Proposed Registration Document PRD2014-03

Fenamidone

(publié aussi en français)

14 January 2014

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

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ISSN: 1925-0878 (print)
1925-0886 (online)

Catalogue number: H113-23/2014-3E (print version)
H113-23/2014-3E-PDF (PDF version)

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Overview

Proposed Registration Decision for Fenamidone

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 Fenamidone Technical Fungicide and Reason 500SC Fungicide, containing the technical grade active ingredient fenamidone, to control seed-borne late blight on potato.

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 Fenamidone Technical Fungicide and Reason 500SC 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.

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 (for example, children) as well as organisms in the environment (for example. 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 Pesticides and Pest Management portion of Health Canada's website at healthcanada.gc.ca/pmra.

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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."

Before making a final registration decision on fenamidone, 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 fenamidone, 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 Fenamidone?

Fenamidone is the active ingredient contained in Reason 500SC Fungicide (500 g a.i./L). It is a member of the imidazolinone chemical group. The mode of action of fenamidone is the inhibition of mitochondrial respiration in susceptible fungi.

Health Considerations

Can Approved Uses of Fenamidone Affect Human Health?

Reason 500SC Fungicide, containing fenamidone, is unlikely to affect your health when used according to the proposed label directions.

Potential exposure to fenamidone may occur through the diet (food and water) or when handling and applying the product. 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 (for example, children and nursing mothers). Only uses for 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 pesticide products are used according to label directions.

In laboratory animals, the acute toxicity of the end-use product Reason 500SC Fungicide was low by the oral and dermal routes of exposure. It was slightly acutely toxic via the inhalation route of exposure. It was mildly irritating to the eyes and slightly irritating to the skin. It did not cause an allergic skin reaction. The hazard signal words "CAUTION – EYE IRRITANT" are required on the label.

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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*.

Health effects in animals given repeated doses of fenamidone included effects on the liver and the thyroid. Fenamidone did not cause cancer in animals and did not damage genetic material. There was no indication that fenamidone caused damage to the nervous system or immune system. When fenamidone was given to pregnant animals, effects (reduced weight gain, delayed bone ossification) in the developing fetus were observed at doses that were toxic to the mother indicating that the young do not appear to be more sensitive to fenamidone than the adult animal. Reduced body weight gain was also observed in the offspring of animals exposed to fenamidone through pregnancy and lactation; however, this may have been the result of a direct consumption of treated diet by the young animals.

The risk assessment protects against the effects of fenamidone by ensuring that the level of human exposure is well below the lowest dose at which these effects occurred in animal tests.

Residues in Water and Food

Dietary risks from food and drinking water are not of health concern.

Aggregate dietary intake estimates (food plus drinking water) revealed that the general population and children 1-2 years old, the subpopulation which would ingest the most fenamidone relative to body weight, are expected to be exposed to less than 20% of the acceptable daily intake. Based on these estimates, the chronic dietary risk from fenamidone is not of health concern for all population subgroups.

Animal studies revealed no acute health effects. Consequently, a single dose of fenamidone is not likely to cause acute health effects in the general population (including infants and children).

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 for *Food and Drugs Act* purposes through the evaluation of scientific data under the *Pest Control Products Act.* Food containing a pesticide residue that does not exceed the established MRL does not pose an unacceptable health risk.

An MRL to cover residues of fenamidone in/on potatoes has been established based on residue data generated following foliar applications. The seed treatment use of fenamidone on this crop is not expected to result in residues exceeding the established MRL.

Occupational Risks From Handling Reason 500SC Fungicide

Occupational risks are not of concern when Reason 500SC Fungicide is used according to the proposed label directions, which include protective measures.

Workers treating potato seed pieces with Reason 500SC Fungicide on-farm and in commercial treating facilities can come into direct contact with fenamidone residues on the skin and through inhalation. Therefore, the label specifies that workers treating and handling treated potato seed pieces wear long sleeved shirt, long pants, shoes plus socks and chemical resistant gloves. Taking into consideration these label statements, and the expectation of the exposure period for handlers and workers, the risk to these individuals is 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 Fenamidone Is Introduced Into the Environment?

Fenamidone is introduced into the environment when used as a fungicide treatment for potato seed pieces.

Fenamidone is non-persistent in soil, while its major transformation products are expected to be moderately persistent to persistent in soil. Although the use pattern of this product does not include direct application to water, the possibility that aquatic systems will be exposed to fenamidone, directly or indirectly, cannot be ruled out. In an aquatic environment, fenamidone readily partitions from water to sediments, where it persists. Laboratory studies of mobility indicated that fenamidone and its major transformation products have moderate to high mobility in soils and sediment; however, no leaching of these compounds was observed below the 15 centimetre depth under field conditions. Based on its low volatility, fenamidone residues are not expected in the air. The *n*-octanol–water partition coefficient of fenamidone and its major transformation products indicate that these compounds have limited potential for bioaccumulation/bioconcentration in biological organisms.

Treatment of potato seed pieces is not expected to significantly increase environmental exposure of fenamidone. The environmental risks to non-target organisms have been previously assessed for expected environmental concentrations exceeding those from the additional treatment of potato seedlings (Regulatory Note REG2003-11, *Fenamidone Technical Fungicide, Reason 500SC Fungicide*). Existing environmental label statements are expected to mitigate known risks.

Value Considerations

What Is the Value of Reason 500SC Fungicide?

Reason 500SC Fungicide is a water-based suspension concentrate fungicide that controls seed-borne late blight when applied as a seed treatment.

It is the first seed treatment registered in Canada for this use, increases stand emergence in late blight-infected potato seeds, and may prevent the spreading of late blight spores during seed piece handling and planting operations. Reason 500SC Fungicide may also be tank-mixed with Titan Insecticide (Registration Number 27449) and/or Emesto Silver (Registration Number 30361) to increase the spectrum of controlled diseases from a single seed treatment application.

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 Reason 500SC 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 Reason 500SC Fungicide on the skin or through inhalation of spray mists, anyone applying Reason 500SC Fungicide to potato seed pieces or planting treated potato seed pieces must wear a long sleeved shirt, long plants, shoes plus socks and chemical resistant gloves.

Next Steps

Before making a final registration decision on fenamidone, 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 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 fenamidone (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

Fenamidone

1.0 The Active Ingredient, Its Properties and Uses

Please refer to Regulatory Note REG2003-11, *Fenamidone Technical Fungicide, Reason 500 SC Fungicide* for information on the identity of the active ingredient and the physical and chemical properties of the active ingredient and end-use product.

1.1 Directions for Use

Reason 500SC Fungicide is to be applied at 10 mL per 100 kg of potato seed pieces for control of seed-borne late blight. Tank-mixes with Titan Insecticide and/or Emesto Silver are permitted to increase the spectrum of controlled diseases.

1.2 Mode of Action

Fenamidone is a member of the imidazolinone chemical group and is classified as a Quinone outside Inhibitor (QoI or Group 11) by the Fungicide Resistance Action Committee. The mode of action of fenamidone is the inhibition of mitrochondrial respiration by blocking electron transport at the cytochrome b site on Complex III.

2.0 Methods of Analysis

Please refer to Regulatory Note REG2003-11 for information on the methods for analysis of the active ingredient, information on the method for formulation analysis, and the analytical methods on fenamidone residues in plant and animal matrices for data generation and enforcement purposes.

3.0 Impact on Human and Animal Health

3.1 Toxicology Summary

A detailed review of the toxicological database for fenamidone was previously conducted in 2003 and published under Regulatory Note REG2003-11. The database is complete, consisting of the full array of toxicity studies currently required for hazard assessment purposes. The studies were carried out in accordance with currently accepted international testing protocols and Good Laboratory Practices. The scientific quality of the data is high and the database is considered adequate to define the majority of the toxic effects that may result from exposure to fenamidone.

The toxicological database was re-examined and two changes were made to study no observed adverse effect limits (NOAELs). These two changes affect the toxicology endpoints for risk assessment.

In the two-generation reproductive toxicity study in rats, the observed decrease in body weight and body weight gain compared to controls among F_2 offspring at 64 mg/kg bw/day is considered adverse. The NOAEL for this effect was 4 mg/kg bw/day. This effect was seen during a period when pups were exposed through both milk and treated diet. An updated entry for this study is included in Appendix 1, Table 2.

In the rabbit developmental toxicity study, a lowest observed adverse effect limit (LOAEL) was established at 100 mg/kg bw/day based on increased liver weight. The NOAEL is 30 mg/kg bw/day. An updated entry for this study is included in Appendix 1, Table 2.

The toxicology endpoints for use in the human health risk assessment have been updated and are summarized in Appendix 1, Table 3.

Incident Reports

Since 26 April 2007, registrants have been required by law to report incidents, including adverse effects to health and the environment, to the PMRA within a set time frame. Information on the reporting of incidents can be found on the Pesticides and Pest Management portion of Health Canada's website. Incidents from Canada and the United States were searched and reviewed for fenamidone. As of 8 October 2013, there were no incident reports for the active ingredient fenamidone.

3.1.1 *Pest Control Products Act* Hazard Charaterization

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 threshold effects 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 as it pertains to the toxicity to infants and children, the fenamidone database contains the required studies including developmental toxicity studies in rats and rabbits and a two-generation reproductive toxicity study in rats.

With respect to potential prenatal and postnatal toxicity, in the rat reproductive toxicity study, there was reduced body weight and body weight gain in the offspring of the second generation in the latter stages of the lactation phase. This effect was observed in the absence of maternal toxicity. Due to the timing of the effect where the juveniles could be receiving fenamidone both through milk and the treated diet, plus the lack of an equivalent effect in the first generation, there was a low level of concern with regards to sensitivity of the young. In the rat developmental toxicity study, there were minor developmental delays in the presence of maternal toxicity. In the rabbit developmental toxicity study there were no treatment-related

developmental effects noted. Overall, the database is adequate for determining the sensitivity of the young. There is a low concern for the sensitivity of the young and effects on the young are well characterized. Given these considerations, the *Pest Control Products Act* factor was reduced to 1-fold.

3.2 Acute Reference Dose (ARfD)

Since no acute endpoints of concern were identified in the toxicology database, an ARfD was not established.

3.3 Acceptable Daily Intake (ADI)

To estimate risk from repeated dietary exposure, a NOAEL of 4 mg/kg bw/day from the rat reproductive toxicity study was selected for risk assessment. At the LOAEL of 64 mg/kg bw/day, decreased body weight and body weight gain were observed in the second generation offspring. Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability were applied. As discussed in the *Pest Control Products Act* Hazard Characterization section, the *Pest Control Products Act* factor was reduced to 1-fold. **The composite assessment factor (CAF) is 100**.

The ADI is calculated according to the following formula:

$$\text{ADI} = \frac{\text{NOAEL}}{\text{CAF}} = \frac{4 \text{ mg/kg bw/day}}{100} = 0.04 \text{ mg/kg bw/day of fenamidone}$$

Cancer Assessment

There was no treatment-related increase in tumours in rats or mice; therefore, a cancer risk assessment was not required.

3.4 Occupational and Residential Risk Assessment

3.4.1 Toxicological Endpoints

Short-term Dermal

The short-term toxicology endpoint remains unchanged from that published in Regulatory Note REG2003-11.

Intermediate-term Dermal

For the intermediate-term dermal risk assessment, the limit dose NOAEL of 1000 mg/kg bw/day from the 28-day dermal toxicity study in rats was selected for risk assessment. While fenamidone does show increased toxicity from short- to long-term durations, there was no significant increase in toxicity between 28- and 90-day exposures. The target margin of exposure (MOE) is 100, which includes uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability. The selection of this study and MOE is considered to be protective of all populations, including nursing infants and unborn children.

Short- and Intermediate-term Inhalation

Toxicology endpoints for short- and intermediate-term inhalation were not previously published in Regulatory Note REG2003-11. For the short-term inhalation risk assessment, the NOAEL of 74 mg/kg bw/day from the 90-day rat oral neurotoxicity study was selected for risk assessment. This study was selected as there was no route-specific study of the appropriate duration. Additionally, this NOAEL represents the highest NOAEL below a relatively consistent set of LOAELs for comparable study durations. In this study, the NOAEL was based on decreased body weight gain and food consumption at the LOAEL of 392 mg/kg bw/day. The target MOE is 100, which includes uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability. The selection of this study and MOE is considered to be protective of all populations, including nursing infants and unborn children.

3.4.1.1 Dermal Absorption

Occupational exposure to fenamidone is characterized as short- to intermediate-term in duration and is predominantly by the dermal and inhalation routes.

3.4.2 Occupational Exposure and Risk

Potato seed pieces can be treated with Reason 500SC Fungicide in commercial treatment facilities, on-farm and planted using conventional potato seed piece planting equipment.

3.4.2.1 Seed Treatment Exposure and Risk Assessment

Individuals have potential for exposure to fenamidone while treating seed in commercial potato seed treatment facilities or while treating on-farm. Chemical specific data for assessing human exposure during potato seed treatment were not submitted. As such, surrogate exposure data were used to estimate risk to workers in commercial treatment facilities and while treating on-farm.

3.4.2.1.1 Cutter/Sorter/Treater Exposure and Risk Assessment

Exposure estimates for treaters and cutters/sorters in on-farm and commercial potato seed treatment operations were estimated using a surrogate passive dosimetry study. Sixteen worker replicate trials were conducted to generate dermal and inhalation exposure data for workers

treating potato seed pieces on-farm using Admire 240 Flowable Systemic Insecticide (Registration Number 24094), a liquid flowable formulation containing the active ingredient imidacloprid. For treaters, the average total task based dermal and inhalation exposures were 291 µg/kg a.i. handled and 11.5 µg/kg a.i. handled, respectively. For cutter/sorters, the average total task based inhalation exposure was 18.0 µg/kg a.i. handled. Exposure estimates are based on workers wearing single layer of clothing and gloves. Although the study was conducted on-farm, exposure to commercial treatment workers should not be underestimated.

The amount of potato seed pieces treated was estimated at 178,000 kg/day for on-farm treatment and 290,400 kg/day for large scale (commercial) treatment. Dermal exposure was estimated by coupling the unit exposure values with the amount of product handled per day. Inhalation exposure was estimated by coupling the unit exposure values with the amount of product handled per day with 100% inhalation absorption. Exposure was normalized to mg/kg bw/day by using 80 kg adult body weight.

Exposure estimates were compared to the NOAEL to obtain the MOE; the target MOE is 100.

Table 1 Mixer/Loader/Applicator Dermal Exposure estimates and MOE

Scenario	Dermal unit exposure (µg/kg a.i. handled)	Inhalation unit exposure (µg/kg a.i. handled)	Dermal exposure (mg/kg bw/day)[1]	Inhalation exposure (mg/kg bw/day)[2]	Dermal MOE[4]	Inhalation MOE[5]
Treating	291	11.5	0.053	0.0021	18,927	35,238
Cutting/sorting	N/A	18.0	N/A	0.0033	N/A	22,424
Treating and cutting/sorting[3]	291	18.0	0.053	0.0033	18,927	22,424

[1] Dermal Exposure (mg/kg bw/day) = $\frac{\text{Unit exposure} \times \text{kg a.i. handled per day}}{80 \text{ kg bw} \times 1000 \text{ µg/mg}}$

[2] Inhalation Exposure (mg/kg bw/day) = $\frac{\text{Unit exposure} \times \text{kg a.i. handled per day}}{80 \text{ kg bw} \times 1000 \text{ µg/mg}}$

The kg a.i. handled per day = 0.005 kg a.i./100 kg seed * 290,400 kg seed treated per day = 14.525 kg a.i./day

[3] The exposure from treating and cutting/sorting were combined since the treater may occasionally provide brief relief to a worker on the cutting/sorting line (dermal exposure for treating + inhalation exposure from cutting/sorting).

[4] Based on a NOAEL of 1000 mg/kg bw/day (target MOE = 100)

[5] Based on a NOAEL of 74 mg/kg bw/day (target MOE = 100)

3.4.2.2 Exposure and Risk Assessment for Workers Entering Treated Areas

Individuals have potential for exposure to Reason 500SC Fungicide while planting treated potato seed pieces. Chemical specific data for assessing human exposure during planting of treated potato seed pieces were not submitted. As such, surrogate exposure data were used to estimate risk to workers planting treated potato seed pieces.

3.4.2.2.1 Exposure and Risk Assessment for Workers Planting Treated Potato Seed Pieces

To address exposure during planting, a surrogate planting study was used. The study was designed to determine operator exposure to pencycuron when applying Monceren DS 12.5 (Great Britain registration, MAPP 11292) in potato fields during planting. A total of five farmers were monitored while wearing a single layer of clothing and gloves. Normalized to the amount of active substance handled, the total dermal exposure averaged 2.86 mg/kg a.i. Inhalation exposure for loading and application averaged 34 µg/kg a.i. during loading and 43.57 µg/kg a.i. during application. Combined total inhalation exposure was 78 µg/kg a.i. Given the small sample size (n=5), it was considered appropriate to use the 90th percentile unit exposure values in the calculation of risk. The 90th percentile values for dermal and combined inhalation exposure are 4.19 mg/kg a.i. handled and 0.145 mg/kg a.i. handled, respectively.

The amount of potato seed pieces treated and planted in one day was estimated at 29,200 kg/day for small farms and 120,800 kg/day for large scale operations.

In smaller operations, a worker often treats and plants. In larger operations, a treater will only treat; a separate individual does the planting. Planter exposure could not be assessed separately from the treater exposure when using the pencycuron study. Nevertheless, since the exposure for a worker who only plants is lower than one who treats and plants (if handling the same amount of active), risk is acceptable for a planter if it is acceptable for a treater/planter in regards to this proposed use. Table 2 presents the exposure estimates and risk of a small grower and a large grower treating/planting potato seed pieces. Risks for workers treating and planting are not of concern.

Exposure estimates were compared to the NOAEL to obtain the MOE; the target MOE is 100.

Table 2 Planter Exposure for Potato Seed Pieces

Scenario	Dermal Unit Exposure (mg/kg a.i. handled)	Inhalation Unit Exposure (mg/kg a.i. handled)	Amount of seed treated/ planted per day (kg)[1]	Total amount of a.i. handled per day (kg)[2]	Dermal exposure (mg/kg bw/day)[3]	Inhalation Exposure (mg/kg bw/day)[4]	Dermal MOE[5]	Inhalation MOE[6]
Treater/ planter (small grower)	4.19	0.145	29,200	1.460	0.076	0.0026	13,077	27,964
Treater/ planter (large grower)	4.19	0.145	120,800	6.040	0.316	0.0109	3,161	6,760

[1] From "Seed Treated/Planted per Day" 2009

[2] Amount treated/planted per day × application rate (5 g a.i./100 kg seed)

[3] Dermal Exposure (mg/kg bw/day) = $\frac{\text{Unit exposure} \times \text{Total amount of a.i. handled per day}}{80 \text{ kg bw}}$

[4] Inhalation Exposure (mg/kg bw/day) = $\frac{\text{Unit exposure} \times \text{Total amount of a.i. handled per day}}{80 \text{ kg bw}}$

[5] Based on a NOAEL of 1000 mg/kg bw/day (target MOE = 100)

[6] Based on a NOAEL of 74 mg/kg bw/day (target MOE = 100)

3.4.3 Bystander Exposure and Risk

Bystander exposure should be negligible since the potential for drift is expected to be minimal when planting treated potato seed pieces.

3.5 Food Residues Exposure Assessment

3.5.1 Residues in Plant and Animal Foodstuffs

Fenamidone is currently registered for foliar application on various crops including potatoes. Please refer to Regulatory Note REG2003-11 and Proposed Registration Decision PRD2007-07, *Fenamidone,* for the residue definition for risk assessment and enforcement purposes, for the field trial data on potatoes resulting from foliar applications, and for the frozen storage stability of fenamidone in plant and animal foodstuffs. The information captured herein only relates to the seed treatment use on potatoes and the change in the chronic dietary exposure estimates due to the revision of the ADI.

Based on foliar applications, an MRL for fenamidone was established at 0.02 ppm for potatoes. The seed treatment use of fenamidone on this crop at a lower rate and longer preharvest interval is not expected to result in residues exceeding the established MRL.

3.5.2 Dietary Risk Assessment

Refined 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 US 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 following criteria were applied to the refined chronic analysis: 100% crop treated, residue levels at supervised trial median residue values (STMdRs) from field trial data if available, or Canadian MRLs and US tolerances, and experimental or default processing factors. Aggregate chronic exposure to fenamidone from food and drinking water is considered acceptable. The PMRA estimates that chronic dietary exposure to fenamidone from food and drinking water is 11.6% (0.004644 mg/kg bw/day) of the ADI for the total population. The highest exposure and risk estimate is for children 1-2 years old, at 19.0% (0.007608 mg/kg bw/day) of the ADI.

3.5.2.2 Acute Dietary Exposure Results and Characterization

No appropriate endpoint attributable to a single dose for the general population (including children and infants) was identified.

3.5.3 Aggregate Exposure and Risk

The aggregate risk for fenamidone consists of exposure from food and drinking water sources only.

3.5.4 Maximum Residue Limits

No revision is required for the established MRLs. Please refer to Regulatory Note REG2003-11 and Proposed Registration Decision PRD2007-07 for detailed discussion of the nature of the residues in animal and plant matrices, analytical methodologies, field trial data, and chronic dietary risk estimates.

4.0 Impact on the Environment

No new environmental data were submitted for the addition of treatment of cut potato seed pieces to the Reason 500SC Fungicide label, nor were any required. Refer to Regulatory Document REG2003-11 for a detailed assessment of the environmental impact of fenamidone. The proposed use will not significantly increase environmental exposure to fenamidone. The PMRA does not anticipate any increased risk to the environment from the use of treated potato seed pieces. Existing environmental label statements are expected to mitigate known risks.

5.0 Value

5.1 Effectiveness Against Pests

5.1.1 Control of Seed-Borne Late Blight on Potatoes

Five efficacy trials were provided in support of Reason 500SC Fungicide for control of seed-borne late blight (*Phytophthora infestans*) on potatoes. Studies were conducted in British Columbia and Ontario during the 2011 and 2012 growing seasons. Severe disease pressure was observed one month after planting, as only 2-15% of the plants emerged in the inoculated controls. In four out of five trials, plant emergence averaged 92% when Reason 500SC Fungicide was applied at 10 mL per 100 kg seed pieces. In comparison, plant emergence averaged 89% in the mancozeb treatment. Lower emergence rates were noted across treatments in the fifth trial, in other words, 65% plant emergence in the non-inoculated control. Reason 500SC Fungicide still significantly increased stand counts compared to the inoculated control. Furthermore, fenamidone treatments were statistically comparable to the non-inoculated controls with respect to marketable yield. However, no late blight assessments were performed on potato foliage or tubers later in the growing season. The weight of evidence supports the use of Reason 500SC Fungicide for control of seed-borne late blight on potatoes.

In three tolerance trials from Prince Edward Island (2012), the three-way tank-mix of Reason 500SC Fungicide, Titan Insecticide and Emesto Silver did not decrease emergence compared to untreated potatoes. Titan Insecticide and/or Emesto Silver may be tank-mixed with Reason 500SC Fungicide to increase the spectrum of controlled diseases from a single seed treatment application.

5.2 Economics

No economic analysis was performed for this application.

5.3 Sustainability

5.3.1 Survey of Alternatives

No fungicide seed treatments are currently registered in Canada for control of seed-borne late blight on potatoes.

5.3.2 Compatibility with Current Management Practices Including Integrated Pest Management

When Reason 500SC Fungicide was tank-mixed with insecticide (Titan Insecticide) and fungicide (Emesto Silver) seed treatments, no adverse effects were noted, which is indicative of fenamidone's compatitility with certain conventional active ingredients. When used as recommended, Reason 500SC Fungicide is not expected to interfere with the cultural and sanitation practices intended to prevent disease development in field crops.

5.3.3 Information on the Occurrence or Possible Occurrence of the Development of Resistance

According to the Fungicide Resistance Action Committee, QoIs such as fenamidone present a high risk of resistance development, while *P. infestans* is identified as having a medium risk of resistance development. Nevertheless, no cases of resistance to QoIs have been reported in field populations of *P. infestans*.

Reason 500SC Fungicide is applied preventatively on potato seed pieces. This single fungicide application targets the seed and seedling stage, when *P. infestans* populations are substantially lower in potato fields. The probability of having resistant fungal genotypes is thus reduced, which contributes to sound resistance management. Based on these considerations, the overall risk of resistance development to fenamidone is not expected to be a major concern.

5.3.4 Contribution to Risk Reduction and Sustainability

By targeting the seed-borne phase of the disease, Reason 500SC Fungicide will prevent the spreading of late blight spores during seed handling and planting operations as well as enhance stand establishment.

6.0 Pest Control Product Policy Considerations

While reviewing fenamidone the PMRA took into account the federal Toxic Substances Management Policy (TSMP) and has followed its Regulatory Directive DIR99-03, *The Pest Management Regulatory Agency's Strategy for Implementing the Toxic Substances Policy*. Based on an assessment of the complete data package, the PMRA has been determined that this product does not meet TSMP Track-1 criteria. This product does not contain any impurities of human health or environmental concerns and does not contain any US EPA or PMRA List 1 or 2 formulants.

Refer to Regulatory Note REG2003-11 for more detail.

7.0 Summary

7.1 Human Health and Safety

The toxicology database submitted for fenamidone is adequate to define the majority of toxic effects that may result from exposure. There was no evidence of carcinogenicity in rats or mice after longer-term dosing. The weight of evidence suggests that fenamidone does not damage genetic material. There was a low level of concern for increased susceptibility of the young in reproduction or developmental toxicity studies. Fenamidone was not neurotoxic. In short-term and chronic studies on laboratory animals, the primary target was the liver. The thyroid was also a target organ for rats. The risk assessment protects against the toxic effects noted above by ensuring that the level of human exposure is well below the lowest dose at which these effects occurred in animal tests.

The proposed seed treatment use of fenamidone on potatoes does not constitute a health risk of concern for chronic dietary exposure (food and drinking water) to any segment of the population, including infants, children, adults and seniors. No revision is required for the established MRLs.

Workers treating potato seed pieces with Reason 500SC Fungicide and workers planting treated potato seed pieces are not expected to be exposed to levels of fenamidone that will result in risks of concern when Reason 500SC Fungicide is used according to label directions. The personal protective equipment on the product label is adequate to protect workers.

7.2 Environmental Risk

The environmental database for fenamidone and Reason 500SC Fungicide are adequate and acceptable. The proposed use for potato seed treatment will not significantly increase environmental exposure to fenamidone. The environmental risk to fenamidone exposure has been fully characterized for rates higher than those expected with the additional potato seed treatment use (refer to Regulatory Note REG2003-11 for more detail). Therefore, increased risk to the environment is not anticipated. Existing environmental label statements are expected to mitigate known risks.

7.3 Value

The submitted value information supports the use of Reason 500SC Fungicide for control of seed-borne late blight on potatoes, when applied according to label directions.

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 Fenamidone Technical Fungicide and Reason 500SC Fungicide, containing the technical grade active ingredient fenamidone, to control seed-borne late blight on potatoes.

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
a.i.	active ingredient
ARfD	acute reference dose
bw	body weight
bwg	bodyweight gain
CAF	composite assessment factor
EEC	estimated environmental concentration
F_0	parental generation
F_1	first generation
F_2	second generation
fc	food consumption
fe	food efficiency
g	gram
kg	kilogram
L	litre
LC_{50}	lethal concentration 50%
LD_{50}	lethal dose to 50%
LOAEL	lowest observed adverse effect level
MAS	maximum average score
mg	milligram
mL	millilitre
MOE	margin of exposure
MRL	maximum residue limit
N/A	not applicable
NOAEL	no observed adverse effect level
NZW	New Zealand white
PMRA	Pest Management Regulatory Agency
ppm	parts per million
SC	suspension concentrate
TSMP	Toxic Substances Management Policy
US	United States
wt	weight

Appendix I Tables and Figures

Table 1 Toxicity Profile of Reason 500SC Fungicide Containing Fenamidone

Study Type/Animal/PMRA #	Study Results
Acute oral toxicity Sprague-Dawley rats PMRA # 777289	LD_{50} > 5000 mg/kg bw Low toxicity
Acute dermal toxicity NZW rabbits PMRA # 777290	LD_{50} > 5000 mg/kg bw Low toxicity
Acute inhalation toxicity (nose-only) Sprague-Dawley rats PMRA # 777291	LC_{50} > 0.9 mg/L Slight toxicity
Dermal irritation NZW rabbits PMRA # 777293	MIS = 17.0/110 Mildly irritating
Eye irritation NZW rabbits PMRA # 777292	MAS = 1.5/8.0 Slightly irritating
Dermal sensitization (Beuhler test) Hartley guinea pigs PMRA # 777296	Non-sensitizer

Table 2 Amended Toxicity studies for Fenamidone
(Effects are known or assumed to occur in both sexes unless otherwise noted; in such cases, sex-specific effects are separated by semi-colons. Organ weight effects reflect both absolute organ weights and relative organ to bodyweights unless otherwise noted)

Study	Species/Strain and Dose	Target Organ/Significant Effects/ Comments
Developmental Toxicity Study (gavage) NZW rabbits	99.8% pure 30 females/dose 0, 10, 30, 100 mg/kg bw/day, days 6-28	Maternal NOAEL = 30 mg/kg bw/day **100 mg/kg bw/day** ↑ liver wt Developmental NOAEL = 100 mg/kg bw/day No treatment-related developmental effects were observed No evidence of sensitivity of the young
Multi-Generation Toxicity Study (diet) Sprague Dawley rats	99.8% pure 25/sex/dose 0, 60, 1000, 5000 ppm = 0, 3.90/4.04, 63.76/68.61, 328.35/353.20 mg/kg bw/day	Parental NOAEL = 64 mg/kg bw/day **≥ 328 mg/kg bw/day** F_0 ↓ bw, bwg, fe, ↑ liver and spleen wt F_1 ↓ bw, bwg, fc, ↑ liver and spleen wt Offspring NOAEL = 4 mg/kg bw/day **≥ 64 mg/kg bw/day** ↓ bw, bwg (at 21 days) F_2 Reproductive NOAEL = 323 mg/kg bw/day No treatment-related reproductive effects were observed Sensitivity of the young

Table 3 Toxicology Endpoints for Use in Health Risk Assessment for Fenamidone

Exposure Scenario	Study	Point of Departure and Endpoint	CAF[1] or Target MOE
Acute dietary	No acute endpoints of concern were identified		
Repeated dietary	2-generation rat dietary reproductive toxicity study	NOAEL = 4 mg/kg bw/day Decreased body weight and body weight gain in F_2 juveniles at the LOAEL of 64 mg/kg bw/day	100
	ADI = 0.04 mg/kg bw/day		
Short and intermediate-term dermal	28-day rat dermal toxicity study	NOAEL = 1000 mg/kg bw/day Highest dose tested, no adverse effects.	100
Short and intermediate - term inhalation[2]	90-day rat oral neurotoxicity study	NOAEL = 74 mg/kg bw/day Decreased body weight gain and food consumption at the LOAEL of 392 mg/kg bw/day	100
Cancer	Not genotoxic. Not oncogenic in rats or mice.		

[1] CAF (composite assessment factor) refers to a total of uncertainty and *Pest Control Products Act* factors for dietary assessments; MOE refers to a target margin of exposure for occupational assessments

[2] Since an oral NOAEL was selected, an inhalation absorption factor of 100% (default value) was used in route-to-route extrapolation.

Table 4 Food Residue Chemistry Overview of Dietary Risk Assessment

DIETARY RISK FROM FOOD AND WATER		
Basic chronic non-cancer dietary risk	**POPULATION**	**ESTIMATED RISK % of ACCEPTABLE DAILY INTAKE (ADI)**
		Food and Water
ADI = 0.04 mg/kg bw/day **Estimated chronic drinking water concentration:** **EEC $_{RPA\ 717879}$ = 60.1 μg a.i./L** **EEC $_{Fenamidone}$ = 0.18 μg a.i./L**	**All infants < 1 year**	15.5
	Children 1-2 years	19.0
	Children 3-5 years	18.0
	Children 6-12 years	12.4
	Youth 13-19 years	10.0
	Adults 20-49 years	10.6
	Adults 50+ years	11.5
	Total population	11.6

Table 5 Use (label) Claims Proposed by Applicant and Whether Acceptable or Unsupported

Proposed claim	Decision
Potatoes: control of seed-borne late blight (*Phytophthora infestans*) with one Reason 500SC Fungicide application at 10 mL per 100 kg seed pieces	Supported
Tank-mix of Reason 500SC Fungicide with Titan Insecticide and/or Emesto Silver. The user must adhere to the most restrictive label precautions and limitations.	Supported

References

A. List of Studies/Information Submitted by Registrant

1.0 Human and Animal Health

PMRA Document Number	Reference
777289	1999, An Acute Oral Toxicty Study In Rats With Exp 10623A, DACO: 4.6.1
777290	1999, An Acute Dermal Toxicity Study In Rabbits With Exp 10623A, DACO: 4.6.2
777291	1999, Acute Inhalation Toxicity Study of EXP10623A in Albino Rats, DACO: 4.6.3
777292	1999, A Primary Eye Irritation Study In Rabbits With Exp 10623A, DACO: 4.6.4
777293	1999, An Primary Skin Irritation Study in Rabbits With Exp 10623A, DACO: 4.6.5
777296	1999, A Dermal Sensitization Study in Guinea Pigs With Exp 10623A. Modified Buehler Method, DACO: 4.6.6
1986272	2006, Metabolism of [N-phenyl-UL-14C]fenamidone in carrots, DACO: 6.3
2280036	2002, Magnitude of fenamidone residues on potatoes after multiple applications of reason fungicide and a 14 day PHI, DACO: 7.2.1,7.2.2,7.2.3,7.2.4,7.2.5,7.4.1
1484699	2007, Admire 240 F - Determination of Dermal and Inhalation Exposure of Workers during On-Farm Seed Piece Treatment of Potatoes, University of Guelph, Centre for Toxicology, DACO 5.4
1525896	2001, Determination of exposure to pencycuron during loading and application of Moncereen®-Droogontsmetter (Monceren DS 12.5) in potato fields, Bayer AG Business Group Crop Protection Development Department Institute for Metabolism Research and Residue Analysis, DACO 5.6a

2.0 Value

PMRA Document Number	Reference
2280043	2012, Reason Fungicide - for control of seed-borne late blight of potato, DACO: 10.1, 10.2.2, 10.2.3.1, 10.2.3.4, 10.3.1, 10.3.2
2280053	2012, Reason Fungicide - for control of seed-borne late blight of potato, DACO: 10.1, 10.2.2, 10.2.3.1, 10.2.3.4, 10.3.1, 10.3.2