar-applied fungicide for use on several cereal and vegetable crops, including barley, wheat (spring, durum and winter), canola, rapeseed, Oriental mustard, chickpeas and lentils.

## Health Considerations

### Can Approved Uses of Prothioconazole Affect Human Health?

**Prothioconazole and its metabolite, prothioconazole-desthio, are unlikely to affect your health when used according to label directions.**

Potential exposure to prothioconazole and its prothioconazole-desthio metabolite may occur through the diet (food and water) or when handling and applying the product. Prothioconazole and prothioconazole-desthio have a similar toxicological profile with prothioconazole-desthio effects occurring at lower doses. Therefore, the endpoints used for this risk assessment were that of the metabolite. When assessing health risks, two key factors are considered: the levels where no health effects occur and the levels to which people may be exposed. The dose levels used to assess risks are established to protect the most sensitive human population (e.g., children and nursing mothers). Only uses for

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

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

which the exposure is well below levels that cause no effects in animal testing are considered acceptable for registration.

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

Prothioconazole and prothioconazole-desthio were considered to be of low acute toxicity by the oral, dermal and inhalation routes in Wistar rats. These compounds were non-irritating when applied to the skin of rabbits. Prothioconazole was considered slightly irritating to the eyes of rabbits while prothioconazole-desthio was non-irritating. The results of skin sensitization testing were negative for both compounds. No signal words are required on the label.

Prothioconazole and prothioconazole-desthio did not cause cancer in animals and were not genotoxic. Decreased motor and locomotor activity were observed following dosing with these compounds. Numerous reproductive effects were also observed. The first signs of toxicity in animals given daily doses of these compounds over longer periods of time were liver, kidney, thyroid and ovary effects. The risk assessment protects against these effects by ensuring that the level of human exposure is well below the lowest dose at which these effects occurred in animal tests.

When prothioconazole was given to pregnant animals, effects on the developing fetus were observed at doses that were toxic to the mother, indication that the fetus is not more sensitive to this compound than the adult animal. When prothioconazole-desthio was given to pregnant animals, effects on the developing fetus were observed at doses that were not toxic to the mother, indicating that the fetus is more sensitive to this compound than the adult animal. Because of this observation, extra protective measures were applied during the risk assessment to further reduce the allowable level of human exposure to prothioconazole-desthio.

**Residues in Water and Food**

**Dietary risks from food and water are not of concern**

Aggregate dietary intake estimates (food plus water) revealed that the general population and all infants <1 year old, the subpopulation which would ingest the most prothioconazole relative to body weight, are expected to be exposed to less than 35% of the acceptable daily intake. Based on these estimates, the chronic dietary risk from exposure to prothioconazole residues is not of concern for any of the population sub-groups.

An acute reference dose was determined for the population subgroup of females 13-49 years of age. An aggregate (food and water) dietary intake estimate for females 13-49 years old used less than 85% of the acute reference dose, which is not a health concern.

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

The poultry feeding study that was submitted to support the conversion from conditional to full registration was reviewed and the data are adequate to establish MRLs in poultry tissues and eggs, as indicated in the Science Evaluation section of this Consultation Document.

**Occupational Risks from Handling Proline 480 SC Foliar Fungicide**

**Occupational risks are not of concern when Proline 480 SC Foliar Fungicide is used according to the proposed label directions, which include protective measures.**

Farmers and custom applicators who mix, load or apply Proline 480 SC Foliar Fungicide as well as field workers re-entering freshly treated fields can come in direct contact with Proline 480 SC Foliar Fungicide residues on the skin. Therefore, the label specifies that anyone mixing and loading Proline 480 SC Foliar Fungicide must wear long pants, long-sleeved shirts, boots, chemical resistant gloves and protective eyewear. The label also requires that workers do not enter treated fields for 24 hours after application. Taking into consideration these label statements, the number of applications and the expectation of the exposure period for handlers and workers, risk to these individuals are not a concern.

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

## Environmental Considerations

### What Happens When Prothioconazole Is Introduced into the Environment?

**Environmental risks to non-target organisms are not of concern when Proline 480 SC Foliar Fungicide is used according to label directions, which include precautionary label statements and buffer zones.**

Prothioconazole and the transformation products prothioconazole-desthio and prothioconazole-*S*-methyl have been considered together in a total toxic residue approach. Total toxic residues of prothioconazole are not expected to persist in soil, nor

are they expected to carryover to the next growing season. These compounds have low potential to leach through the soil profile and enter groundwater. Total toxic residues of prothioconazole are not expected to persist in aquatic environments under aerobic conditions, but they are expected to be persistent under anaerobic conditions. Residues of prothioconazole are not expected to be present in air due to its low volatility.

Proline 480 SC Foliar Fungicide, when used according to label directions, does not present a risk to earthworms, bees, beneficial arthropods and other insects, small mammals, birds, and terrestrial plants. However, Proline 480 SC Foliar Fungicide may pose a risk to some aquatic organisms. Precautionary label statements are thus included on the label and buffer zones up to 10 metres are required to mitigate exposure of sensitive aquatic habitats from spray drift.

## Value Considerations

### What Is the Value of Proline 480 SC Foliar Fungicide?

**Proline 480 SC Foliar Fungicide contains prothioconazole, a new active ingredient which will allow for greater alternation of fungicides in an integrated pest management program for foliar diseases of canola, chickpeas and lentils. This will contribute to reducing resistance development in fungal populations.**

Proline 480 SC Foliar Fungicide will provide a new chemical mode of action for use in controlling foliar diseases on canola, chickpea and lentils. In addition, suppressing fusarium head blight with Proline 480 SC Foliar Fungicide will also decrease the deoxynivalenol level in wheat and barley, thereby reducing the level of mycotoxin in the grain. This is a direct benefit in the quality of grain destined for animal and human consumption.

## Measures to Minimize Risk

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

The key risk-reduction measures being proposed on the label of Proline 480 SC Foliar Fungicide to address the potential risks identified in this assessment are as follows.

### Key Risk-Reduction Measures

### Human Health

Because there is a concern with users coming into direct contact with Proline 480 SC Foliar Fungicide on the skin, anyone mixing and loading Proline 480 SC Foliar Fungicide must wear long pants, long-sleeved shirts, boots, chemical resistant gloves and protective eyewear. In addition, standard label statements to protect against drift during application were added to the label.

### Environment

Precautionary label statements are included on the label to identify runoff concerns.

To protect non-target aquatic organisms, precautionary label statements are required on the label and Proline 480 SC Foliar Fungicide cannot be sprayed within up to 10 metres of sensitive aquatic habitats. The distance allowed depends on the method of application and the depth of the aquatic habitat.

## Next Steps

Before making a final registration decision on prothioconazole, the PMRA will consider all comments received from the public in response to this consultation document. The PMRA will accept written comments on this proposal up to 45 days from the date of publication of this document. Please note that, to comply with Canada's international trade obligations, consultation on the proposed MRLs will also be conducted internationally via a notification to the World Trade Organization. Please forward all comments to Publications (contact information on the cover page of this document). The PMRA will then publish a Registration Decision, which will include its decision, the reasons for it, a summary of comments received on the proposed final decision and the Agency’s response to these comments.

## Other Information

When the PMRA makes its registration decision, it will publish a Registration Decision on prothioconazole (based on the Science Evaluation of this consultation document). In addition, the test data referenced in this consultation document will be available for public inspection, upon application, in the PMRA’s Reading Room (located in Ottawa).

# Science Evaluation

## Prothioconazole

## 1.0 The Active Ingredient, Its Properties and Uses

Refer to the PMRA Regulatory Note REG2007-03 *Prothioconazole* for a detailed chemistry assessment of prothioconazole and its associated end-use product Proline 480 SC Foliar Fungicide.

The applicant has provided data for the characterization of the five batches of the Prothioconazole Technical Fungicide. The data have been assessed and found to be acceptable with the exception that additional studies are requested for one source under the open application 2009-0947. The chemistry requirements are complete to convert the registration for Prothioconazole Technical Fungicide from conditional to full registration.

## 2.0 Methods of Analysis

Detailed information on methods of analysis can be found in REG2007-03.

## 3.0 Impact on Human and Animal Health

### 3.1 Toxicology Summary

As a condition of registration, the registrant was required to submit histopathological results from the low and mid dose groups from the rat developmental neurotoxicity study. The registrant responded to all deficiencies. With respect to the histopathological data, there was an apparent effect at the high dose and a no observed adverse effect level (NOAEL) could not be set without information from all dose groups. From the submitted data, there was no evidence of peripheral nerve axonal degeneration or abnormalities in brain morphometrics at low and mid doses. As such, there is no longer any concern for potential neurotoxicity at these dose levels. The other outstanding questions were adequately addressed. The toxicological endpoints were revised to account for this new information.

Results of the acute and repeat-dose tests conducted on laboratory animals with prothioconazole, Proline 480 SC Foliar Fungicide, and prothioconazole-desthio are available in REG2007-03.

### 3.1.1 PCPA Hazard Characterization

For assessing risks from potential residues in food or from products used in or around homes or schools, the *Pest Control Products Act* requires the application of an additional 10-fold factor to take into account completeness of the data with respect to the exposure of and toxicity to infants and children and potential prenatal and postnatal toxicity. A different factor may be determined to be appropriate on the basis of reliable scientific data.

With respect to the completeness of the toxicity database, the data are adequate for determining pre- and post-natal toxicity and no additional studies are required at this time. For both prothioconazole and prothioconazole-desthio, there were 2-generation reproductive toxicity studies in the rat, preliminary and definitive rat developmental toxicity studies and a rabbit developmental toxicity study. A rat developmental neurotoxicity study was performed with prothioconazole-desthio. Prothioconazole-desthio proved to be the more toxic compound.

With respect to identified concerns relevant to the assessment of risk to infants and children, sensitivity of the young was identified in the oral rabbit developmental toxicity study. This study showed an increased incidence of arthrogryposis (a rare malformation) in the absence of maternal toxicity. Additionally, at slightly higher dose levels in the rat developmental neurotoxicity study, observations included progressive malocclusion and deviated snouts and increased stillborn pups. This information was taken into account in determining the appropriate factors in the risk assessment.

Overall, the toxicological database for prothioconazole is adequate for determining the sensitivity of the young. Due to the observed malformations in the absence of maternal toxicity, the 10-fold PCPA factor will be retained for endpoints relevant to the sensitive subpopulation.

## 3.2 Determination of Acute Reference Dose (ARfD)

**ARfD determination for females aged 13–49**

The NOAEL of 2 mg/kg bw/day established in the prothioconazole-desthio rabbit developmental toxicity study is considered appropriate for the determination of the ARfD for females 13–49. At the lowest observed adverse effect level (LOAEL) of 10 mg/kg bw/day, there was an increased incidence of arthrogryposis in the developing fetus in the absence of maternal toxicity. As outlined in Section 3.1.1, the PCPA factor was retained at 10-fold along with the standard uncertainty factors of 10-fold for inter-species extrapolation and 10-fold for intra-species variability. The composite assessment factor (CAF) is 1000.

$$\text{ARfD} = \frac{\text{NOAEL}}{\text{CAF}} = \frac{\text{2 mg/kg bw}}{1000} = 0.002 \text{ mg/kg bw}$$

**ARfD determination for the general population (excluding females aged 13–49)**

Based on the toxicological profile for prothioconazole and prothioconazole-desthio, no ARfD for the general population is required.

## 3.3 Determination of Acceptable Daily Intake (ADI)

**ADI determination for females aged 13–49**

The NOAEL of 2 mg/kg bw/day established in the prothioconazole-desthio rabbit developmental toxicity study is considered appropriate for the establishment of an ADI. At the LOAEL of 10 mg/kg bw/day, there were increased fetal malformations (arthrogryposis) in the absence of maternal toxicity. The applied factors included the standard 100-fold uncertainty factor to account for the inter-species extrapolation and intra-species variability, and the aforementioned PCPA factor of 10-fold. The CAF is 1000. The ADI proposed for females aged 13–49 is:

$$\text{ADI} = \frac{\text{NOAEL}}{\text{CAF}} = \frac{2 \text{ mg/kg bw/day}}{1000} = 0.002 \text{ mg/kg bw/day}$$

**ADI determination for the general population (excluding females aged 13–49)**

In determining the ADI, the results of the prothioconazole-desthio rat chronic and oncogenicity study were considered appropriate. The NOAEL of 1.1 mg/kg bw/day was established based on liver toxicity at the LOAEL of 8.0 mg/kg bw/day. The ADI is 0.011 mg/kg bw/day, based on the standard uncertainty factor of 100 to account for the inter-species extrapolation and intra-species variability. The PCPA factor is reduced from 10-fold to 1-fold because the database is considered adequate to assess potential pre- and post-natal toxicity and the endpoint of concern with respect to pre- and post-natal toxicity has been addressed in a population specific risk assessment (i.e. females aged 13–49). The composite assessment factor is 100.

The ADI is calculated according to the following formula:

$$\text{ADI} = \frac{\text{NOAEL}}{\text{CAF}} = \frac{1.1 \text{ mg/kg bw/day}}{100} = 0.011 \text{ mg/kg bw/day}$$

## 3.4 Occupational and Residential Risk Assessment

### 3.4.1 Toxicological Endpoints

Occupational exposure is characterized as short-term or intermediate-term and is predominately by the dermal route. A dermal developmental study with prothioconazole-desthio and a 28-day dermal toxicity study with prothioconazole were available. The prothioconazole-desthio study with a developmental NOAEL of 30 mg/kg bw/day based on increased incidences of supernumerary ribs at 100 mg/kg bw/day was considered appropriate for use as a toxicological endpoint. The worker population could include females of child bearing age (13–49). For this reason, the target Margin of Exposure (MOE) is 300, accounting for standard uncertainty factors

of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability, as well as the additional 3-fold factor to protect the unborn children of exposed female workers. This additional factor was applied in consideration of the seriousness of the endpoint (i.e. variations at maternally non-toxic doses) and the potential susceptibility of the foetus to the endpoint.

For short-term and intermediate-term inhalation exposures, the most appropriate toxicological endpoint was selected from the prothioconazole-desthio rabbit developmental toxicity study with a NOAEL of 2 mg/kg bw/day and arthrogryposis at the LOAEL of 10 mg/kg bw/day (a maternally non-toxic dose level). Again, the worker population could include females of child bearing age (13–49). For this reason, the target Margin of Exposure (MOE) is 1000, accounting for standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability, as well as the additional 10-fold factor to protect the unborn children of exposed female workers. This additional factor was applied in consideration of the seriousness of the endpoint (i.e. malformations at maternally non-toxic doses) and the potential susceptibility of the fetus to the endpoint.

The dermal and inhalation assessments are not to be combined. The two studies used for individual assessments do not share a common endpoint with the rat dermal developmental study having supernumerary ribs, whereas the rabbit developmental study has the malformation arthrogryposis.

### 3.4.2 Occupational Exposure and Risk

#### 3.4.2.1 Mixer/Loader/Applicator Exposure and Risk Assessment

Exposure and risk to workers mixing, loading and applying Proline 480 SC Foliar Fungicide to chickpeas, lentils, canola, rapeseed, Oriental mustard, wheat and barley were derived for workers wearing long pants, long-sleeved shirts, boots, and chemical resistant gloves and using groundboom and aerial application equipment and are presented in REG2007-03. Risk was found to be acceptable.

#### 3.4.2.2 Exposure and Risk Assessment for Workers Entering Treated Areas

Exposure and risk to workers entering fields treated with Proline 480 SC Foliar Fungicide were calculated and are presented in REG2007-03. Risk was found to be acceptable.

### 3.4.3 Bystander Exposure and Risk

Bystander exposure should be negligible since the potential for drift is expected to be minimal. Application is limited to agricultural crops only when there is low risk of drift to areas of human habitation or activity such as houses, cottages, schools and recreational areas, taking into consideration wind speed, wind direction, temperature, application equipment and sprayer settings.

## 3.5 Food Residues Exposure Assessment

### 3.5.1 Residues in Plant and Animal Foodstuffs

Refer to REG2007-03 for a summary of the data previously reviewed for residues in plant and animal foodstuffs. The information captured herein relates to the freezer storage stability data and poultry feeding study provided to the PMRA in support of the conversion from conditional to full registration.

The freezer storage stability data and poultry feeding study requirements identified in REG2007-03 were submitted and deemed to be adequate. Residues of prothioconazole and the metabolite prothioconazole-desthio are stable in most plant matrices when stored frozen at -10ºC for thirty six months. Residues of prothioconazole and the metabolite prothioconazole-4-hydroxy in bovine fat declined 68% and 58%, respectively, after 48 days of frozen storage. The poultry feeding study confirms that no secondary residues are expected in poultry tissues and eggs.

### 3.5.2 Dietary Risk Assessment

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

#### 3.5.2.1 Chronic Dietary Exposure Results and Characterization

The refined chronic dietary exposures from all supported prothioconazole food uses for the total population, including infants and children, and all representative population subgroups are <11% of the ADI. Aggregate exposure from food and water is considered acceptable. The PMRA estimates that chronic dietary exposure to prothioconazole from food and water is 7.6% (0.000838 mg/kg bw/day) of the ADI for the total population. The highest risk estimate is for females 13-49 years old at 35% (0.000699 mg/kg bw/day) of the ADI.

#### 3.5.2.2 Acute Dietary Exposure Results and Characterization

The refined acute dietary exposure (food alone) for all supported prothioconazole registered commodities is estimated to be 36% of the ARfD for females 13–49 years old (95$^{th}$ percentile, deterministic). Aggregate exposure from food and water is considered acceptable: 84% (0.001689 mg/kg/day) of the ARfD for females 13–49 years old.

### 3.5.4 Maximum Residue Limits

| Commodity | Recommended MRL (ppm) |
|---|---|
| Eggs | 0.01 |
| Meat and meat byproducts of poultry | 0.02 |

The established residue definition for prothioconazole currently includes the parent chemical only for animal commodities. However, in accordance with REG2007-03, the residue definition should reflect the parent chemical, prothioconazole-desthio and their conjugates. Therefore, this action is also proposed to modify the established prothioconazole residue definition for all animal commodities.

## 4.0 Impact on the Environment

Refer to REG2007-03 for a detailed assessment of the environmental impacts of prothioconazole and its end-use product, Proline 480 SC Foliar Fungicide.

No environmental incident reports were found for prothioconazole since the conditional registration was granted. Specific information regarding the mandatory reporting system regulations that came into force on April 26 2007 under the *Pest Control Products Act* can be found at http://canadagazette.gc.ca/partII/2006/20061115/html/sor260-e.html.

## 5.0 Value

Refer to REG2007-03 for a detailed value assessment.

## 6.0 Pest Control Product Policy Considerations

Refer to REG2007-03 for information on the Pest Control Product Policy considerations of prothioconazole and its end-use product, Proline 480 SC Foliar Fungicide.

## 7.0 Summary

### 7.1 Human Health and Safety

The toxicology database submitted is adequate to define the majority of toxic effects that may result from exposure to prothioconazole. In subchronic and chronic studies on laboratory animals, target organs included the liver, kidneys, thyroid, and ovaries. There was no evidence of carcinogenicity, but there was evidence of increased susceptibility of the young in developmental toxicity studies. Prothioconazole is not considered to be a neurotoxicant.

Mixer/loaders and applicators handling Proline 480 SC Foliar Fungicide and workers entering treated areas are not expected to be exposed to levels of Proline 480 SC Foliar Fungicide that will result in an unacceptable risk when Proline 480 SC Foliar Fungicide is used according to label directions. The personal protective equipment on the product label is adequate to protect workers.

Based on the submitted poultry feeding study, the PMRA recommends that maximum residue limits of 0.02 ppm and 0.01 ppm be established for residues of prothioconazole in/on poultry meat and meat byproducts, and eggs, respectively.

### 7.2 Environmental Risk

A detailed assessment of the environmental impact of prothioconazole and its end-use product, Proline 480 SC Foliar Fungicide, is provided in REG2007-03.

### 7.3 Value

A detailed assessment of the value of Proline 480 SC Foliar Fungicide is presented in REG2007-03.

## 8.0 Proposed Regulatory Decision

Health Canada's PMRA, under the authority of the *Pest Control Products Act* and Regulations, is proposing full registration for the sale and use of Prothioconazole Technical Fungicide and Proline 480 SC Foliar Fungicide, containing the technical grade active ingredient prothioconazole, for the control or suppression of Ascomycetes, Basiduimycetes and Deuteromycetes diseases on chickpeas, lentils, canola, rapeseed, Oriental mustard, wheat and barley.

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

# List of Abbreviations

| | |
|---|---|
| µg | micrograms |
| ADI | acceptable daily intake |
| ALS | acetolactate synthase |
| ARfD | acute reference dose |
| bw | body weight |
| CAF | composite assessment factor |
| kg | kilogram |
| km | kilometre |
| L | litre |
| LOAEL | lowest observed adverse effect level |
| LOQ | limit of quantitation |
| mg | milligram |
| MOE | margin of exposure |
| MRL | maximum residue limit |
| NOAEL | no observed adverse effect level |
| PCPA | *Pest Control Products Act* |
| PMRA | Pest Management Regulatory Agency |
| ppm | parts per million |
| USEPA | United States Environmental Protection Agency |

# Appendix I Tables and Figures

## Table 1 Integrated Food Residue Chemistry Summary

| Storage Stability | PMRA# 1626303 |
|---|---|
| Samples of canola seed, canola oil, mustard greens, tomato fruit, tomato paste, turnip root, wheat bran, wheat flour and wheat (forage, straw and grain) spiked with prothioconazole and prothioconazole-desthio separately at 0.25 ppm were stored at ≤ –10° C for a duration of 36 months. Residues of prothioconazole and prothioconazole-desthio were analyzed using method RPA JA/03/01 (LC-MS/MS). The results show that residues of prothioconazole-desthio were stable in all crop matrices during the 3 year interval. Residues of prothioconazole were stable in canola seed, canola oil, mustard greens, tomato fruit, turnip root, wheat flour, wheat forage and wheat straw for 3 years; but declined 45%, 36% and 38%, respectively, in tomato paste, wheat bran and wheat grain. | |

| Storage Stability | PMRA# 1626304 |
|---|---|
| Bovine fat samples spiked with prothioconazole and prothioconazole-4-hydroxy separately at 1.0 ppm were stored at ≤ –10° C for a duration of 48 days. The average storage stability recoveries data showed that prothioconazole and prothioconazole-4-hydroxy declined in this matrix by 68% and 58%, respectively, after 48 days of freezer storage.<br><br>As samples in poultry feeding study were analysed within 7 days of collection, freezer storage stability study were not required. | |

| LIVESTOCK FEEDING – Laying hens | PMRA# 1626305 |
|---|---|
| Three treatment groups of 12 laying hens each were dosed with prothioconazole at target dose rates of 0.26 ppm, 0.79 ppm and 2.59 ppm in feed for 29 consecutive days. Eggs were collected twice daily. After 29 days of dosing, hens were sacrificed within 22 hours of the final dose, and samples of liver, muscle and fat were collected. Egg and tissue samples were analysed for residues of prothioconazole, prothioconazole-desthio and prothioconazole-4-hydroxy using LC-MS/MS. The limit of quantitation (LOQ) for each analyte was 0.005 ppm in eggs, and 0.01 ppm in poultry tissues.<br><br>Residues were <LOQ in poultry liver, fat, muscle and eggs, at the maximum feeding level (2.59 ppm). | |

| Matrix | Feeding Level (ppm) | n | Min | Max | Median | Mean | Standard Deviation |
|---|---|---|---|---|---|---|---|
| Liver | 2.59 | 3 | <0.03 | <0.03 | <0.03 | <0.03 | -- |
| Fat | | 3 | <0.03 | <0.03 | <0.03 | <0.03 | -- |
| Muscle | | 3 | <0.03 | <0.03 | <0.03 | <0.03 | -- |
| Egg | | 6 | <0.015 | <0.015 | <0.015 | <0.015 | --- |

Residues were calculated as the sum of prothioconazole + prothioconazole-desthio + prothioconazole-4-hydroxy.

Based on the poultry feeding study conducted, no residues of prothioconazole are expected in/on poultry liver, fat, muscle and eggs as a result of registered uses. Therefore, MRLs for poultry commodities are recommended at the method LOQs.

**Table 2 Food Residue Chemistry Overview of Metabolism Studies and Risk Assessment**

| Dietary Risk from Food And Water | | | |
|---|---|---|---|
| **Chronic Non-Cancer Dietary Risk** | **POPULATION** | **ESTIMATED RISK (% of ADI)** | |
| | | **Food (MRLs)** | **Food + EEC** |
| **ADI = 0.011 mg/kg bw/day** | **All infants < 1 yr old** | 3.3 | 19.0 |
| **EEC = 25.1 µg/L (level 2)** | **Children 1 to 2 yrs** | 10.0 | 17.1 |
| | **Children 3 to 5 yrs** | 7.3 | 14.0 |
| Refined assessment | **Children 6 to 12 yrs** | 4.6 | 9.2 |
| | **Youth 13 to 19 yrs** | 2.6 | 6.1 |
| | **Adults 20 to 49 yrs** | 2.0 | 6.5 |
| | **Adults 50+ yrs** | 1.8 | 6.6 |
| | **Total Population** | 2.8 | 7.6 |
| **Chronic Non-Cancer Dietary Risk** | **Females 13 to 49 yrs** | 10.4 | 35.0 |
| **ADI = 0.002 mg/kg bw/day** | | | |
| **Acute Dietary Exposure** | **POPULATION** | **ESTIMATED RISK (% of ARfD)** | |
| **Analysis, Deterministic, 95$^{th}$ percentile** | | **Food (refined)** | **Food + EEC (refined)** |
| **ARfD = 0.002 mg/kg bw (females 13–49)** | **Females 13–49** | 36.2 | 84.5 |
| **EEC = 25.6 µg/L (level 2)** | | | |

Please refer to REG2007-03.

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

**Table 1 Difference between MRLs in Canada and in Other Jurisdictions**

| Commodity | Canada (ppm) | U.S. (ppm) | Codex* (ppm) |
|---|---|---|---|
| Eggs | 0.01 | none | Not established by Codex |
| Meat and meat byproducts of poultry | 0.02 | 0.02 (poultry liver) | |

* Codex is an international organization under the auspices of the United Nations that develops international food standards, including MRLs.

MRLs may vary from one country to another for a number of reasons, including differences in pesticide use patterns and the locations of the field crop trials used to generate residue chemistry data. For animal commodities, differences in MRLs can be due to different livestock feed items and practices.

Under the North American Free Trade Agreement (NAFTA), Canada, the United States and Mexico are committed to resolving MRL discrepancies to the broadest extent possible. Harmonization will standardize the protection of human health across North America and promote the free trade of safe food products. Until harmonization is achieved, the Canadian MRLs specified in this document are necessary. The differences in MRLs outlined above are not expected to impact businesses negatively or adversely affect international competitiveness of Canadian firms or to negatively affect any regions of Canada.

# References

## A. List of Studies/Information Submitted by Registrant

### 1.0 Chemistry

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### 2.0 Human and Animal Health

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