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Agence de réglementation de la lutte antiparasitaire

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PROPOSED REGISTRATION DECISION

Fenamidone

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FOREWORD

Proposed Registration Decision for Fenamidone

Health Canada's Pest Management Regulatory Agency (PMRA), under the authority of the *Pest Control Products Act*[1] and in accordance with the Pest Control Products Regulations, is proposing full registration for the sale and use of Reason 500 SC Fungicide containing the technical grade active ingredient fenamidone and applied with ground or aerial equipment to control early and late blight on potatoes.

An evaluation of available scientific information found that, under the approved conditions of use, the end-use 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 section provides detailed technical information on human health, environmental and value assessment of Reason 500 SC 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[2] to people and the environment from the use of pest control products. Health or environmental risk is considered acceptable 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 conditions or proposed conditions of registration. The Act also requires that products have value[3] 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 (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 present 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 www.pmra-arla.gc.ca.

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1 As per subsection 28(1) of the *Pest Control Products Act*.

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

3 "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".

What Is Fenamidone?

Fenamidone is the active ingredient in Reason 500 SC Fungicide. Reason 500 SC Fungicide, containing 500 g/L of fenamidone, is a flowable concentrate fungicide to control early and late blight on potatoes. Reason 500 SC Fungicide can be applied with ground or aerial equipment when it is tank-mixed with Dithane DG or Bravo 500. The rates of application are Reason 500 SC Fungicide at 200 ml/ha with Dithane DG at 1.25 kg/ha or Bravo 500 at 1.25 L/ha at 7–10 day intervals. A maximum of 6 applications of Reason 500 SC Fungicide in a tank mix is allowed per year (maximum rate of application of fenamidone is 0.60 kg a.i./ha per season based on 6 applications of 100 g a.i./ha).

❖ Health Considerations

♦ Can Approved Uses of Fenamidone Affect Human Health?

Fenamidone is unlikely to affect your health when used according to the proposed label directions.

A toxicology assessment of fenamidone and Reason 500 SC Fungicide is presented in Regulatory Note REG2003-11, *Fenamidone Technical Fungicide, Reason 500 SC Fungicide*.

♦ Residues in Water and Food

Dietary risks from food and water are not of concern.

A dietary risk assessment of fenamidone and Reason 500 SC Fungicide is presented in Regulatory Note REG2003-11.

Aggregate dietary intake estimates (food plus 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 5.0% of the acceptable daily intake. Based on these estimates, the chronic dietary risk from fenamidone is not of concern for all population subgroups. There is no lifetime cancer risk from the use of fenamidone.

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 food containing a pesticide residue that exceeds the established maximum residue limit (MRL). Each MRL value determines the maximum concentration in parts per million (ppm) of a pesticide allowed in or on certain foods. Pesticide MRLs are established for the *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.

Information submitted was sufficient to show that N-phenyl anilines do not form from the metabolism of fenamidone in plants. No new MRLs are being recommended at this time.

♦ Occupational Risks From Handling Fenamidone

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

An occupational risk assessment of fenamidone and Reason 500 SC Fungicide is presented in Regulatory Note REG2003-11.

Direct skin contact can occur with fenamidone when farmers and pesticide applicators are mixing, loading or applying Reason 500 SC Fungicide as well as when field workers re-enter freshly treated fields. Therefore, the label specifies that anyone mixing or loading Reason 500 SC Fungicide must wear a long-sleeved shirt, pants, boots, protective eye wear and chemical-resistant gloves. Taking into consideration these label requirements and that occupational exposure is expected to be of short to intermediate duration, risk to farmers, applicators or workers is not a concern.

For bystanders, the exposure is expected to be much less than that of field workers, which 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 on potatoes. 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.

Fenamidone will pose a negligible risk to earthworms, honeybees, wild birds, wild mammals (based on acute exposure) and non-target terrestrial plants, at the proposed application rate. However, the level of concern is exceeded for wild mammals (based on dietary and chronic exposure), beneficial insects, amphibians, freshwater and saltwater invertebrates. Therefore, buffer zones to protect sensitive aquatic habitats are required during application. In addition, environmental hazard statements are required for protection of beneficial insects.

❖ Value Considerations

♦ What Is the Value of Fenamidone?

A value assessment of Reason 500 SC Fungicide is presented in Regulatory Note REG2003-11. Since the publication of Regulatory Note REG2003-11, the directions for application of Reason 500 SC alone at the rate of 400 mL/ha have been removed from the label. Application with aerial equipment has been added to the Reason 50 SC Fungicide label.

Reason 500 SC Fungicide is a foliar fungicide for control of early blight and late blight on potatoes applied with ground or aerial equipment. It is a preventative, protecting fungicide that inhibits fungal spore germination, and acts as an antisporulant.

Reason 500 SC must be tank-mixed with Dithane DG (mancozeb) or Bravo 500 (chlorothalonil) when applied. When Reason 500 SC fungicide is applied as directed, it controls early and late blight disease to commercially acceptable levels.

The value of Reason 500 SC Fungicide is its strong activity against early and late blight on potatoes. In addition, it is an alternative to some of the older, less effective fungicide chemistries currently used as stand-alone products for control of late blight on potatoes. The rates at which the tank mix partners are tank mixed with Reason 500 SC are at the low end of their registered rates. Therefore, less of these older chemistries are required to be applied.

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.

Key Risk-Reduction Measures on the Reason 500 SC Label

- **Human Health**

Because there is a concern with direct skin contact with fenamidone, people mixing or loading Reason 500 SC Fungicide must wear a long-sleeved shirt, pants, boots, protective eye wear and chemical-resistant gloves.

- **Environment**

Field sprayer application: **DO NOT** apply during periods of dead calm. Avoid application of this product when winds are gusty. **DO NOT** apply with spray droplets smaller than the American Society of Agricultural Engineers (ASAE) medium classification.

Aerial application: **DO NOT** apply during periods of dead calm. Avoid application of this product when winds are gusty. **DO NOT** apply when wind speed is greater than 16 km/h at flying height at the site of application. **DO NOT** apply with spray droplets smaller than the American Society of Agricultural Engineers (ASAE) coarse classification. To reduce drift caused by turbulent wingtip vortices, the nozzle distribution along the spray boom length **MUST NOT** exceed 65% of the wing or rotorspan.

Buffer Zones

The buffer zones specified in the table below are required between the point of direct application and the closest downwind edge of sensitive freshwater habitats (such as lakes, rivers, sloughs, ponds, prairie potholes, creeks, marshes, streams, reservoirs and wetlands) and estuarine/marine habitats.

Method of Application	Crop	Buffer Zones (metres) Required for the Protection of Aquatic Habitat of Depths:	
		Less than 1 m	Greater than 1 m
Field sprayer*	Potatoes	1	0
Aerial—fixed and rotary wing		5	0

*For field sprayer application, buffer zones can be reduced with the use of drift reducing spray shields. When using a spray boom fitted with a full shield (shroud, curtain) that extends to the crop canopy or ground, the labelled buffer zone can be reduced by 70%. When using a spray boom where individual nozzles are fitted with cone-shaped shields that are no more than 30 cm above the crop canopy or ground, the labelled buffer zone can be reduced by 30%.

Consult the labels of the tank mix partners and observe the largest (most restrictive) buffer zone of the products involved in the tank mixture.

Do not contaminate aquatic habitats when cleaning and rinsing spray equipment or containers.

Next Steps

Before making a final registration decision on Reason 500 SC Fungicide, the PMRA will consider all comments received from the public in response to this Consultation Document[4]. The PMRA will then publish a Registration Decision Document[5] on Reason 500 SC Fungicide, which will include the decision, the reasons for it, a summary of comments received on the proposed final registration decision and the Agency's response to these comments.

Other Information

At the time the PMRA makes its final registration decision, it will publish a Registration Decision Document on fenamidone (based on the Science Evaluation section of this Consultation Document and Regulatory Note REG 2003-11). 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).

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4 "Consultation statement" as required by subsection 28(2) of the *Pest Control Products Act* (http://laws.justice.gc.ca/en/P-9.01/92455.html).

5 "Decision statement" as required by subsection 28(5) of the *Pest Control Products Act* (http://laws.justice.gc.ca/en/P-9.01/92455.html).

SCIENCE EVALUATION

1.0 Chemical Properties of the Technical Grade Active Ingredient, End Use Product and Use Information

A detailed assessment of the chemical properties and use information of fenamidone and Reason 500 SC Fungicide are presented in Regulatory Note REG2003-11, *Fenamidone Technical Fungicide, Reason 500 SC Fungicide*.

The previously outstanding batch analysis data from full scale production and analytical standards have been submitted to the PMRA and has been found to be satisfactory.

2.0 Methods of Analysis

Refer to the Regulatory Note REG2003-11, *Fenamidone Technical Fungicide, Reason 500 SC Fungicide* for a detailed assessment of the methods of analysis for fenamidone and Reason 500 SC Fungicide.

3.0 Impact on Human and Animal Health

Refer to the Regulatory Note REG 2003-11, *Fenamidone Technical Fungicide, Reason 500 SC Fungicide* for a detailed assessment of the toxicological database for fenamidone and Reason 500 SC Fungicide.

3.1 Mixer, Loader and Applicator Exposure and Risk Assessment

Following is the mixer, loader and applicator exposure and risk assessment for the currently registered use pattern for fenamidone.

Farmers using groundboom application equipment can typically treat 65 ha of potatoes in a typical 8 hour workday while custom applicators can treat 300 ha per day using groundboom equipment or 490 ha per day using aerial application equipment. Based on the proposed use pattern, farmers mixing, loading and applying Reason 500 SC could handle 13.0 kg a.i. per day and custom applicators mixing, loading and/or applying Reason 500 SC could handle 60.0 kg a.i./day with groundboom equipment and 98 kg a.i./day with aerial equipment. Farmer exposure is considered short term, custom applicator exposure is considered short to intermediate term.

Pesticide Handlers' Exposure Database (PHED) Version 1.1 data provided an adequate basis for estimating operator exposure for the proposed uses. The data were based on high confidence PHED runs with similar personal protective equipment (PPE) as proposed on the label and adequate numbers of replicates and A and B grade data. PHED data does not provide exposure estimates for clean-up/repair activities nor quantify the variability of exposure estimates.

PHED unit exposure values are presented in Table 3.1.1. The primary route of exposure was dermal.

Table 3.1.1 PHED Unit Exposure Estimates (µg-ai/kg-ai handled)

Scenario	PHED Unit exposure (µg-ai/kg-ai handled)	
	Dermal Deposition	Inhalation
Groundboom Mixer/loader[1]	51.14	1.6
Groundboom Applicator[2]	32.98	0.96
Groundboom Mixer/loader/applicator	84.12	2.56
Aerial Mixer/loader[1]	51.14	1.6
Aerial Applicator[2]	9.66	0.07

[1] PPE Mixer/Loader: long pants, long sleeves, gloves
[2] PPE Applicator: long pants, long sleeves, no gloves

As the no observable adverse effects level (NOAEL) for the short term risk assessment (i.e., farmers mixing/loading and applying) is from a dermal toxicity study, daily exposure estimates for farmers are not adjusted for dermal absorption. As the NOAEL for the intermediate term risk assessment (i.e., custom workers mixing/loading and applying) is based on an oral toxicity study, daily exposure estimates for custom applicators are adjusted for dermal absorption.

A summary of operator exposure estimates is provided in Table 3.1.2.

Table 3.1.2 Daily Exposure Estimates (µg-ai/kg-bw/day)

Exposure pattern	Scenario	Daily Exposure (µg-ai/kg-bw/day)[a]			
		Dermal Deposition	Dermal Absorbed[b]	Inhalation	Total[c]
Groundboom					
13 kg-ai/day (0.2 kg-ai/ha x 65 ha/day)	Farmer - mixer/ loader[1]	9.49	N/A	0.30	9.79

Exposure pattern	Scenario	Daily Exposure (µg-ai/kg-bw/day)[a]			
		Dermal Deposition	Dermal Absorbed[b]	Inhalation	Total[c]
	Farmer - applicator[2]	6.13	N/A	0.18	6.31
	Farmer - mixer/ loader/ applicator	15.62	N/A	0.48	16.10
60 kg-ai/day (0.2 kg-ai/ha x 300 ha/day)	Custom - mixer/ loader[1]	N/A	7.50	1.37	8.87
	Custom - applicator[2]	N/A	4.83	0.82	5.66
	Custom - mixer/ loader/ applicator	N/A	12.33	2.19	14.50
Aerial					
98 kg-ai/day (0.2 kg-ai/ha x 490 ha/day)	Custom - mixer/ loader[1]	N/A	12.24	2.24	14.48
	Custom - applicator[2]	N/A	2.31	0.10	2.41

a Calculated as µg-ai/kg-ai handled x application rate x area treated / body weight (70 kg)
b Dermal absorption 17.1%
c Total daily exposure estimates for farmers represents dermal deposition plus inhalation; daily exposure estimates for custom operators represents systemic exposure from dermal and inhalation routes.
1 PPE Mixer/Loader: long pants, long sleeves, gloves
2 PPE Applicator: long pants, long sleeves, no gloves

For short to intermediate term duration, the exposure estimates for custom workers were compared to a NOAEL of 68.3 mg/kg bw/day from a 3 month dietary study on rats. For short-term exposure durations the exposure estimates for farmers were compared to a NOAEL of 1000 mg/kg bw/day from a 28 day dermal study on rats. These NOAELs were chosen, based on

the route of exposure, duration of exposure and end point of concern. The margins of safety (MOEs) were compared to the target MOE of 100 and found to be acceptable (See Table 3.1.3).

Table 3.1.3 Margins of Exposure[c]

Application Equipment	Scenario	MOE (NOAEL 1000[a])	MOE (NOAEL 68.3[b])
Groundboom	Farmer M/L/A	62121[c]	N/A
	Custom M/L	N/A	7699
	Custom A	N/A	12069
	Custom M/L/A	N/A	4701
Aerial	Custom M/L	N/A	4717
	Custom A	N/A	28340

a 28 Day Dermal Rat
b 3-Month Dietary Rat
c Target MOE 100

3.2 Food Residues Exposure

Refer to Regulatory Document REG 2003-11, *Fenamidone Technical Fungicide, Reason 500 SC Fungicide* for a detailed assessment of food residue exposure.

The previously outstanding information on the presence of free N-phenyl anilines in plant metabolism studies have been submitted to the PMRA and has been found to be satisfactory. The information provided indicates there is no evidence that aniline or related compounds formed from the metabolism of fenamidone in plants or in soil, these compounds are not expected in rotational crops.

Import MRLs for several crops have been accepted for fenamidone since the initial registration. Following is the food residue risk assessment for the currently registered use pattern.

Analytical methodology in plant and animal matrices
Fenamidone, RPA 408056, RPA 717879 and RPA 405862 were tested through FDA Multiresidue Method of Protocols. Residues of fenamidone and all three metabolites were completely recovered using Protocol D. Adequate method validation, radiovalidation, and independent laboratory validation of the proposed LC-MS/MS enforcement method have been provided. Since no finite residues of fenamidone are expected in livestock matrices, information pertaining to a livestock enforcement method is not relevant to the current petition.

Nature of the residue in animals
Twenty-three hours following the last dose of a seven day daily dosing regime (10 ppm in the diet) with [N-phenyl-U-^{14}C]-fenamidone and [C-phenyl-U-^{14}C]-fenamidone, using lactating

goats, the total administered radioactivity was found to be almost completely eliminated via urine and feces. Radioactive residues in the feces accounted for 45-79.8% of the administered dose. The total ^{14}C-residues in the urine accounted for 36.1-40.4% of the administered dose in the N-phenyl label and 17.4-26 % in the C-phenyl label. The total combined ^{14}C residues in the liver, kidney, muscle, fat, blood, and milk accounted for less than 1.1 % of the administered dose (<0.11 µg eq/g). The radioactive residue levels in the milk ranged from 0.1-0.2% of the total radioactive residues. The only tissues containing significant levels of radioactive residues were liver and kidney which was not unexpected bearing in mind the anticipated degree of metabolism of absorbed compound as well as the large extent of urinary elimination. The major components (> 10% of the TRRs) were identified as fenamidone in fat (52.7% of the TRRs; 0.013 ppm), and the metabolite RPA 717879 in kidney (15.3% of the TRRs; 0.018 ppm), and milk (11.1% of the TRRs; 0.002 ppm). Therefore, the residue of concern in livestock commodities was defined as parent fenamidone and RPA 717879 for enforcement and risk assessment purposes. The pathway was similar to that in plants. In general there was cleavage of the amino-phenyl group and the thiomethyl group to yield RPA717879 as the major pathway. Further metabolism was via hydroxylation to yield hydroxy fenamidone and RPA 412708-OH (s-enantiomer of 408056-OH); sulfation to yield RPA 410193 sulfate (s-enantiomer of 406862-sulfate); glucuronidation to yield RPA 407213-glucoside-conjugate and the addition of an amine group to yield s-enantiomer of RPA 409445.

Nature of the residue in plants

[C-Phenyl-U-^{14}C]-fenamidone and [N-Phenyl-U-^{14}C]-fenamidone, were each applied directly to the leaf canopy (haulm) of different **potato** plants. Therefore, the metabolites present in the potato tubers encompassed radiolabelled material translocated from the haulm to the tubers as well as material taken into the tubers from the soil. At final harvest, ^{14}C-residues in potato tubers were 0.038 ppm [N-phenyl] and 0.087 ppm [C-Phenyl], in contrast with 5.895 ppm [N-Phenyl] and 6.575 ppm [C-Phenyl] in potato haulms. In the potatoes treated with [C-Phenyl-U-^{14}C]-fenamidone, the parent compound was identified in intact tubers (2.3% of the TRRs; 0.002 ppm) with the following two metabolites RPA 717879 (6.3% of the TRRs; 0.005 ppm) and RPA 408056 (6.4% of the TRRs; 0.006 ppm). A conjugated form of RPA 717879 was also identified in the intact tubers. In the [N-Phenyl-U-^{14}C]-fenamidone-treated potatoes, there was no evidence of free metabolites containing only the N-phenyl ring. Other than the parent fenamidone (5.8% of the TRRs; 0.002 ppm), the metabolite RPA 405862 was identified (0.2% of the TRRs; <0.001 ppm) and RPA 409446 (0.2% of the TRRs; <0.001 ppm).

[C-Phenyl-U-^{14}C]-fenamidone and [N-Phenyl-U-^{14}C]-fenamidone were each applied as foliar application to **tomato** plants. Samples were collected at first interim, second interim, and at final harvest. At final harvest, ^{14}C-residues residues in tomatoes were 0.186 ppm [N-phenyl] and 0.207 ppm [C-phenyl]. Fenamidone was the major component identified in tomatoes from all intervals, accounting for 91.7% and 63.9% TRR (0.011 and 0.039 ppm) in first interim C-phenyl and N-phenyl label tomatoes, respectively; 64.0% and 46.2% TRR (0.114 and 0.018 ppm) in second interim C-phenyl and N-phenyl label tomatoes, respectively; and 65.1% and 77.3% TRR (0.114 and 0.160 ppm) in final harvest C-phenyl and N-phenyl label tomatoes, respectively. Metabolite RPA 405862 was, in general, the second most significant component in tomatoes, accounting for 6.6% TRR (0.004 ppm) in first interim N-phenyl label tomatoes; <12.4% TRR (<0.022 ppm) and <15.4% TRR (<0.006 ppm) in second interim C-phenyl and N-phenyl label

tomatoes, respectively; and 10.3% TRR (0.018 ppm) and 8.7% TRR (0.018 ppm) in final harvest C-phenyl and N-phenyl label tomatoes, respectively. One additional metabolite, RPA 407599, was tentatively identified at ≤5.2% TRR (≤0.005 ppm) in tomatoes from both labels at the second interim and final harvest. Remaining radioactivity in tomatoes was attributed as unknowns present at individual levels ≤15.4% TRR (≤0.007 ppm; all but one unknown ≤7.7% TRR).

[C-Phenyl-U-^{14}C]-fenamidone and [N-Phenyl-U-^{14}C]-fenamidone, were each applied directly to **lettuce** plants by foliar application. Samples were collected at first interim, second interim, and at final harvest. At final harvest, ^{14}C-residues in/on heads were 0.291 ppm [C-phenyl] and 0.214 ppm [N-phenyl] and 12.446 ppm [C-phenyl] and 11.589 ppm [N-phenyl] in/on wrapper leaves of lettuce plants. Fenamidone was the major component identified from all intervals in the C-phenyl and N-phenyl label lettuce samples, accounting for 52.7% and 62.3% TRR (1.286 and 1.217 ppm) in first interim lettuce plants, respectively; 35.2 and 42.4% TRR (0.056 and 0.049 ppm) in second interim lettuce heads, respectively; 71.8% and 74.5% TRR (5.058 and 4.167 ppm) in second interim wrapper leaves, respectively; 70.4% and 73.4% TRR (0.205 and 0.157 ppm) in final harvest heads, respectively; and 92.0% and 91.4% TRR (11.444 ppm and 10.595 ppm) in final harvest wrapper leaves, respectively. Additional identified metabolites, accounting for ≤5.9% TRR in any given lettuce matrix, included RPA 405862 (identified in all lettuce matrices from all intervals), RPA 717879 (identified in all lettuce matrices from all intervals except final harvest wrapper leaves), RPA 406012 (identified in first and second interim lettuce), and 408056/407213 glucoside (coeluted; identified in all samples except final harvest wrapper leaves).

There is no evidence that aniline or related compounds formed from the metabolism of fenamidone in potatoes, tomatoes, or in lettuce. Metabolism of fenamidone in a variety of crops is understood. The residue definition in plants is fenamidone.

Confined rotational crops

Soil was treated with [^{14}C-phenyl]-fenamidone at an application rate equivalent to 2020 g a.i./ha. The exception was the 30 and 120 day lettuce, where the equivalent to 1600 g a.i./ha was applied. Soil was aged for 30, 120/150 and 365 days before planting rotational crops (lettuce, barley and turnip). The radioactive residues identified in the soil included parent fenamidone and the metabolites RPA 405862, RPA 408056 and RPA 717879. The ^{14}C-residues declined significantly 120/150 days after the planting of lettuce, turnip and barley (57% to 95% of the TRRs). **No parent residue was observed in any of the plant matrices.** The major plant metabolites identified were a conjugate of RPA 408056 (16-56% of the TRRs) as well as RPA 717879 (11-29% of the TRRs).

There is no evidence that aniline or related compounds formed from the metabolism of fenamidone in plants or in soil. Based on this information, these compounds are not expected in rotational crops.

Limited Field Accumulation in rotational crops

A limited field accumulation study was conducted in Zone 10 and 11 where soil was treated with EXP 10623A 50 SC at 1200 g a.i./ha/season (200 g a.i./ha applied 6 times on 7-day intervals).

The rotational crops grown were spinach (leafy vegetable), radish (root crop) and wheat (small grain) planted at 30 days and at 200 days after the last application of the fungicide. Residues of RPA 407213 (fenamidone), RPA 408056, RPA 405862 and RPA 717879 were not detected (ND) or less than 0.02 ppm (LOQ) in all crop fractions from the Zone 11 test site. However, residues of the metabolite RPA 717879 were found only in plant fractions from the Zone 10 test site following the 30-day replant interval (<0.02 to 0.45 ppm). Therefore, an extended field accumulation in wheat was conducted to further elucidate the residue profile.

Extended Field Accumulation in rotational crops

At each of the twenty-two residue trials conducted as an extended field accumulation study, a single broadcast application of fenamidone (EXP 10623A soluble concentrate containing 500 g fenamidone per litre) was made to bare soil at 1200 g a.i./ha in the fall. The winter wheat was planted 30 days after application and was harvested the following summer. No residues of fenamidone or metabolites were found in wheat grain from any of the 22 trials. The limit of detection was 0.0067 ppm. The residues of RPA 717879 ranged from 0.02 to 0.321 ppm in the wheat fractions. Residues of the metabolite RPA 408056 were 0.02 to 0.071 ppm in wheat forage and wheat hay. Although the metabolites RPA 717879 and RPA 408056 increased with plantback intervals in wheat straw, forage and hay, these metabolites were not considered to be of toxicological concern. Therefore, there is no uptake of soil degradates expected to be of toxicological concern at a 30-day PBI.

Supervised residue trials

Field trials were conducted using the test substance, EXP 10623A 50SC, containing 50% fenamidone in a soluble concentrate (SC) formulation, to treat potato plants. This involved 6 foliar applications of 200 g a.i./ha, at an interval of 5 days, for a total of 1200 g a.i./ha/season and a 14-day preharvest interval. Residue levels of fenamidone and the metabolites (RPA 408056, RPA 405862, RPA 717879) in whole tubers were each less than 0.02 ppm in the major potato growing regions examined in Canada and the United States (Regions 1, 1A, 2, 3, 4, 5, 5B, 7, 10, 11, 12 and 14). As no residues were detected, the residue decline data did not show any trends in fenamidone residues with PHI.

Field trials were also conducted to treat cucurbits, tomatoes, grapes, leaf and head lettuce, and dry bulb and green onions.

Storage stability

Residues of fenamidone and the metabolites (RPA 408056, RPA 405862, RPA 717879) are stable for up to 12 months in a variety of crops and their processed fractions which covers the length and condition of storage used in the various studies. Therefore, no corrections to residue values due to in-storage dissipation are necessary.

Processing studies

Potato crops were treated at 6000 g a.i./ha/season (tenfold the maximum recommended label rate) and processed into potato flakes, chips and wet peel. A comparison of the residues of fenamidone and the metabolites (RPA 408056, RPA 405862, RPA 717879) in the RAC with those in each processed fraction resulted in concentration factors of fenamidone in wet peel (2.3); RPA 408056 in potato flakes (1.6) and RPA 717879 in potato flakes (1.1).

Livestock feeding

Dairy cattle were administered fenamidone orally (capsules) at either 0.8, 2.4 and 8 mg/kg feed twice daily for 35 consecutive days. Residues of fenamidone and the metabolites RPA 408056 and RPA 717879 were each less than LOQ in whole milk (0.01 ppm) and tissues (0.05 ppm), with the exception of the metabolite RPA 408056 in milk fat (0.011 ppm). The dietary burden was estimated to be 0.3 ppm. Residues of fenamidone are anticipated to occur in milk and in the tissues at levels less than LOQ. At this time, there are no proposed uses for fenamidone that would result in residues on significant poultry feed items and a poultry feeding study is not required.

Dietary risk assessment

The use of fenamidone (Reason 500 SC Fungicide) on potatoes grown in Canada and the importation of grapes, tomatoes, bulb vegetables, cucurbits, and leaf and head lettuce into Canada that have been treated with fenamidone do not pose an unacceptable chronic dietary (both food and water) risk to any segment of the population, including infants, children, adults and seniors.

The integrated food residue chemistry is summarized in Appendix I, Table 1.

4.0 Impact on the Environment

Refer to Regulatory Document REG2003-11, *Fenamidone Technical Fungicide, Reason 500 SC Fungicide* for a detailed assessment of the environmental impact of fenamidone.

The previously outstanding information on the formation of aniline and substituted aniline in soil, octanol/water partitioning data for two major transformation products and sediment toxicity data with a sediment dwelling species have been submitted to the PMRA and has been found to be satisfactory.

Following is the environmental assessment for the currently registered use pattern.

4.1 Fate and Behaviour in the Environment

Fenamidone enters the environment when used as a fungicide on potatoes. Fenamidone is non-persistent in soil, while its major transformation products (RPA 717879 and RPA 408056) are expected to be moderately persistent to persistent in soil.

Production of aniline and substituted aniline in soil, due to biotransformation of fenamidone, was identified as a concern during the original review of this product. Aniline was not tracked in any of the soil biotransformation studies and there were a large number of unidentified peaks in these studies.

To address this concern, a HPLC analysis of standard mixture of aniline, 2-nitroaniline, 4-nitroaniline, fenamidone and its metabolites (RPA409446, RPA410995, RPA406012, RPA405862, and RPA410914) was conducted using the same chromatographic conditions as the original soil biotransformation study. The chromatograms of these compounds were compared

with the chromatograms from the original soil biotransformation study to determine the potential for formation of aniline, 2-nitroaniline, 4-nitroaniline compounds in soil. This analysis established that no aniline or substituted anilines were detected during soil biotransformation study. Aniline rapidly converted to CO_2 with the half-life of 4-7 days. Given that the half-life of fenamidone in soil is almost a week any possible aniline formed in the soil would have been degraded as fast as it is formed, thus resulting in no detection of the material. Therefore, even if anilines are formed in soil they are short-lived and do not accumulate to measurable levels.

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 octanol–water partition coefficient of fenamidone and its major transformation products (RPA 408056 and RPA 717879) indicate that these compounds have limited potential for bioaccumulation/bioconcentration in biological organisms. The fate and behaviour of fenamidone in terrestrial and aquatic environment are summarized in Appendix I, Tables 2 and 3, respectively.

4.2 Effects on Non-Target Species

There was a concern in the previous review that as fenamidone partitions extensively to the sediment, where it transforms very slowly, the sediment dwelling organisms are expected to have chronic exposure to this compound. In response to this concern the applicant submitted a chronic toxicity study of fenamidone to a sediment dwelling larvae of the freshwater dipteran *Chironomus riparius*. This study assessed the impact of fenamidone on full maturation of the larvae to adult midge based on the water column exposure scenario. The No Observable Exposure Concentration (NOEC) and Lowest Observable Exposure Concentration (LOEC) of fenamidone to *Chironomus riparius* were estimated to be 50.0 µg/L, and 100.0 µg/L, respectively.

The environmental risk is characterized using the quotient method. At the screening level, a risk quotient (RQ), which is the ratio of the Expected Environmental Concentration (EEC) to the most sensitive endpoint, is determined. The RQ =1 is the level of concern (LOC). If the screening level assessment indicates negligible risk (RQ less than 1), then no further assessment is required. However, if the screening level assessment results in a potential risk (RQ greater than 1), then a refined assessment is undertaken for the organisms of concern. Refinement of the risk assessment takes into consideration more realistic exposure scenarios (e.g., drift to non-target habitats and runoff to water bodies) and may consider different toxicity endpoints. Data derived from monitoring studies may also be used in refining a risk assessment.

Terrestrial organisms will be exposed to fenamidone in the soil as well as from the consumption of contaminated vegetation. However, fenamidone is non-persistent in aerobic soil, therefore, chronic exposure is limited. Fenamidone may be expected to enter the aquatic environment through direct overspray, spray drift and from runoff via sorption to soil particles. Once in the aquatic environment fenamidone is expected to partition to the sediments and be moderately persistent to persistent. Aquatic organisms will be exposed to fenamidone in the water column and sediments. Sediment exposure is expected to be chronic. Based on the physicochemical properties of fenamidone, volatilization is not an expected route of exposure of non-target organisms.

4.2.1 Effects on Terrestrial Organisms

- **Risk to terrestrial organisms**

Fenamidone and its major transformation products (RPA 717879 and RPA 408056) will pose a negligible risk to earthworms, honeybees, wild birds and non-target terrestrial plants at the proposed application rate. Fenamidone and its major transformation products will pose a negligible risk to wild mammals based on acute exposure, however, the LOC for wild mammals is exceeded 5 times based on dietary and reproductive study results. The LOC is exceeded 60 times for beneficial predators and parasites associated with the use of fenamidone at the proposed rate (RQ = 60). Environmental hazard statements are required on the label for protection of beneficial insects. The risk calculated for wild mammals are very conservative and are based on direct overspray of food and consuming a 100% contaminated diet. It is unlikely that wild mammals would be exposed to fenamidone at the concentrations predicted on food chronically.

4.2.2 Effects on Aquatic Organisms

- **Risk to aquatic organisms**

Based on the previous risk characterization of fenamidone, the most sensitive aquatic organisms were *Daphnia magna* (chronic concern) for freshwater systems and Mysid shrimp (chronic concern) for marine systems. In the current review the risk to these two organisms was re-calculated, using the current rate and current practices. In addition, the toxicity endpoints of the early life stage study on Fatheads minnow and *Chironomus riparius* were used to calculate the risk to amphibians and sediment dwelling organisms. The following toxicity endpoints were used for these organisms:

Daphnia magna : NOEC of 0.0125 mg/L
Mysid shrimp: NOEC of 0.0095 mg/L
Chironomus riparius : NOEC of 0.05 mg/L
Fatheads minnow (for amphibians) : NOEC of 0.041 mg/L

The screening level RQs for *Daphnia magna*, mysid, *Chironomus riparius*, and amphibians are 5, 6.7, 1.2 and 8, respectively. Therefore, the LOC is exceeded for these organisms at the proposed rate. Buffer zones of one and five metres, depending on the method of application and the depth of the aquatic habitat, to protect sensitive aquatic habitats are required to mitigate the risks.

5.0 Value

Refer to the Regulatory Note REG 2003-11, *Fenamidone Technical Fungicide, Reason 500 SC Fungicide* for a detailed assessment of the value and efficacy of Reason 500 SC Fungicide. The treatment of Reason 500 SC alone at the rate of 400 ml/ha has been removed from the label since the initial registration.

6.0 Toxic Substances Management Policy Considerations

While reviewing fenamidone the PMRA took into account the federal Toxic Substances Management Policy 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, *Fenamidone Technical Fungicide, Reason 500 SC Fungicide* for more detail.

7.0 Summary

7.1 Human Health and Safety

The toxicology database for fenamidone and Reason 500 SC Fungicide are adequate and acceptable.

Mixer, loader, applicators and workers entering treated potato fields are not expected to be exposed to levels of fenamidone that will result in unacceptable risk when Reason 500 SC Fungicide is used according to label directions. The personal protective equipment on the product label is adequate to protect workers and no additional personal protective equipment is required.

Dietary risks from food and water are not of concern. The reside database is complete. No new MRLs are being recommended at this time.

7.2 Environmental Risk

The LOC is exceeded for some non-target organisms at the proposed rate of use of Reason 500 SC Fungicide, however, buffer zones, to protect sensitive aquatic habitats are required to mitigate the risks. Environmental hazard statements are required on the label for protection of beneficial insects.

7.3 Value

The value data submitted supported the use of Reason 500 SC Fungicide when applied according to label directions.

8.0 Proposed Regulatory Decision

Health Canada's PMRA, under the authority of the *Pest Control Products Act*, is proposing full registration for the sale and use of the technical grade active ingredient fenamidone and the end-use product Reason 500 SC Fungicide to control early and late blight on potatoes applied with ground or aerial equipment. An evaluation of current scientific data from the applicant has resulted in the determination that, under the proposed conditions of use, the end-use product has value and does not present an unacceptable risk to human health or the environment.

List of Abbreviations

µg	micrograms
a.i.	active ingredient
ADI	acceptable daily intake
ASAE	American Society of Agricultural Engineers
DAT	days after treatment
DT_{50}	dissipation time 50% (the dose required to observe a 50% decline in the test population)
EEC	expected environmental concentration
g	gram
ha	hectare(s)
HPLC	high performance liquid chromatography
kg	kilogram
K_F	Freundlich adsorption coefficient
K_{oc}	organic-carbon partition coefficient
K_{ow}	*n*–octanol-water partition coefficient
L	litre
LOC	level of concern
LOEC	low observed effect concentration
mg	milligram
MOE	margin of exposure
ND	not detected
MRL	maximum residue limit
NOAEL	no observed adverse effect level
NOEC	no observed effect concentration
PBI	plantback interval
pH	potential hydrogen
PHED	pesticide handlers exposure database
PHI	preharvest interval
pKa	dissociation constant
PMRA	Pest Management Regulatory Agency
PPE	personal protective equipment
ppm	parts per million
RQ	risk quotient
SC	soluble concentrate
TRR	total radioactive residue
TSMP	Toxic Substances Management Policy

References

2.0 CHEMISTRY

PMRA 1108221 Stability of Reason 500 SC.

PMRA 1108382 Analytical Profile of Five Production Batches Produced By SNPE, Toulouse, France. AE C649693, Fenamidone.

3.0 IMPACT ON HUMAN AND ANIMAL HEALTH

PMRA 1108222 2005, Fenamidone and the Potential Formation of Aniline and Substituted Anilines in Crops., Bayer CropScience Inc., N/S, MRID: N/S, DACO: 7.4.3

4.0 IMPACT ON ENVIRONMENT

PMRA 1108383 1997. RPA 408056 and RPA 717879 n-octanol/water partition coefficient. Study No. 97-136, Report No. R003445.

PMRA 1108384 2005. Data on the Formation of Aniline and Substituted Anilines in Soil

PMRA 1108385 1998. RPA 407213, Toxicity to the Sediment Dwelling Chironomid Larvae (*Chironomus riparius*) - 28 days.

Appendix I

Table 1 Integrated Food Residue Chemistry Summary Table

Directions for Use of Fenamidone (domestic use)					
Crop	**Pest**	**a.i.**			
Potatoes	**Late blight on potato caused by** *Phytophthora infestans* **and early blight caused by** *Alternaria solani*.	100 g a.i./ha x 6 for a total of 600 g a.i./ha/season by ground or aerial application. PHI of 14 days. 100 g a.i./ha x 6 in tankmix with Dithane DG (mancozeb) or Bravo 500 (chlorothalonil) at 1.25 kg/ha at 7 to 10 days interval.			
Direction for Use of Fenamidone (imported commodities)					
Crop	**Interval (days)**	**Rate (g a.i./ha)**	**application/ season**	**Maximum rate kg a.i./ha**	**PHI (days)**
Tomatoes	5-10	200-300	-	897	14
Green and dry bulb onion	5-10	200	-	795	7
Lettuce (head and leaf)	5-10	200-300	-	897	2
Cucurbit vegetables	5-10	200	-	796	14
Grapes	-	133.2	5	660	28
Physicochemical Properties					
Water solubility at 20°C (mg/L)	7.8				
Solvent solubility at 20°C (g/L)	acetone 250 acetonitrile 86.1 dichloromethane 330 methanol 43 *n*-octanol 9.7				
Octanol/water partition coefficient (Log K_{ow}) at X °C	2.8				
Dissociation constant (pKa)	Not ionizable in water				
Vapour pressure at 25°C (mPa)	3.4×10^{-4}				
Relative density	1.285				
Melting point °C	137				
UV/Visible absorption spectrum	medium / λ (nm) / ϵ acidic 203.0 25138 230.0 15734 neutral 202.5 36941 230.0 18297 basic 208.5 93570 228.5 19419 No absorption observed from 200 to 800 nm.				

Analytical Methodology		
Parameters	**Plant matrices**	**Animal matrices**
Method ID	AR 186-98; AR 150-97 (plant RACs); AR 188-98 (plant processed commodities)	AR 200-99 (milk); AR 188-98 (tissues)
Type	Data gathering (AR 186-98, AR 150-97, AR 188-98) and enforcement (AR 186-98)	Data gathering and proposed enforcement (AR 200-99, AR 188-98)
Analytes	AR 186-98: Fenamidone, RPA 717879, RPA 408056, RPA 405862 AR 150-97 & AR 188-98: Fenamidone and RPA 405862	fenamidone, RPA 408056, RPA 717879
Instrumentation	LC/MS/MS (AR 186-98), GC/TID or GC/TSD (AR 150-97 & AR 188-98)	GC-TID; GC-MSD (liver only)
LOQ	0.02 ppm for each analyte	0.01 ppm (milk); 0.05 ppm (tissues)
Standard	external standards	
ILV	Potatoes (AR 186-98): average recoveries of 106 ± 5.7 % for fenamidone, 93 ± 9.7 % RPA 717879, 93 ± 7.9 % for RPA 405862, and 97 ± 6.2 % for RPA 408056. Potatoes (AR 150-97): average recoveries of 86 ± 3 % (0.02 ppm fenamidone), 81 ± 6 % (0.5 ppm fenamidone), 105 ± 2 % (0.02 ppm RPA 405862), and 84 ± 6 % (0.5 ppm RPA 405862). Grape (AR 150-97): average recoveries of 94 ± 8 % (0.02 ppm fenamidone), 86 ± 3 % (0.5 ppm fenamidone), 97 ± 7 % (0.02 ppm RPA 405862), and 95 ± 5 % (0.5 ppm RPA 405862). Tomato (AR 150-97): average recoveries of 98 ± 7 % (0.02 ppm fenamidone), 83 ± 11 % (0.5 ppm fenamidone), 100 ± 4 % (0.02 ppm RPA 405862), and 88 ± 3 % (0.5 ppm RPA 405862)..	Method AR 200-99: average recoveries of fenamidone were 79%±7% (milk); RPA 408056 was 102%±13% (milk); RPA 717879 was 77%±8% (milk). Method AR 178-98: average recoveries of fenamidone were 91%±8% (muscle); 89%±5% (liver); RPA 408056 was 86%±5% (muscle), 84%±5% (liver); RPA 717879 was 80%±9% (muscle), 81%±6% (liver).
Extraction/clean-up	AR 186-98 Aqueous acetonitrile or accelerated solvent extraction (ASE) with cleanup using HR-P polymeric solid phase extraction cartridge (SPE) and an amino SPE cartridge. AR150-97 & AR 188-98 Extraction with acetone:water (9:1), and clean-up using polystyrene divinyl benzene and aminopropyl cartridges.	Method AR 200-99: aqueous acetonitrile extraction with cleanup on C-18 SPE. Method AR 178-98: aqueous acetonitrile extraction with cleanup using HR-P polymeric SPE and an amino SPE cartridge.

Radiovalidation	AR 186-98 Extraction efficiency in potato tubers (0.021 ppm and 0.023 ppm) from the potato metabolism study compare well with that obtained using ASE (0.025 ppm). AR150-97 Extraction efficiency of fenamidone from grapes in the metabolism study (55.6 %) compared well with the data collection method (46.3 %, as did extraction of RPA 405862 (17.1 % in metabolism study and 16.7 % using data collection method).	Extraction efficiencies in milk (76%) and goat liver (7.3% of the TRRs) are in agreement with levels found during the metabolism studies in milk (81%) and in goat liver (6.2% of the TRRs).
Multiresidue method	PAM I Protocol D appears to be suitable for the analysis of fenamidone, RPA 405862, RPA 408056, and RPA 717879.	

Nature of the Residue in Lettuces				
Radiolabel	[N-Phenyl-U-^{14}C]-Fenamidone		[C-Phenyl-U-^{14}C]-Fenamidone	
Test Site	Outdoor plots consisting of containment vessels in Essex, UK			
Treatment	Four foliar applications to transplanted lettuce plants (growth stage at transplantation not specified)			
Rate	1) 316 g a.i./ha (16 days after transplanting, DATr) 2) 183 g a.i./ha (28 DATr) 3) 573 g a.i./ha (40-41 DATr) 4) 350 g a.i./ha (50 DATr)		1) 319 g a.i./ha (16 days after transplanting, DATr) 2) 232 g a.i./ha (28 DATr) 3) 537 g a.i./ha (40-41 DATr) 4) 350 g a.i./ha (50 DATr)	
EP	Emulsifiable concentrate			
PHI	1) Immediately prior to the 2nd application (first interim harvest) 2) Immediately prior to the 4th application (second interim harvest) 3) 7 days after 4th (final) application			
The majority of the ^{14}C-residues were in the wrapper leaves (98 %; 5.521-12.536 ppm) for samples collected at the second interim harvest and at the final harvest. Samples from the first interim harvest were not separated into head and wrapper leaves prior to their analysis.				
Metabolites identified	Major metabolites (>10% TRRs)		Minor metabolites (<10% TRRs)	
Radiolabel	[N-Phenyl-U-^{14}C]-Fenamidone	[C-Phenyl-U-^{14}C]-Fenamidone	[N-Phenyl-U-^{14}C]-Fenamidone	[C-Phenyl-U-^{14}C]-Fenamidone
Head	Fenamidone	Fenamidone	RPA 405862	RPA 405862 RPA 717879
Wrapper	Fenamidone	Fenamidone	RPA 405862	RPA 405862 RPA 717879* RPA 406012* RPA 408056* *not found in wrapper leaves from final harvest

Nature of the Residue in Tomatoes				
Radiolabel	[N-Phenyl-U-^{14}C]-Fenamidone		[C-Phenyl-U-^{14}C]-Fenamidone	
Test Site	Potted transplanted plants were maintained in a greenhouse (growth stage at transplantation not specified)			
Treatment	Three foliar applications			
Rate	1) 487 g a.i./ha (30 days after transplanting, DATr) 2) 443 g a.i./ha (51 DATr) 3) 464 g a.i./ha (65 DATr)		1) 487 g a.i./ha (30 DATr) 2) 443 g a.i./ha (51 DATr) 3) 464 g a.i./ha (65 DATr)	
EP	Emulsifiable concentrate			
PHI	1) Immediately prior to the 2nd application (first interim harvest) 2) Immediately prior to the 3rd application (second interim harvest) 3) 7 days after 3rd (final) application			
The ^{14}C-residues from whole tomatoes ranged from 8.3-41.1 % (0.001-0.085 ppm) in ACN rinse, 51.2-83.3 % (0.010-0.106 ppm) in ACN extract, and 7.7-16.4 % (0.001-0.022 ppm) were non-extractable for samples obtained from all three sampling events.				
Metabolites identified	Major metabolites (>10% TRRs)		Minor metabolites (<10% TRRs)	
Radiolabel	[N-Phenyl-U-^{14}C]-Fenamidone	[C-Phenyl-U-^{14}C]-Fenamidone	[N-Phenyl-U-^{14}C]-Fenamidone	[C-Phenyl-U-^{14}C]-Fenamidone
Tomatoes, 1st interim harvest	Fenamidone	Fenamidone	RPA 405862	-
Tomatoes, 2nd interim harvest	Fenamidone RPA 405862	Fenamidone RPA 405862	RPA 407599	RPA 407599
Tomatoes, final harvest	Fenamidone	Fenamidone RPA 405862	RPA 405862 RPA 407599	RPA 407599
Nature of the Residues in Potatoes				
Radiolabel	[N-Phenyl-U-^{14}C]-Fenamidone		[C-Phenyl-U-^{14}C]-Fenamidone	
Test Site	Outdoor plots under ambient environmental conditions in Essex, UK.			
Treatment	Foliar applications			
Rate	434 g a.i./ha x 3 at 15-day intervals		454 g a.i./ha x 3 at 15-day intervals	
Seasonal Rate	1302 g a.i./ha		1362 g a.i./ha	
EP	10 % emulsifiable concentrate formulation			
PHI	14 days			
The majority of the 14C-residues were in the haulm (73-78 %; 5.9-6.6 ppm), peel (47-66 %; 0.0320.12 ppm), intact tubers (46-73%; 0.04-0.09 ppm) and peeled tubers (45-76 %; 0.06-0.08 ppm).				

Metabolites identified	Major metabolites (>10% TRRs)		Minor metabolites (<10% TRRs)	
Radiolabel	[N-Phenyl-U-^{14}C]-Fenamidone	[C-Phenyl-U-^{14}C]-Fenamidone	[N-Phenyl-U-^{14}C]-Fenamidone	[C-Phenyl-U-^{14}C]-Fenamidone
Tubers (peeled)	-	-	RPA 717879 RPA 408056 Fenamidone	-
Peel	-	Fenamidone	RPA 717879 RPA 408056 Fenamidone	RPA 405862
Intact tubers	RPA 717879 C	-	Fenamidone RPA 717879 RPA 408056	Fenamidone RPA 405862
Haulm	Fenamidone	Fenamidone	RPA 408056 RPA 405862 Fenamidone	RPA 405862

Confined Rotational Crop Study - Lettuce, turnip, barley, wheat

Application rate and timing	[^{14}C]-Phenyl-fenamidone used for treatment of soil at 1600 or 2020 g a.i./ha. Soil was aged 30, 120/150 and 365 days before planting crops. Fenamidone was not identified in any crop fractions. "C" represents conjugated metabolite.

Metabolites	Major metabolites (>10% TRRs)			Minor metabolites (<10% TRRs)		
PBI	30 d	120-150 d	365 d	30 d	120-150 d	365 d
Lettuce	RPA 717879 RPA 408056 C	RPA 717879 RPA 408056 C	RPA 408056 RPA 405862	RPA 405862 RPA 408056	RPA 408056	-
Turnip top	RPA 408056 C	RPA 408056 C	RPA 717879 RPA 408056 C	RPA 717879	RPA 717879	RPA 717879
Turnip root	-	RPA 408056 C	RPA 408056 C	RPA 717879 RPA 408056 C	RPA 717879	RPA 717879
Barley chaff	RPA 408056 C	RPA 408056 C RPA 717879	RPA 717879 RPA 408056 C	RPA 717879	RPA 408056	-
Barley grain	RPA 408056 C	RPA 408056 C	RPA 408056 C	RPA 717879	RPA 717879	RPA 717879
Barley straw	RPA 408056 C RPA 717879	RPA 408056 C	RPA 717879 RPA 408056 C	-	RPA 717879	-

Nature of the Residue in Lactating Goat

Species	**Radiolabel**	**Dose Level**	**Sacrifice**
Goat (*Saanen*)	C-phenyl-^{14}C and N-phenyl-^{14}C	10 ppm for 7 days	24 hrs after last dose

N-phenyl-^{14}C residues accounted for 52.2% (feces) and 36.1% (urine) of the administered dose. C-phenyl-^{14}C residues were eliminated at 79.8% (feces) and 17.4% (urine) of the administered dose. The sum of the total ^{14}C residues in liver, kidney, muscle, fat, blood, and milk accounted for 1.0% of the administered dose. The remaining radioactivity was presumed to be in the gastrointestinal tract (2%).

Metabolites identified	Major metabolites (>10% TRRs)		Minor metabolites (<10% TRRs)	
Radiolabel	C-phenyl-^{14}C	N-phenyl-^{14}	C-phenyl-^{14}C	N-phenyl-^{14}C
Liver	-	-	Fenamidone RPA 407213-OH RPA 717879 RPA 408056-OH	RPA 407213-OH

Kidney	RPA 717879	-	Fenamidone RPA 407213-OH RPA 408056 RPA 408056-OH	RPA 407213-OH
Fat	Fenamidone	-	-	-
Milk	RPA 717879	-	RPA 407213-OH	Fenamidone RPA 407213-OH RPA 408056 RPA 408056-OH RPA 409445

Crop Field Trials-Potatoes, Cucurbits (summer squash, cucumber, cantaloupe), Tomatoes, Grapes, Leaf and Head Lettuce, and Dry Bulb and Green Onions

Potatoes: Twenty nine trials (3 in Region 1; 4 in Region 1A; 2 in Region 2; 1 in Region 3; 4 in Region 4; 1 in Region 5; 1 in Region 5B; 3 in Region 7A; 1in Region 10; 6 in Region 11; 1 in Region 12; 2 in Region 14) were conducted at ~1.2 kg a.i./ha.

Cucurbits: Nine cucumber trials (4 in Region 2; 1 in Region 3; 2 in Region 5; 1 in Region 6; 1 in Region 10), eight cantaloupe trials (1 in Region 5; 2 in Region 6; 5 in Region 10), and nine summer squash trials (1 in Region 1; 3 in Region 2, 1 in Region 3; 1 in Region 5; 1 in Region 6; 1 in Region 10; 1 in Region 11) were conducted at ~1.2 kg a.i./ha.

Tomatoes: Seventeen tomato trials (1 in Region 1; 2 in Region 2; 2 in Region 3; 1 in Region 5, 11 in Region 11) were conducted ~1.2 kg a.i./ha. Four of the seventeen trials were conducted with cherry tomatoes.

Grapes: Eight wine grape trials (5 in South France and 3 in South Italy) were conducted at 660-870 g a.i./ha. In addition, residue data from 7 grape processing studies (all in South Italy) were conducted at 500-870 g a.i./ha.

Leaf Lettuce: Nine leaf lettuce trials (1 in Region 1; 1 in Region 3; 7 in Region 10) were conducted at ~1.2 kg a.i./ha.

Head Lettuce: Nine head lettuce trials (1 in Region 1; 1 in Region 3; 7 in Region 10) were conducted at ~1.2 kg a.i./ha.

Dry bulb Onion: Eight dry bulb trials (1 in Region 1; 1 in Region 5; 1 in Region 6; 1 in Region 8; 2 in Region 10; 1 in Region 11; 1 in Region 12) were conducted at ~1.2 kg a.i./ha).

Green Onion: Four green onion trials (1 in Region 5; 1 in Region 8; 2 in Region 10) were conducted at ~1.2 kg a.i./ha.

Commodity	**Rate kg a.i./ha**	**PHI (days)**	**Residue Levels (ppm)**						
			n	**Min.**	**Max.**	**HAFT**	**Median**	**Mean**	**SD**
Fenamidone									
Potatoes	1.2	14	58	<0.02	<0.02	<0.02	<0.02	<0.02	-
Cucumbers	1.2	39096	18	0.02	0.04	0.03	0.02	0	0.01
Summer squash	1.2	13.-15	18	0.02	0.08	0.06	0.02	0	0.014
Cantaloupe	1.2	39096	16	0.02	0.1	0.09	0.06	0.1	0.028
Tomato	1.2	14	34	0.02	0.78	0.64	0.21	0.26	0.195
Grapes	500-870	24-30	30	0.04	0.54	0.53	0.2	0.21	0.133
Leaf lettuce	1.2	2	18	0.02	17.5	15.9	6.4	6.81	5.2
Head lettuce	1.2	2	17	0.7	11.7	10.72	3.91	4.53	3.08
Dry bulb onion	1.2	7	16	0.02	0.13	0.07	0.02	0	0.028
Green onion	1.2	7	8	0.22	1.1	0.93	0.59	0.61	0.361

Residue Decline

Residue decline data show that fenamidone decreases with time in all commodities listed above.

Maximum Residue Limits	
Potatoes	0.02 ppm
Cucurbits CG 9	0.15 ppm
Tomatoes	1.0 ppm
Tomato, paste	2.2 ppm
Tomato, puree	2.0 ppm
Grapes	1.0 ppm
Leaf Lettuce	20 ppm
Head Lettuce	15 ppm
Dry bulb onion	0.20 ppm
Green onion	1.5 ppm

FIELD ACCUMULATION IN ROTATIONAL CROPS - SPINACH, RADISH, WHEAT

Two trials (WA and CA) with EXP 10623A 50SC at 200 g a.i./ha x 6 at 7 day intervals for a total of 1200 g a.i./ha/season.

Commodity	Replant interval	Mean Residue Levels (ppm)	
		Fenamidone	RPA 408056
Spinach leaf	28/30	< 0.02	< 0.02
	201/234	< 0.02	< 0.02
Radish tops	28/30	< 0.02	< 0.02
	201/234	< 0.02	< 0.02
Radish roots	28/30	< 0.02	< 0.02
	201/234	< 0.02	< 0.02
Wheat forage	28/30	< 0.02	< 0.02
	201/234	< 0.02	< 0.02
Wheat hay	28/30	< 0.02	< 0.02
	201/234	< 0.02	< 0.02
Wheat straw	28/30	< 0.02	< 0.02
	201/234	< 0.02	< 0.02
Wheat grain	28/30	< 0.02	< 0.02
	201/234	< 0.02	< 0.02

Processing Studies

Processing studies were conducted with potatoes treated at 10-fold the recommended label rate, tomatoes treated at 6.7-fold the recommended label rate, and the processing studies for wine grapes were conducted at 0.8-1.3-fold the recommended rate.

Fraction	Mean fenamidone residue levels (ppm)	Calculated Concentration factor
Potato tubers	<0.02	-
Potato flakes	<0.02	≤1
Potato chips	<0.02	≤1
Potato wet peels	0.05	2.3
Tomato	0.426	-
Tomato puree	0.75	1.8
Tomato paste	1.162	2.7
Wine grapes	0.03-0.276	-
Wine	<0.02-0.022	<0.1-<0.4

Livestock Feeding				
Dairy cattle orally dosed at 0.8, 2.4 and 8 mg/kg feed twice daily for 35 consecutive days. MTDB estimated to be 0.3 ppm.				
Commodity	**Dose (mg/kg)**	**Fenamidone (ppm)**	**RPA 408056 (ppm)**	**RPA 717879 (ppm)**
Whole milk	8	<0.01	<0.01	<0.01
Milk fat	8	<0.01	0.011	<0.01
Muscle, liver, kidney, fat	8	<0/05	<0.05	<0.05

Storage Stability
Residues of fenamidone (RPA 497213) and the metabolites RPA 408056, RPA 405862 and RPA 717879 were stable in potatoes and processed fractions up to 12 months. Additional data show that residues of fenamidone and its metabolite RPA 405862 are stable in variety of crops and their processed fractions for up to 12 months.

OVERVIEW OF METABOLISM STUDIES AND RISK ASSESSMENT

Plant Studies -	
ROC for Enforcement and Risk Assessment - **Rotational crops**	Fenamidone Fenamidone
Metabolic Profile in Diverse Crops	Fenamidone metabolism is understood in a variety of crops.
Animal Studies -	
ROC for Enforcement and Risk Assessment	Fenamidone + RPA 717879 If MRLs established on meat/milk/eggs, include RPA 717879 for use expansion on feed items.
Metabolic Profile in Animals	Metabolism is understood in ruminants only.
Fat-Soluble Residue	na

DIETARY RISK from food and water

Chronic Non-Cancer Dietary Risk
ADI = 7.07 mg/kg bw/day
EEC = 0.0603 mg/L

Chronic dietary exposure analyses were performed in order to determine the exposure and risk estimates which resulted from the use of fenamidone on potatoes in Canada, including cucurbits, wine grapes, tomatoes, head and leaf lettuce, and dry bulb and green onions imported into Canada. Therefore, the above noted EEC represents the domestic use on potatoes only. The assessment used the maximum residues limits, residue data, and assumed 100% crop treated.

POPULATION	ESTIMATED RISK (% of ADI)	
	Food (MRLs)	Food + EEC
All infants < 1 yr old	0.9	6.8
Children 1 to 2 yrs	5	7.6
Children 3 to 5 yrs	5	7.5
Children 6 to 12 yrs	3.8	5.5
Youth 13 to 19 yrs	3	4.3
Adults 20 to 49 yrs	2.9	4.6
Adults 50+ yrs	2.4	4.1
Females 13 to 49 yrs	2.9	4.6
Total Population	3	4.8

Table 2 Fate and Behaviour in the Terrestrial Environment

Property	Test substance	Value	Comments
Abiotic transformation			
Phototransformation on soil	Fenamidone (RPA 407213)	DT_{50}: Not significantly different from dark treatment	Not a major route of transformation.
	Major transformation products	RPA 717879 and RPA 408056	
Biotransformation			
Biotransformation in aerobic soil	Fenamidone (RPA 407213)	DT_{50}: 3.46 d (sandy loam) DT_{50}: 7.8 d (loam)	A major route of transformation. Fenamidone is non-persistent in soil under aerobic conditions. Major transformation products were RPA 717879 and RPA 408056
Biotransformation in aerobic soil	RPA 412636 (s-enantiomer of the racemic of the major transformation product RPA 717879)	DT_{50}: 421 d (sand) DT_{50}: 100 d (clay loam) DT_{50}: 459 d (silt loam)	Not a major route of transformation. RPA 412636 is moderately persistent to persistent in soil under aerobic conditions.
Mobility			
Adsorption / desorption in soil	Fenamidone	Adsorption K_f : Silt loam: 2.43 sandy loam: 5.93 loam: 6.89 Silt loam: 4.93 sediment: 8.9 Adsorption K_{oc}: Silt loam: 486 sandy loam: 494 loam: 313 Silt loam: 259 sediment: 387	Adsorption K_f values would classify fenamidone as having low mobility to moderate mobility in the soils/sediments tested. Adsorption K_{oc} values would classify fenamidone as having moderate mobility in the soils/sediments tested.

Property	Test substance	Value	Comments
	RPA 412636 (s-enantiomer of the racemic of the major degradation product RPA 717879)	Adsorption K_f : Silt loam: 0.11 sandy loam: 0.43 loam: 0.56 Silt loam: 0.32 sediment: 0.64 Adsorption Koc: Silt loam: 22.0 sandy loam: 35.8 loam: 28.0 Silt loam: 16.8 sediment: 28.8	Adsorption K_f values would classify RPA 412636 as being very highly mobile to mobile in the soils/sediments tested. Adsorption K_{oc} values would classify RPA 412636 as being very highly mobile to highly mobile in the soils/sediments tested.
	RPA 412708 (s-enantiomer of the racemic of the major degradation product RPA 408056)	Adsorption K_f : Silt loam: 0.26 sandy loam:0.38 loam: 0.66 Silt loam: 0.40 sediment: 0.51 Adsorption K_{oc}: Silt loam: 52.00 sandy loam:31.66 loam: 21.05 Silt loam: 33.00 sediment: 15.00	Adsorption K_f values would classify RPA 412708 as being very highly mobile to highly mobile in the soils/sediments tested. Adsorption K_{oc} values would classify RPA 412708 as being very highly mobile to highly mobile in the soils/sediments tested.
Field studies			
Field dissipation	Fenamidone (RPA 407213) RPA 717879 RPA 408056	DT_{50}= 8.4-24 days No residues below 15cm DT_{50}= 110-128 days No residues below 15cm DT_{50}= 28-255 days No residues below 15cm	Non-persistent to persistent Moderately persistent (no clear pattern of dissipation established) slightly persistent to persistent

Table 3 Fate and Behaviour in the Aquatic Environment

Property	Test material	DT_{50}	Comments
Abiotic transformation			
Hydrolysis	Fenamidone	pH 4: 41.7 d pH 5: 222 d pH 7: 411 d pH 9: 28 d	Stable at environmentally relevant pHs

Property	Test material	DT_{50}	Comments
Phototransformation in water	Fenamidone	25.7-29.5 hours (equivalent to approx. 5-5.8 days in Florida respectively)	Not a major route of transformation because rapidly partitions to sediment. The major transformation products were RPA 717879 and RPA 408056
Biotransformation			
Biotransformation in aerobic water	Not applicable		Fenamidone rapidly partitions to sediment, therefore, this study is not applicable.
Biotransformation in aerobic water/sediment systems	Fenamidone	**clay loam system:** water 31.0 d sediment: 313.15 d system: 108.54 d **sandy loam system** water:17.52 d sediment: 85.7 d system: 67.2 d **sandy silt loam system** water: 5.1 d sediment: NA system: 136.4 d	Not a major route of transformation. The fate of fenamidone in aerobic water/ sediment systems is partitioning to sediment. Fenamidone is expected to be non-persistent in water and persistent in sediment. The major transformation product was RPA 408056
Biotransformation in anaerobic water/sediment systems	Fenamidone	**clay system** water: 6.3 d sediment: NA system: 1115 d	Not a major transformation pathway. Fenamidone rapidly partitions to the sediment were it is persistent