Pest Management Regulatory Agency
Agence de réglementation de la lutte antiparasitaire

Regulatory Note REG2003-11

Fenamidone Technical Fungicide, Reason 500 SC Fungicide

The active ingredient Fenamidone Technical fungicide and the associated end-use product, Reason 500 SC Fungicide, have been granted temporary registration under Section 17 of the Pest Control Products (PCP) Regulations for the control of late blight in potatoes.

This Regulatory Note provides a summary of data reviewed and the rationale for the proposed regulatory decision regarding these products.

(publié aussi en français)

October 17, 2003

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

Publications Coordinator
Pest Management Regulatory Agency
Health Canada
2720 Riverside Drive
A.L. 6605C
Ottawa, Ontario
K1A 0K9

Internet: pmra_publications@hc-sc.gc.ca
www.hc-sc.gc.ca/pmra-arla/
Information Service:
1-800-267-6315 or (613) 736-3799
Facsimile: (613) 736-3798

ISBN:0-662-34653-X (0-662-34654-8)
Catalogue number: H113-7/2003-11E (H113-7/2003-11E-PDF)

Foreword

Health Canada's Pest Management Regulatory Agency (PMRA) has issued temporary registration for Fenamidone Technical fungicide and the associated end-use product, Reason 500 SC Fungicide, for the control of late blight in potatoes.

Methods for analyzing fenamidone in some environmental media are available to research and monitoring agencies upon request to the PMRA.

Bayer CropScience Inc. (formerly Aventis CropScience Canada Co.) will be carrying out additional chemistry, storage stability, information on anilines, environmental chemistry and environmental toxicity studies as a condition of this temporary registration. Following the review of this information, the PMRA will publish a proposed registration decision document and request comments from interested parties before proceeding with a final regulatory decision.

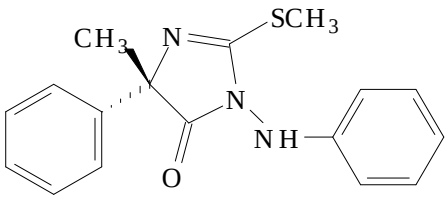
A summary of the Agency's findings in support of this decision is found in this Regulatory Note.

Table of Contents

1.0 The active substance, its properties and uses

1.1 Identity of the active substance and imprities (OECD 2.1.1)

Table 1.1.1 TGAI Identification

Active substance	Fenamidone
Function	Fungicide
Chemical name	
1. International Union of Pure and Applied Chemistry (IUPAC)	(S)-1-anilino-4-methyl-2-methytlhio-4-phenylimidazolin-5-one
2. Chemical Abstracts Service (CAS)	(5S)-3,5-dihydro-5-methyl-2-(methylthio)-5-phenyl-3-(phenylamino)-4H-imidazol-4-one
CAS number	161326-34-7
Molecular formula	$C_{17}H_{17}N_3OS$
Molecular weight	311.4
Structural formula	
Nominal purity of active	98.5% (limits 97–100%)
Identity of relevant impurities of toxicological, environmental or other significance	The technical grade Fenamidone does not contain any impurities or microcontaminants known to be Toxic Substances Management Policy (TSMP) Track-1 substances

1.2 Physical and chemical properties (OECD 2.1.2)

Table 1.2.1 Technical product: Fenamidone Technical fungicide

Property	Result	Comment
Colour and physical state	White to cream	
Odour	No detectable odour	

Property	Result	Comment
Melting point or range	135.5°C	
Boiling point or range	Decomposition at 230°C	
Density	PAI TGAI SG 20/20 1.288 1.293 Density (g/mL) 1.285 1.290	
Vapour pressure at 25°C	3.4×10^{-7}Pa (= 2.6×10^{-9} mmHg), by extrapolation of data obtained at 3 temperatures over the range 30–50°C	Fenamidone is non-volatile under field conditions.
Henry's Law constant at 20°C	1.366×10^{-10} atm·m^3/mol or 1.76×10^{8} (1/H)	Fenamidone is non-volatile from moist soils or water.
Ultraviolet (UV)–visible 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 300 to 800 nm.	Fenamidone has a low potential for light-induced phototransformation under normal environmental conditions.
Solubility in water at 20°C	7.8 mg/L	The solubility of fenamidone in water is classified as low.
Solubility (g/L) in organic solvents at 20°C	Solvent g/L acetone 250 acetonitrile 86.1 dichloromethane 330 ethyl acetate 105.7 n-heptane 0.3 toluene 40.1 methanol 43.1 n-octanol 9.7	
n-Octanol–water partition coefficient (K_{ow})	log K_{ow} = 2.8	There is a low potential for fenamidone to bioaccumulate.

Property	Result	Comment
Dissociation constant (pK_a)	N/A	
Stability (temperature, metal)	The product undergoes decomposition at 240°C and shows a slight change with iron powder and ferric sulphate. There is a possibility of reaction with iron or ferric sulphate at elevated temperature. The active is not an oxidizer (no reaction with $NH_4.H_2PO_4$ or Fe^0) or a reducer (no reaction with 0.1N $KMnO_4$).	

Table 1.2.2 End-use product: Reason 500 SC

Property	Result
Colour	White
Odour	No detectable odour
Physical state	Opaque liquid
Formulation type	Suspension concentrate
Guarantee	500 g/L (nominal) (limits: 485–515 g/L)
Formulants	The product does not contain any EPA List 1 formulants or formulants known to be TSMP Track-1 substances.
Container material and description	1L high-density polyethylene (HDPE) white, opaque container.
Bulk density	1.121 g/mL
pH	7.1
Oxidizing or reducing action	Not an oxidizer or reducer
Storage stability	The product was found to be stable at 54°C for 14 days. The study was not in compliance with GLP and the container type was not specified. ***A 1-year ambient temperature storage study in commercial packages is required. A 2-year GLP compliant study is expected to be submitted Jan 2003.***
Explodability	Not explosive

1.3 Details of uses and further information (OECD 2.1.3)

Reason 500 SC, containing 500 g/L of fenamidone, is a flowable concentrate fungicide for use in potatoes. It is recommended for use as a preventative fungicide for control of late blight on potatoes. It can be applied alone at 400 mL/ha or tank mixed with Dithane DG or Bravo 500 at a rate of 200 mL/ha of Reason 500 SC with 1.25 kg/ha of Dithane DG or 1.25 L/ha of Bravo 500, at 7–10 day intervals. Alternation with fungicides having a different mode of action (i.e., other than Group 11) 7–10 days after each Reason 500 SC application is recommended for resistance management. A maximum of six applications of Reason 500 SC, alone or as a tank mix, is allowed per year.

2.0 Methods of analysis (OECD 2.2)

2.1 Analytical methods for analysis of the active substance as manufactured (OECD 2.2.1)

Three reversed phase HPLC/UV methods, one using a chiral column, were provided for the determination of the active, fenamidone, and structurally related impurites in the technical product. Based on the validation data and the chromatograms provided, the methods were assessed to be sufficiently specific, precise and accurate.

2.2 Method for formulation analysis

A reversed phase HPLC/UV method was provided for determination of fenamidone present in Reason 500 SC. Based on the validation data and the chromatograms provided, the method was assessed to be specific, precise and accurate for use as an enforcement analytical method.

2.3 Analytical methods for residue analysis (OECD 2.2.3)

2.3.1 Methods for environmental residue analysis

An HPLC/MS method was submitted for the determination of the parent compound, fenamidone and its major transformation products RPA 408056, RPA 406012, RPA 410914, RPA 717879, RPA 409446 and RPA 410995 in soil. Based on the validation data and the chromatograms provided, the methods were assessed to be sufficiently sensitive, precise, accurate and specific for the determination.

The method for the determination of fenamidone in sediment was not provided.

A method using gas chromatogaphy with thermoionic detection (GC-TID) was provided for the determination of the parent compound, fenamidone and its major transformation products RPA 405862, RPA 408056 and RPA 717879 in drinking water, mineral water and surface water. Based on the validation data and chromatograms provided, the method

was assessed to be sufficiently sensitive, precise, accurate and specific for the determination.

An HPLC-MS-MS analytical method was provided for the determination of parent compound and the transformation products RPA 405862, RPA 408056 and RPA 717879 in a range of crops. A GC-TID method was provided for the determination of parent compound and the transformation products RPA 405862 and RPA 717879 in bovine tissues and other animal substrates, with a GC-MSD method being used for some tissues. These methods were extended to environmental plant and animal matrices.

2.3.2 Multi-residue methods for residue analysis

Fenamidone, RPA 408056, RPA 717879 and RPA 405862 were tested through FDA Multi-residue Method of Protocols. Protocol A was not fully tested because the compounds were not found to exhibit fluorescence. Protocol B was not tested because fenamidone and the three metabolites are not acids or phenols. Residues of fenamidone and all three metabolites in lettuce were completely recovered using Protocol D (GLC-NPD with a DB-1 column). Mean recoveries for substances tested were as follows: fenamidone (RPA 407213) at 112.3% ± 27.3%; RPA 408056 at 95.8% ± 4.6%; RPA 717879 at 118.3% ± 9.4%; and RPA 405862 at 92.4% ± 13.8%. No interference was noted for any of the substances in reagent blanks or controls. Low recoveries of fenamidone were observed from Protocols E (31%) and F (54%). Metabolites RPA 408056, RPA 717879, and RPA 405862 were not recovered using Protocols E and F.

2.3.3 Methods for residue analysis of plants and plant products

In the plant method, residues were first extracted from the potato crop matrix by blending or shaking with a mixture of acetonitrile and water. After filtration, an aliquot of the extract was rotary evaporated to near dryness, then diluted with water. Cleanup was accomplished on a HR-P polymeric solid phase extraction (SPE) cartridge and an aminopropyl SPE cartridge. Residues of fenamidone, and the metabolites RPA 405862, RPA 408056 and RPA 717879 were also extracted using an accelerated solvent extractor (ASE). Potato plant samples (~10 grams) were mixed with hydromatrix, packed in 33 MI stainless steel cells and extracted using 70:30 acetone and water mix at 50°C for 3, five minute cycles. The extraction solution was diluted and filtered prior to direct injection in the system. Regardless of the extraction method used, residues were quantified by HPLC (C-18 column) with tandem mass spectrometric detection (LC-MS/MS) using a turbo-ion spray source. The method limit of quantitation (LOQ) was 0.02 ppm for each of fenamidone and the metabolites RPA 412636, RPA 412708, and RPA 410193 in potatoes, tomatoes, cucumbers, cantaloupes, lettuce, onions, spinach, and wheat raw agricultural commodities and processed fractions. The limit of detection was estimated to be 0.007 ppm. All calibration curves were linear with a correlation coefficient of 0.99 in the range of 0.075 ng/mL to 0.750 ng/mL. The average recoveries in potato matrices were 106 ± 5.7% (fenamidone); 93% ± 7.9% (RPA 405862); 97% ± 6.2% (RPA 408056) and 93% ± 9.7% (RPA 717879).

2.3.4 Methods for residue analysis of food of animal origin

Residue analytical methods were developed for the analysis of fenamidone residues in milk (AR 200-99) and all animal matrices (AR 188-98). Residues were extracted from milk by blending with acetonitrile followed by filtration. An aliquot of the filtrate was evaporated to dryness and was reconstituted in water:acetonitrile (80:20). Additional cleanup was accomplished on a C-18 SPE cartridge with elution using water:acetonitrile (70:30, 50:50 and 40:60). Two fractions were eluted from the SPE cartridge. One fraction contained the metabolites RPA 412708 and RPA 412636, and the other fraction contained fenamidone. The two fractions were each evaporated to dryness and reconstituted with toluene before analysis, using gas chromatography with thermionic detection (GC-TID). The method limit of quantitation (LOQ) was 0.01 ppm for each fenamidone and the metabolites RPA 412636 and RPA 412708 in milk. Average recoveries of fenamidone were 79% ± 7%; RPA 408056 was 102% ± 13%; RPA 717879 was 77% ± 8%. The detector response was linear with a correlation coefficient of 0.99 in the range of 50 to 1000 µg/L injected.

Residues were extracted from animal tissues by macerating with acetonitrile. After filtration, an aliquot was evaporated to dryness, then reconstituted in a mixture of methanol and water. Cleanup was accomplished on a polystyrene divinyl benzene cartridge (elution with acetonitrile) and with an aminopropyl cartridge (elution with cyclohexane:acetone). Three fractions were eluted from the amino SPE cartridge. One fraction contained fenamidone; the second fraction contained RPA 412708 and the third fraction contained RPA 412636. The three fractions were separately evaporated to dryness and reconstituted with toluene before analysis. For liver, residues were quantified using gas chromatography and mass selective detection (GC-MSD) with electron impact ionisation. For all other matrices (muscle, whole egg and kidney), residues were quantified using gas chromatography with thermionic detection (GC-TID). The method limit of quantitation (LOQ) was 0.05 ppm for each fenamidone and the metabolites RPA 412636 and RPA 412708 in animal matrices. 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). The detector response was linear with a correlation coefficient of 0.99 in the range of 50 to 1000 µg/L injected.

Enforcement residue analytical methodology for animal commodities was not required at this time because no finite residues of fenamidone were expected in livestock matrices and maximum residue limits are not being proposed.

3.0 Impact on human and animal health (OECD 2.3)

3.1 Integrated toxicological summary

A detailed review of the toxicology database available for the new fungicide, fenamidone, has been completed. Data submitted were complete and well presented, and included the

full battery of studies currently required for registration purposes. The submitted studies were conducted in conformance with currently acceptable international testing protocols.

Following oral dosing, radiolabelled fenamidone was rapidly absorbed, distributed and excreted, with > 96% of the administered dose (AD) being eliminated within 96 hours post-dosing. After dosing with fenamidone radiolabelled on the N-phenyl group, the feces was the major route of elimination for males, accounting for 52.0% to 64.3% of the AD. Recovery from urine ranged from 26.6% to 40.6%. For females, fecal excretion accounted for 44.7% to 49.6% of the AD, and urinary excretion accounted for 40.5% to 46.5% of the AD. After dosing with fenamidone radiolabelled on the C-phenyl group, the feces was the major route of excretion, accounting for 80.7% to 84.7% of the AD for males, and 52.1% to 91.0% of the AD for females. Recovery from urine ranged from 10.6% to 12.8% of the AD for males and 13.0% to 39.9% of the AD for females. Biliary excretion data indicated that systemic absorption was ~90% to 95% following a single oral low dose of either C-phenyl-[U-^{14}C]-fenamidone or N-phenyl-[U-^{14}C]-fenamidone, and a part of the radioactivity excreted via the bile could be reabsorbed (enterohepatic circulation) and subsequently re-excreted via the urine. At low doses, peak concentrations of radioactivity in the blood occurred at 4 hours post-dosing for both sexes, and at high doses, peak concentrations of radioactivity in the blood occurred at 8 and 24 hours for males and females, respectively. Tissue distribution and bioaccumulation were minimal, with < 0.66% of the AD recovered in tissues at 7 days. There were up to 24 metabolites identified in the excreta indicating extensive metabolic breakdown. Fenamidone was metabolized by both phase I reactions, i.e., oxidation, reduction and hydrolysis, and phase II reactions, i.e., conjugation. There were no significant differences in the total metabolite profile among all dose groups for both male and female rats, although the quantities of some metabolites varied between males and females, and between the dose groups. A dose-related difference in metabolism was evident; the higher amount of unmetabolized parent compound in the feces of the high-dose group, compared to the low-dose and repeated-dose groups, indicates that saturation of the metabolic pathway may be occurring at the high dose.

Acute dosing revealed that technical fenamidone was of low toxicity by the oral, dermal and inhalation routes. It was non-irritating to the skin, minimally irritating when instilled into the eyes and was not a skin sensitizer (Maximization method). The Reason 500 SC formulation, containing 45.12% fenamidone, was of low toxicity by the oral, dermal and inhalation routes. It was minimally irritating to the skin, mildly irritating when instilled into the eyes and was not a dermal sensitizer (modified Buehler method).

Short-term (28 days) repeated dermal dosing in rats with technical fenamidone did not result in any adverse treatment-related systemic or dermal effects up to and including the highest dose level tested of 1000 mg/kg bw/day (limit dose).

Short-term (3 months) exposure to technical fenamidone via the oral route in mice did not result in any adverse, treatment-related effects up to and including the high dose level of 1064 mg/kg bw/day (limit dose). In dogs, short-term exposure for 28 days or 3 months

did not elicit any adverse, treatment-related effects up to and including the high dose levels of 100 and 500 mg/kg bw/day, respectively. The target organ for dogs after short-term (1 year) exposure was the liver. Findings were increased liver weight, biliary proliferation and an increase in alkaline phosphatase, noted at the high dose of 1000 mg/kg bw/day (limit dose). There were no other treatment-related changes. The target organ noted for rats after short-term (28 days and 3 months) exposure was the liver. In the 28-day study, and both of the 3-month studies, liver weight was increased at dose levels of 389 mg/kg bw/day and higher, with corresponding histopathological changes, i.e., hepatocyte hypertrophy, hepatocyte macro/microvacuolization, bile duct hyperplasia and ground glass appearance to the cytoplasm. There was no corresponding increase in liver enzyme activity. In the 28-day study, spleen weight was increased at the high dose level of 1203 mg/kg bw/day, and hypertrophy/hyperplasia of the splenic germinative follicles of the white pulp was observed at dose levels of 389 mg/kg bw/day and higher. In the 3-month studies, findings in the spleen were observed in only one study, manifest as prominent germinal centres at the high dose level of 306 mg/kg bw/day. Additional treatment-related findings in the rat were increased thyroid weight and decreased thymus weight, observed in both of the 3-month studies at the high dose levels of 306 and 344 mg/kg bw/day, but without corresponding histopathological findings; renal extramedullary hyperplasia was noted in one of the 3-month studies at the high dose of 306 mg/kg bw/day. Based on the available short-term data, it is concluded that fenamidone has a low subchronic toxicity profile.

The target organ for mice and rats, after long-term exposure to technical fenamidone, was the liver. For mice, liver weight was increased at dose levels of 526 mg/kg bw/day and higher. Corresponding histopathological changes included increased pleomorphism with or without increased cytoplasmic eosinophilia, occasional giant cells and eosinophilic globules within the cytoplasm and clear cell foci. For rats, liver weight was increased at dose levels of 48 mg/kg bw/day and higher. However, histopathological changes to the liver were only observed at the high dose level of 260 mg/kg bw/day, and included foamy hepatocyte cytoplasm, eosinophilic inclusions, hepatocyte hypertrophy and hepatocyte vacuolation. There was no corresponding increase in liver enzyme activity for either mice or rats. The thyroid was also a target organ for rats, with increased thyroid weight, enlarged thyroids, follicular cell hypertrophy/hyperplasia, increased colloid basophilia and increased follicular diameter observed at dose levels of 48 mg/kg bw/day and higher. In addition, at the high dose level of 260 mg/kg bw/day, there was an increased incidence of diffuse C-cell hyperplasia in the thyroid, males only.

There was no evidence of oncogenic potential of fenamidone in mice and rats up to the highest dose levels tested of 1064/1375 mg/kg bw/day and 260/335 mg/kg bw/day, respectively. Fenamidone was not considered to be genotoxic based on the weight of evidence obtained from the results of in vitro and in vivo mutagenicity assays.

Fenamidone did not affect reproductive performance or reproductive parameters at any dose level tested. Toxicologically significant parental findings were noted at the high dose level of 328/353 mg/kg bw/day and included slightly lower body-weight gain (F_0

and F_1 males and females), decreased food intake (F_1 males and females), decreased food efficiency (F_0 males and females) and increased spleen and liver weights (F_0 and F_1 males and females). For offspring, the only toxicologically significant treatment-related finding was lower pup body-weight gain for F_1 pups at 328/353 mg/kg bw/day. Based on the above data, there was no evidence for increased susceptibility of rat pups following exposure to fenamidone.

Fenamidone was not teratogenic to rat or rabbit fetuses at dose levels up to and including 1000 mg/kg bw/day (rats) and 100 mg/kg bw/day (rabbits). For rats, maternal toxicity was noted at 1000 mg/kg bw/day, manifest as lower body-weight gain and decreased food intake during the dosing period. Slightly lower fetal body weight was noted at 1000 mg/kg bw/day (maternally toxic dose). In addition, there was an increased incidence of incomplete ossification of the parietal bone and hyoid body, slightly increased incidence of unossified 5th sternebrae and incomplete ossification of the 6th sternebrae. However, the total number of litters/fetuses exhibiting skeletal variations were comparable at all dose levels tested. Hence, these minor variations were not considered to be adverse, toxicologically significant findings. For rabbits, the only maternal finding was increased liver weight, observed at 30 and 100 mg/kg bw/day. At dose levels of 200 mg/kg bw/day and higher the maximum tolerated dose was exceeded due to severe maternal toxicity. There were no treatment-related developmental effects noted at any dose level tested. There was no evidence for increased susceptibility of rat or rabbit fetuses following in utero exposure to fenamidone.

Fenamidone showed no evidence of neurotoxicity in rats by either acute or subchronic exposure up to and including the highest dose levels tested of 1000 mg/kg bw/day in the acute study and 392/414 mg/kg bw/day in the subchronic study.

Three metabolites of fenamidone were tested for acute oral toxicity and genotoxicity, 2 of which were also tested for short-term (3-month) toxicity. The first metabolite, RPA 412636, is a major plant, animal and environmental metabolite of fenamidone. RPA 412636 was slightly acutely toxic by the oral route, and was not considered to be genotoxic. The target organs after short-term (3 months) exposure were the liver, thymus, adrenal (males) and thyroid (males). Liver weight was increased at dose levels of 33 mg/kg bw/day and higher, with corresponding histopathological changes, i.e., hepatocyte hypertrophy and hepatocyte vacuolation; serum cholesterol was increased at 162 mg/kg bw/day. Thymus weight was decreased for both sexes, with a minor increase in the severity of thymus involution noted for males only. Increased adrenal weight and diffuse hypertrophy of the adrenals was noted for males. Histopathological examination revealed colloid depletion, colloid agglomeration and a slight increase in follicular epithelial height in the thyroid of males, and a minor increase in the severity of eosinophilic droplets in the proximal tubules in the kidneys of males.

The second metabolite, RPA 410193, is a major plant metabolite in tomatoes and grapes, and was found in poultry (egg whites). RPA 410193 was of low acute toxicity by the oral route, and was not considered to be genotoxic. The target organ after short-term (3

months) exposure was the liver. At dose levels of 93 mg/kg bw/day and higher, liver weight was increased with corresponding hepatocyte hypertrophy, and serum cholesterol was increased. The only other finding was decreased thymus weight noted at dose levels of 9 mg/kg bw/day, with an increase in the severity of thymus involution noted at doses of 93 mg/kg bw/day and higher.

The third metabolite, RPA 412708, is a major plant, animal and environmental metabolite. RPA 412708 was of high acute toxicity by the oral route, and was not considered to be genotoxic.

Based on the submitted data, it was demonstrated that the metabolites RPA 412636 and RPA 410193 have a similar subchronic toxicity profile to fenamidone and are therefore not considered to be more toxic than the parent compound. Although metabolite RPA 412708 was only tested for acute oral toxicity and genotoxic potential, it was found in significant quantities as a metabolite in the rat metabolism studies, i.e., > 10%, and it is therefore assumed that its toxicological potential has been evaluated in the toxicity studies conducted on the parent compound.

3.2 Determination of acceptable daily intake (ADI)

The lowest NOEL was 150 ppm, equal to 7.07/9.24 mg/kg bw/day, established in the 2-year combined chronic/oncogenicity feeding study in rats, based on increased thyroid weights and thyroid histopathology at higher dose levels. For the calculation of the ADI for all populations, an uncertainty factor (UF) of 100 is recommended, i.e, 10× for interspecies differences and 10× for intraspecies differences. The ADI recommended is calculated according to the following formula:

$$\text{ADI} = \frac{\text{NOAEL}}{\text{UF}} = \frac{7.07 \text{ mg/kg bw/day}}{100}$$

= 0.071 mg/kg bw/day of fenamidone.

3.3 Acute reference dose (ARfD)

No acute endpoints of concern were identified, and so an ARfD is not required.

3.4 Toxicological endpoint for assessment of occupational and bystander risks—AOEL/MOE (OECD 2.3.4)

There is a potential for short to intermediate duration of exposure to workers mixing, loading and applying fenamidone for 1 to 3 months of the year. Treatments would normally start in July and continue up until harvest. There is also potential for short–intermediate duration exposure to workers re-entering treated fields to set up irrigation, scout and hand-weed. Dermal deposition is the predominant route of exposure.

Short- and intermediate-term occupational dermal exposures:
For short-term occupational exposures via the dermal route, the rat 28-day dermal toxicity study with a NOAEL of 1000 mg/kg bw/day was selected. Dermal exposure to fenamidone for 28-days did not result in any adverse treatment-related systemic or dermal effects up to and including the highest dose level tested of 1000 mg/kg bw/day (limit dose). The target margin of exposure (MOE) for this scenario is 100.

For intermediate-term occupational exposures via the dermal route, the rat 90-day feeding toxicity study with an NOAEL of 68.27 mg/kg bw/day was considered most appropriate. The NOAEL of 68.27 mg/kg bw/day was based on decreased body-weight gain and food consumption, increased liver weight (females), liver histopathology and increased cholesterol The target MOE for this scenario is 100.

3.5 Impact on human or animal health arising from exposure to the active substance or to impurities contained in it (OECD 2.3.6)

3.5.1 Operator exposure assessment

Dermal absorption
Male Crl:CD® (SD) BR rats were administered doses of 2.69, 2.71, 28.1, 28.0, 257 and 256 µg/cm^2 of fenamidone, a commercial agricultural fungicide for control of late blight on potatoes. Doses were applied in a vehicle similar to the end-use product formulation. Subjects either remained exposed until sacrifice (0.5, 1, 2, 4, 10 and 24 hours) or were washed at 8 hours and sacrificed at 8, 24 or 48 hours post-application. Recovery levels were adequate (94.82–102%) and were calculated using mass balance.

Following dermal administration of rats with the fenamidone, the majority of the administered dose was recovered from the skin wash. The percent of the applied dose accounted for by skin washes and rinses of the dose site ranged from 76.3 to 95.7%. Significant amounts were also present at the application site after washing (ie., 3.38 to 15.5%). Skin site residues did not decline significantly with time over the 48-hour post-dosing period and there was no change in residues with increasing dose levels or exposure duration and there was no correlation with concentration versus time. For the groups with exposure up until sacrifice, the majority of the systemic absorbed dose was found in the carcass (i.e., 0.10 to 3.13%) with some being found in the feces (ie., 0.02 to 2.10%). Only small amounts were found in the blood (≤ 0.03%), and urine + cage wash + cage wipe (≤ 0.47%). There was a trend for residues to increase with exposure duration for both the carcass, urine and feces for all dose groups. For the 8-hour exposure groups the majority of the systemic absorbed dose was found in the carcass (ie., 0.51 to 3.93%) with some being found in the feces (ie., 0.06 to 3.08%). Only small amounts were found in the blood (≤ 0.03%), and urine + cage wash + cage wipe (≤ 1.53%). There was a trend for residues in the carcass to decrease with time for all dose groups and urine to increase with time for the medium and high dose groups and feces to increase for all dose groups.

For the low, medium and high dose groups, urine plus fecal excretion increased with increased exposure duration (up until sacrifice). Similarly, carcass levels increased with increased exposure duration for all dose levels.

The expected exposure time for workers using this product as an agricultural fungicide is expected to be 8 hours. Given the uncertainty regarding exposure under actual field conditions, it is considered appropriate to derive an estimate of dermal absorption based on the results from the 8-hour exposure time with sacrifice at 24 hours using a high dose (3,200.0 µg a.i./animal), as the percent dermal absorption (17.1%) was greatest at this dose level. This value is considered conservative as approximately 91% of this value was retained at the skin site and it is unlikely that all of the skin residues will become systemically available.

Operator exposure and risk assessment

Farmers using groundboom application equipment can typically treat 65 ha potatoes in a typical 8-hour workday while custom applicators can treat 300 ha per day. 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. Farmers' exposure is considered short term, custom applicators' exposure is considered short- to intermediate-term.

Estimates of exposure to workers mixing, loading and applying (M/L/A) Reason 500 SC to potatoes were based on Pesticide Handlers' Exposure Database (PHED) Version 1.1 subsets which measured the potential dermal and inhalation exposure during open mixing and load and open cab groundboom application:

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

This PHED assessment was designed to quantify exposure to Reason 500 SC, a suspension concentrate formulation of fenamidone while mixing/loading and applying by groundboom. Reason 500 SC is packaged in 2, 4, or 10 litre plastic containers. The PHED subsets for liquid open mixing/loading and groundboom application were used to estimate exposure during mixing/loading/application and were considered acceptable and applicable to the use scenario and the confidence in the data was high (A, B grade data). The number of replicates ranged from 22 to 119 and sample time ranged from 0.75 hours to 3.5 hours. The PPE on the proposed label is mixer/loaders wear long pants, long-sleeved shirts, boots, goggles or face shield, and chemical-resistant gloves. The PPE used in the PHED assessment was single layer and chemical resistance gloves for mixer/loaders and single layer for applicator, this was almost identical to the PPE on the label. This is adequate engineering controls used for mixer/loaders and conservative for custom applicators as it is not often that high capacity groundboom rigs are "open cab".

All exposure estimates were based on summing the measure of central tendency for each body part that is most appropriate to the distribution of data for that body part (best-fit). Systemic exposure estimates were determined based on a 17.1% dermal absorption value.

Unit exposure values, based on PHED v. 1.1, are presented in Table 3.5.1. The primary route of exposure was dermal.

Table 3.5.1 PHED unit exposure estimates (µg a.i./kg a.i. handled)

Scenario	PHED unit exposure (µg a.i./kg a.i. handled)	
	Dermal deposition	Inhalation
Mixer/loader[1]	51.14	1.6
Applicator[2]	32.98	0.96
Mixer/loader/applicator	84.12	2.56

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

As the NOAEL for the short-term risk assessment (i.e., farmers M/L/A) 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 (ie., custom M/L/A) 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 3.5.2.

Table 3.5.2 Daily exposure estimates (µg a.i./kg-bw/day)

Exposure pattern	Scenario	Daily exposure (µg a.i./kg-bw/day)[a]			
		Dermal deposition	Dermal absorbed[b]	Inhalation	Total[c]
13 kg a.i./day (0.2 kg a.i./ha × 65 ha/day)	Farmer—mixer/loader[1]	9.49	N/A	0.30	9.79
	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 a.i./day (0.2 kg a.i./ha × 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	14.53

[a] Calculated as µg a.i./kg a.i. handled × application rate × 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 M/L, A and custom M/L/A 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 farmer M/L/A 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 endpoint concern. The MOEs were compared to the target MOE of 100 and found to be acceptable (See Table 3.5.3).

Table 3.5.3 Margins of exposure[c]

Scenario	MOE (NOAEL 1000[a])	MOE (NOAEL 68.3[b])
Farmer M/L/A	62 121[c]	N/A
Custom M/L	N/A	7699
Custom A	N/A	12 069
Custom M/L/A	N/A	4701

[a] 28-day dermal rat
[b] 3-month dietary rat
[c] Target MOE 100

3.5.2 Bystanders

Potential for bystander exposure was considered minimal and significantly less than exposures estimated for operators and re-entry workers.

3.5.3 Workers

The potential for re-entry exposure during harvesting is low. Potato harvesting is usually mechanical and harvesters generally wear long clothes, dust masks and gloves. As well, the proposed PHI is 14 days. There is potential re-entry exposure to scouts who enter the fields throughout the growing season looking for signs of disease. Scouts may pull diseased plants to avoid disease transmission (rouging). Scouts typically spend less than one hour and up to five hours total in a typical workday in contact with the foliage. Scouting may be conducted by professional scouts or by growers. As scouts must kneel to closely examine plants, foliage may brush against their face and neck.

Estimates of exposure to individuals who re-enter treated fields were based on a dislodgeable foliar study which measured the amount of residue that could be available to workers that come into contact with treated crops (Determination of dislodgeable foliar residue in cantaloupe treated with fenamidone).

This study was designed to collect data to calculate dislodgeable foliar residue (DFR) dissipation curves for Reason 500 SC on cantaloupe at test sites in California, Florida and Pennsylvania. The application rates (200 g a.i./ha) and number (6) were relevant to the use pattern proposed but were not conducted on the crop that is proposed on the draft label. The application timing was not the same as on the proposed label (5 days apart versus 7–10 days on the label). All three sites were monitored: with 3 replicates per sampling time per site (total replicates per sampling time = 9). No Canadian sites were monitored. The study was found to be acceptable as a surrogate for a potato dislodgeable foliar residue study. The design of the study is consistent with acceptable guidelines.

The results indicate that the dislodgeable foliar residues (DFR) of fenamidone decline rapidly with time in environments with rainfall. Dissipation rates after the last application were modelled utilizing pseudo first-order kinetics to estimate the half-lives for California $t_{½}$ = 144 days, Florida $t_{½}$ = 2 days and for Pennsylvania $t_{½}$ = 12 days. The limit of detection (LOD) was not reached during the 35 days following the last of 6 applications for both the California and Pennsylvania sites but was reached after 21 days for the Florida site. The Florida and Pennsylvania site had R^2 values of 0.94 and 0.95, respectively, while the California R^2 value was low (0.1594). The equations for the dissipation curves were y = -0.0589× + 0.0094 for Pennsylvania, y = -0.3356× - 0.4089 for Florida and y = -0.0048× - 0.1273 for California. After the first application, DFR accounted for 23%, 34% and 20% of the application rate (2 µg/cm^2) at the California, Florida, and Pennsylvania sites respectively. The highest DFR values for Pennsylvania was 1.359 µg/cm^2 the first day after application six, and for Florida was 1.003 µg/cm^2 on the day of the sixth application, and for California was 1.077 µg/cm^2 on the day of the sixth application. From the decay curves, there is a 14% daily decline in DFR at the Pennsylvania site and a 28% decline at the Florida site. Data from the Pennsylvania site was considered most appropriate for the current risk assessment.

The DFR value from the first day after the final application at the Pennsylvania site (i.e., 1.359 µg/cm^2) was combined with standard defaults including an assumption that workers spend 4 hours per day scouting, irrigating, or 8 hours a day hand weeding potatoes. Since the applicant is a member of the Agricultural Re-entry Task Force (ARTF), the ARTF transfer coefficient for scouting and irrigation of 1500 cm^2/h and 300 cm^2/h for hand weeding will be used for risk assessment purposes. As the NOAEL for the intermediate-term risk assessment is based on an oral toxicity study, daily exposure estimates are adjusted for dermal absorption.

A summary of post-application exposure estimates, on the day of application, are presented in Table 3.5.4.

Table 3.5.4. Post-application exposure estimates for Reason 500 SC

Scenario	Transfer coefficient (cm^2/h)[a]	DFR value (µg/cm^2)	Time (h/day)	Systemic exposure (mg/kg bw/day)[b]
Scouting	1500	1.359	4	0.0199
Irrigation	1500	1.359	4	0.0199
Hand weeding	300	1.359	8	0.0080

[a] ARTF Proprietary Transfer Coefficient. The applicant, Aventis CropScience Canada Co., is a member of ARTF.

[b] Exposure estimates were calculated using the following formula:

$$\frac{\text{DFR Value (µg/cm}^2\text{)} \times \text{Transfer coefficient (cm}^2\text{/h)} \times \text{hours worked per day (h)} \times \text{conversion Factor (1mg/1000µg)} \times 17.1\%}{\text{Body weight (70 kg)}}$$

For short- to intermediate-term exposure, estimates for workers re-entering treated fields to scout, irrigate and hand weed, were compared to the NOAEL of 68.3 mg/kg bw/day from a 3-month dietary rat study. These MOEs were compared to the target MOE of 100 and found to be acceptable (See Table 3.5.5.).

Table 3.5.5. Margins of exposure for post-application activities[a]

Scenario	MOE (NOAEL 68.3)[b]
Scouting (TC = 1500)	3427
Irrigating (TC = 1500)	3427
Hand Weeding (TC = 300)	8568

[a] Target MOE 100
[b] 3-month dietary rat

4.0 Residues

4.1 Residue Summary

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 to 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 RPA 717879 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). Therefore, the residue of concern in potato plants is defined as parent fenamidone for enforcement and risk assessment purposes.

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). Since fenamidone contains more than one ring, and the submitted study indicated that metabolism in rotational crops included compounds as a result of cleavage of the molecule, an N-phenyl study should have been conducted. However, based on the plant metabolism studies, the major plant residues consisted of metabolites containing both the C-phenyl and N-phenyl ring systems, along with C-phenyl products also identified in soil. Therefore, it is not expected that residues of toxicological concerns will be taken up by the succeeding crops.

Limited field accumulation in rotational crops
A limited field accumulation study was conducted in Zones 10 and 11 where soil was treated with EXP 10623A 50SC 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 pre-harvest 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 (Zones 1, 1A, 2, 3, 5, 5A, 5B, 7, 7A, 10, 11, 12 and 14). As no residues were detected, the residue decline data did not show any trends in fenamidone residues with PHI.

Storage stability
Residues of fenamidone and the metabolites (RPA 408056, RPA 405862, RPA 717879) are stable for up to 12 months in potatoes 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 (fivefold 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 raw agricultural commodity (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 proposed domestic use of fenamidone (Reason 500) on potatoes does not pose an unacceptable chronic dietary (both food and water) risk to any segment of the population, including infants, children, adults and seniors.

5.0 Fate and behaviour in the environment

Studies on the environmental fate and behaviour of fenamidone were provided by the registrant.

5.1 Physical and chemical properties relevant to the environment

The physical and chemical properties of fenamidone that are relevant to the environment are presented in Table 5.1.1. Fenamidone has low solubility in water. The vapour pressures and Henry's Law constant indicate that fenamidone is non-volatile under field conditions or from moist soils or water. The octanol–water partition coefficient indictates that fenamidone is unlikely to bioaccumulate in aquatic organisms. Fenamidone is unlikely to be in ionic form at environmentally relevant pHs. Data on the UV–visible light absorption spectrum indicate that fenamidone has a low potential for phototransformation under normal environmental conditions.

Table 5.1.1 Physical and chemical properties of the active ingredient relevant to the environment

Property	Value	Comments
Water solubility	7.8 mg/L	The solubility of fenamidone in water is classified as low.
Vapour pressure	3.4×10^{-7}Pa (= 2.6×10^{-9} mmHg), by extrapolation of data obtained at 3 temperatures over the range 30–50°C, using the Clapeyron-Clausius equation.	Fenamidone is non-volatile under field conditions.
Henry's Law constant	1.366×10^{-10} atm·m^3/mol or 1.76×10^{8} (1/H)	Fenamidone is non-volatile from moist soils or water.
Octanol–water partition coefficient	K_{ow} = 631 log K_{ow} = 2.8	There is a low potential for fenamidone to bioaccumulate.
pK_a	No value provided.	Fenamidone is not expected to dissociate in water.
UV–visible absorption	medium λ (nm) ϵ acidic 203.0 25 138 230.0 15 734 neutral 202.5 36 941 230.0 18 297 basic 208.5 93 570 228.5 19 419 No absorption observed from 300 to 800 nm.	Fenamidone has a low potential for light-induced phototransformation under normal environmental conditions.

5.2 Abiotic transformation

Laboratory studies on the hydrolysis, phototransformation on soil, and phototransformation in water were submitted to determine the effect of abiotic processes on fenamidone.

In a hydrolysis study, the half-lives of fenamidone were 41.7, 221.8 , 411.0 and 27.6 d at pH 4, pH 5, pH 7, and pH 9, respectively. At environmentally relevant pHs (pH 5 and pH 7) there are no major transformation products resulting from the hydrolysis of fenamidone over a period of 30 days. The half-lives of fenamidone at environmentally relevant pHs are greater than 25 weeks.

The results from the soil phototransformation studies indicate no evidence of phototransformation on soil. The DT_{50} values in the irradiated samples were greater than those in the dark treatment. The two major transformation products identified in the irradiated treatments were RPA 717879 and RPA 408056 which reached maximum concentrations of 11.8 and 16.8% of the AR, respectively. The two studies on the photodegradation of fenamidone in water indicate that the DT_{50} is less than 30 hours (equivalent to less than 6 days in Florida), this value will probably be longer in Canada due to our higher latitude. In water, the major transformation products were RPA 405862 and RPA 408056 which reached maximum concentrations of 13.4 and 35.6% of the applied radioactivity, respectively. As fenamidone is not expected to be volatile, studies on the phototransformation in air were not required.

These results indicate that fenamidone does not readily undergo hydrolysis or photolysis on soil but some photolysis in water is likely to occur.

5.3 Biotransformation

Laboratory studies on the biotransformation of fenamidone in aerobic soil, aerobic water/sediment and anaerobic water/sediment systems were reviewed to determine the effect of biotic (microbial) processes on this compound.

Biotransformation processes were examined in aerobic sandy loam and loam soils. Fenamidone transformed rapidly in the sandy loam with a first-order DT_{50} of approximately 7 days. In the loam soil, transformation was slightly less rapid with an estimated DT_{50} of approximately 8 days. The major transformation products detected in the sandy loam were RPA 717879, RPA 408056, RPA 409446, RPA 410995, RPA 406012, and RPA 410914. After 365 days the only major transformation product in the sandy loam which remained at levels greater than 10% of the AR was RPA 717879 at a concentration of 34.9% of the AR and was still increasing at study termination. In the loam soil the major transformation products were RPA 717879 and RPA 408056.

The aerobic transformation of RPA 412636 (an enantiomer of the major degradation product 717879) was also examined in a sand, clay loam and silt loam. At the end of 365 days 53.5%, 7.63% and 55.3% of the applied radioactivity remained in the sand, clay loam, and silt loam respectively. The estimated DT_{50} values for RPA 412636 were 421, 100, and 459 days in the sand, clay loam and silty loam respectively. There were no major transformation products detected in any soil over the course of the study.

Two studies on the biotransformation of fenamidone in aerobic water/sediment systems were reviewed. The first study examined the transformation of C-phenyl labelled fenamidone in clay loam and sandy loam sediments over the course of 152 days. In both systems there was a steady transfer of the applied radioactivity from the water to the sediment so that by study termination 63.18% and 72.16% of the applied radioactivity was in the clay loam and the sandy loam sediments respectively. The estimated first-order DT_{50} values in the clay loam were 31.04, 313.15, and 108.54 days in the water, sediment

and total system respectively. In the sandy loam the first-order DT_{50} values were 17.36, 85.87, and 67.19 days in the water, sediment, and entire system respectively. The major transformation product in both systems was RPA 408056.

The second study examined the transformation of N-phenyl labelled fenamidone in a sandy silt loam sediment over the course of 102 days. As in the previous study, fenamidone transferred steadily to the sediments from the overlying water. At the end of the incubation 80.14% of the applied radioactivity was in the sediments. The estimated first-order DT_{50} values for fenamidone were 5.09 and 136.4 days in the water and total system, respectively. There were no major transformation products unique to the N-phenyl ring.

The transformation of [C-phenyl-U-^{14}C]-fenamidone under anaerobic aquatic conditions was studied over the course of 364 days in a clay sediment. Applied radioactivity moved rapidly to the sediments such that 78% of the applied radioactivity was in the sediments by day 7. By the end of the incubation levels had increased to 92% of the applied. The estimated first-order DT_{50} 6.25 days in the water. DT_{50} values could not be estimated in the sediment, but the value for the entire system was 1115 days. There were no major transformation products detected.

Overall, biotransformation is an important route for the transformation of fenamidone under aerobic conditions in soil. In aquatic environments, fenamidone appears to be rapidly removed from water and is partitioned to sediments, which may act as a sink for this compound. Based on studies of biotransformation, fenamidone is expected to be non-persistent in soil but much more persistent in water/sediment systems (i.e. in the sediment portion). This is especially true in anaerobic sediments where the compound is expected to persist for years.

5.4 Mobility

The mobility of fenamidone was studied in an American silt loam and a sandy loam, a UK loam and silty loam, and a UK sandy clay loam sediment. The adsorption K_f values were 2.43, 5.93, 6.89, 4.93 and 8.90 in the American silt loam and a sandy loam, the UK loam and silty loam, and the UK sandy clay loam sediment, respectively. The adsorption K_{oc} values ranged from 259 to 494. The desorption K_f values were 3.17, 6.56, 7.9, 5.96, and 9.08 in the American silt loam and a sandy loam the UK loam and silty loam, and the UK sandy clay loam sediment, respectively.

Based on adsorption K_{oc} values fenamidone is classified as moderately mobile in soils and sediment, according to the classification scheme of McCall *et al*. (1981). Results also indicate that some degree of hysteresis occurs indicating that this molecule desorbs less readily than it adsorbs to soils and sediments. The data do not indicate any strong correlation between mobility and any one of organic carbon, pH, cation exchange capacity (CEC), or clay content.

In a second study, the adsorption/desorption characteristics of RPA 412636 (s-enantiomer of the major transformation product RPA 717879) were studied in two American soils, a silt loam and a sandy loam, two UK soils, a loam and a silty loam, and a UK sediment classified as a sandy clay loam.

The adsorption K_f values were 0.11, 0.43, 0.32, 0.56 and 0.64 in the American silt loam and sandy loam, the UK loam and silty loam, and the UK sediment, respectively. The adsorption K_{oc} values ranged from 17.0 to 36.0. The desorption K_f values were 0.12, 0.88, 0.79, 0.99, and 1.32 in the American silt loam and sandy loam, the UK loam and silty loam, and the UK sediment, respectively. The desorption K_{oc} values ranged from 24.0 to 73.3. The desorption K_f and K_{oc} values were generally higher than those obtained for adsorption.

Based on K_{oc} values, the transformation product RPA 412636 is classified as very highly mobile in soils and sediment, according to the classification scheme of McCall *et al*. (1981). The data do not indicate any strong correlation between mobility and any one of organic carbon, pH, cation exchange capacity (CEC), or clay content.

The third mobility study determined at the adsorption/desorption characteristics of RPA 412708 (s-enantiomer of the major degradation product RPA 408056) in two American soils, a silt loam and a sandy loam, two UK soils, a loam and a silty loam, and a UK sediment classified as a sandy clay loam.

The adsorption K_f values were 0.26, 0.38, 0.40, 0.66 and 0.51 in the American silt loam and sandy loam, the UK silt loam and loam, and the UK sediment, respectively. The adsorption K_{oc} values ranged from 15.0 to 52.0. The desorption K_f values were 0.46, 0.65, 0.94, 0.84, and 1.09 in the American silt loam and sandy loam, the UK silt loam and loam, and the UK sediment, respectively. The desorption K_{oc} values ranged from 27.65 to 92. The desorption K_f and K_{oc} values were generally higher than those obtained for adsorption.

Based on K_{oc} values, the transformation product RPA 412708 is classified as highly to very highly mobile in soils and sediment, according to the classification scheme of McCall *et al*. (1981). The data do not indicate any strong correlation between mobility and any one of organic carbon, pH, cation exchange capacity (CEC), or clay content.

Thus, from the laboratory studies of mobility, RPA 407213 is not highly mobile in soils and sediments, however the two degradation products examined have high mobility and may be expected to leach.

Based on the Henry's Law constant and vapour pressure , fenamidone is not expected to volatilize from moist soils or water surfaces. The K_{oc} and K_{ow} indicate that fenamidone may be expected to partition to sediments. Partitioning to sediments was confirmed in the study on biotransformation in aerobic water/sediment.

5.5 Dissipation and accumulation under field conditions

Field studies were conducted using EXP 10623A, a suspension concentrate formulation similar to the end-use product and containing 500 g fenamidone/L, at field sites in Canada (Prince Edward Island, Ecoregion 5.3; Ontario, Ecoregion 8.1; and Manitoba, Ecoregion 9.2) and the northern United States (North Dakota, Ecoregion 9.2; Washington, Ecoregion 10.1). Additional sites in the United States were included in the US studies but these sites were not applicable to Canadian conditions and were not reviewed.

Results from the reviewed field studies supported the results determined in the laboratory in that fenamidone is not persistent in soil. Dissipation rates for the parent compound ranged from 8.4 to 24 days which would classify fenamidone as non-persistent to slightly persistent. Fenamidone was not detected at concentrations above the LOQ (10 ppb and 5 ppb in the US and Canada, respectively) below a soil depth of 15 cm which tends to support the laboratory studies that found fenamidone to have moderate mobility in soils. The low solubility of fenamidone further supports the conclusion that fenamidone is not likely to be very mobile in most soils.

Several transformation products were detected in the dissipation studies of which two, RPA 717879 and RPA 408056, at concentrations that bear more scrutiny. Both these transformation products were identified in laboratory studies at levels that would classify them as major products. The persistence of RPA 717879 in aerobic soils was established in a laboratory study and the results indicated that this transformation product would be classified as persistent to moderately persistent in aerobic soils. No laboratory studies were conducted with RPA 408056, however, studies with the parent established that this transformation product can be present at concentrations in excess of 10% of the applied parent compound for periods of up to a year. The laboratory studies on mobility for these compounds classified them as very highly mobile in various soils. The field dissipation studies show a clear trend of dissipation for RPA 408056 and the reported DT_{50} values range from 28 to 255 days. Despite its mobility classification, RPA 408056 was not found below the 15 cm soil depth. A clear dissipation pattern was not established for RPA 717879 in the field studies and DT_{50} values could only be estimated in two out of five sites due to lack of dissipation. Even the reported DT_{50} values of 110 and 128 days are suspect because of insufficient data points in the latter half of the study. RPA 717879 was not found below the 15 cm soil depth at quantifiable concentrations despite its high mobility and persistence.

5.6 Bioaccumulation

The octanol–water partition coefficient for fenamidone is 631 (log K_{ow} = 2.8). Therefore, given that the log K_{ow} does not exceed three, there is no requirement for data on bioaccumulation.

5.7 Summary of fate and behaviour in the terrestrial environment

Fenamidone undergoes limited hydrolysis and does not produce any major hydrolysis products at environmentally relevant pHs. Fenamidone undergoes limited phototransformation on soil resulting in two major transformation products, RPA 717879 and RPA 408056. As fenamidone is non-volatile, studies on the phototransformation in air are not required. Therefore, abiotic processes are not expected to be important routes of transformation in the terrestrial environment.

Biotransformation in aerobic soils is expected to be an important route of transformation of fenamidone. Fenamidone is classified as non-persistent in the aerobic soils tested. Two major transformation products were detected in aerobic soils (RPA 717879 and RPA 408056). One of these products, RPA 717879, is expected to be persistent in aerobic soils, based on a study on its enantiomer, RPA 412636.

The mobility of fenamidone was investigated in laboratory studies of adsorption/desorption in a variety of soils from the US and the UK The adsorption K_f values for fenamidone range from 2.4 to 8.9, with corresponding adsorption K_{oc} values ranging from 259 to 494. These results indicate that fenamidone has moderate mobility in soil and sediment. The desorption K_f values ranged from 3.2 to 9.1, and results indicated that some hysteresis occurred and fenamidone desorbed less readily than it adsorbed.

The mobility of two major transformation products, RPA 412636 and RPA 412708, was also studied in a variety of soils from the US and the UK.

The K_f adsorption values for RPA 412636 (s-enantiomer of the major transformation product RPA 717879) ranged from 0.11 to 0.64 with corresponding K_{oc} values ranging from 17.0 to 36.0. These results indicate that RPA 412636 is very highly mobile in the soil and sediment.

The K_f adsorption values for RPA 412708 (s-enantiomer of the major degradation product RPA 408056) ranged from 0.26 to 0.51 with corresponding K_{oc} values ranging from 15.0 to 52.0. These results indicate that RPA 412708 is highly to very highly mobile in the soils/sediments tested. When normalized to organic carbon the resultant K_{oc} values would also classify RPA 412708 as highly to very highly mobile in the soils/sediments tested.

Field studies were conducted in three potato growing regions of Canada (Ecoregion 5.3, 8.1, and 9.2) and two regions in the US (Ecoregions 9.2 and 10.1). Results from these trials indicate that fenamidone will not be persistent in soils under field conditions (DT_{50}s ranging from 8.4 to 24 days) and are in general agreement with the laboratory studies on biotransformation. No leaching of the parent compound was observed below the 15 centimetre depth in these trials. There were five metabolites detected in the field studies, RPA 406012, RPA 410914, RPA 409446, which were seen at low levels and RPA 408056, and RPA 717879 which were the predominant residues. DT_{50} values were only

calculated for the latter two compounds and the results classify RPA 408056 as slightly persistent to moderately persistent (DT_{50} = 28–173 d) and RPA 717879 as moderately persistent (DT_{50} = 110–128 d). A DT_{50} could not be calculated for RPA 717879 in the Manitoba or the US soils because residues did not show a clear pattern of decline over the course of the study and it should be noted that this same trend was observed at the other sites even though DT_{50} values were generated. No leaching of these transformation products was observed in the field studies despite the reported persistence and mobility of RPA 408056 and RPA 717879 from the laboratory studies.

Given the octanol–water partition coefficient for fenamidone of 631 (log K_{ow} = 2.8), there is little potential for the compound to bioaccumulate in biological organisms. No data on the K_{ow} values for the major transformation products was provided.

Summaries of the environmental fate and behaviour of fenamidone in the terrestrial environment are presented in Appendix IV, Table 1.

5.8 Summary of fate and behaviour in the aquatic environment

Fenamidone may be expected to enter the aquatic environment through direct overspray, spray drift from field application, and(or) runoff via sorption to soil particles.

Fenamidone does not undergo hydrolysis at environmentally relevant pHs. Phototransformation in water is an important pathway, however fenamidone rapidly partitions to sediments and therefore the significance of phototransformation as a pathway is reduced. No major or minor transformation products were identified as a result of hydrolysis at environmentally relevant pHs, however RPA 405862 and RPA 408056 were two major transformation products identified in the aquatic phototransformation study.

In studies on the biotransformation of fenamidone in several aerobic water/sediment systems, the 50% decline times (DT_{50}) for water ranged from 5.09 to 31.04 days indicating that fenamidone is non-persistent to slightly persistent in water. The DT_{50} values in sediments ranged from 85.87 to 313.15 days which would classify fenamidone as moderately persistent to persistent in sediments. One major transformation product (RPA 408056) was detected. Aerobic biotransformation in water/sediment is not expected to be an important route of transformation for fenamidone. The fate of fenamidone in aerobic water/sediment systems is partitioning to sediment where it transforms quite slowly.

In anaerobic water/sediment systems fenamidone partitions rapidly to the sediment. Within 7 days, over 77% of the applied radioactivity had migrated to the sediments. The first-order DT_{50} for water is 6.25 days, which would classify fenamidone as non-persistent in water. A DT_{50} for sediment could not be calculated, however the DT_{50} for the entire system was 1115 days which classifies fenamidone as persistent in anaerobic aquatic systems. As in aerobic aquatic systems, biotransformation is not expected to be a major

transformation pathway, instead fenamidone is expected to rapidly partition to the sediments where it will transform quite slowly.

Fenamidone is not expected to volatilize from water surfaces and no data are available on the dissipation of fenamidone under aquatic field conditions.

The octanol–water partition coefficient of fenamidone indicates that there is a limited potential for bioaccumulation in organisms.

Summaries of the environmental fate and behaviour of fenamidone in the aquatic environment are presented in Appendix IV, Table 2.

5.9 Expected environmental concentrations

The expected environmental concentrations (EEC) of fenamidone in environmental compartments of concern were estimated based on calculations made using simple scenarios. These concentrations were used as initial approximations for estimating the potential exposure to non-target organisms. It was assumed that fenamidone was applied at the maximum proposed Canadian label rate of 1.2 kg a.i./ha per season. The application pattern was based on six applications of 200 g a.i./ha per season with applications 14 d apart and assumes that resistance management practices are being adhered to (i.e., fenamidone applications are alternated with applications of non type 11 fungicides). The scenario assumes that the concentrations in the various environmental compartments were obtained immediately following the last of the applications.

5.9.1 Soil

The EEC of fenamidone in soil was calculated assuming application to bare soil, soil bulk density of 1.5 g/cm^3 and a soil depth of 15 cm. Six applications at the maximum proposed Canadian label rate were used in the pattern outlined in Section 5.9. The simulation was run over three seasons and the results indicate that no significant carryover is expected. Using the most conservative DT_{50} of 24 d in soil (field dissipation study, DACO 8.3.2.2), the concentration of fenamidone in soil immediately following the sixth application is equivalent to a cumulative application of 548.3 g a.i./ha. Based on the maximum cumulative application rate, the EEC in soil was estimated to be 0.243 mg a.i./kg soil dry weight.

5.9.2 Aquatic systems

For pelagic organisms, a DT_{50} value of 31 d from the biotransformation in aerobic water/sediment study was used to calculate the EEC resulting from direct overspray of fenamidone to aquatic systems. Using the application pattern outlined in Section 5.9 (six applications at the maximum proposed Canadian label rate of 200 g a.i./ha at 14-d intervals), the EECs of fenamidone in water immediately following the sixth application are the equivalent of a cumulative application of 635.6 g a.i./ha for the pelagic

compartment. Assuming a scenario in which a body of water 30 cm deep is oversprayed with the equivalent of the cumulative application rate for one season, the EECs for pelagic organisms is 0.212 mg a.i./L water. Although these scenarios may be unrealistic for ground application, they are useful as first approximations and are used to compare the EECs in aquatic systems and no observed effect concentrations (NOEC) from environmental toxicology studies. Laboratory test indicate that in aquatic environments more than 80% of the fenamidone entering a water body may rapidly partition into sediments were it will remain persistent. At the present time, the Agency's current risk assessment methods do not allow a determination of the EECs in sediment and pore water.

Based on the potential use pattern of fenamidone, residues of fenamidone in potential drinking water sources in these areas (i.e., groundwater, reservoirs and dugouts) were modelled using the input parameters listed in Appendix IV, Table 3 by the models LEACHM for groundwater and PRZM/EXAMS for surface water.

The results from Level 1 LEACHM modelling indicate that fenamidone is expected to reach groundwater sources of drinking water. LEACHM predicts acute (yearly peak) and chronic (yearly average) concentrations at the 90th percentile. By factoring in surface runoff into reservoirs and dugouts, Level 1 PRZM/EXAMS modelling predicts acute (yearly peak) and chronic (yearly average) concentrations at the 90th percentile. These values are considered to be "upper bound" concentrations in surface water that potentially may be used as a source of drinking water. Because Manitoba is a major potato-producing region, concentrations for a dugout scenario are included. The estimated drinking water concentrations are outlined in Table 5.9.1

Table 5.9.1 Summary of concentrations of fenamidone in potential drinking water sources from the water models PRZM/EXAMS and LEACHM (90th percentile value

Groundwater		Reservoir		Dugout	
Acute concentration (µg a.i./L)	**Chronic concentration (µg a.i./L)**	**Acute concentration (µg a.i./L)**	**Chronic concentration (µg a.i./L)**	**Acute concentration (µg a.i./L)**	**Chronic concentration (µg a.i./L)**
0.22 µg/L	0.18 µg/L	13.0 µg/L	3.85 µg/L	15.0 µg/L	7.73 µg/L

Six major transformation products have been identified as being of potential concern with respect to drinking water (RPA 717879, RPA 408056, RPA 409446, RPA 410995, RPA 406012, and RPA 410914). RPA 717879 is the transformation product present in the largest concentration in both the laboratory soil metabolism study and field studies, is highly mobile and persistent. The EAD used the mobility and persistence data of RPA 717879 along with the combined concentration of all the major transformation products (approx. 58% of parent application rate) to provide a conservative estimate of potential

fenamidone transformation products in surface water and ground water. The EECs for fenamidone transformation products expressed as RPA 717879 in drinking water for the acute and chronic scenarios are outlined in Table 5.9.2.

Table 5.9.2 Summary of concentrations of fenamidone transformation products (expressed as RPA 717879) in potential drinking water sources from the water models PRZM/EXAMS and LEACHM (90th percentile value)

Groundwater		Reservoir		Dugout	
Acute concentration (µg a.i./L)	Chronic concentration (µg a.i./L)	Acute concentration (µg a.i./L)	Chronic concentration (µg a.i./L)	Acute concentration (µg a.i./L)	Chronic concentration (µg a.i./L)
68.3 µg/L	60.1 µg/L	7.24 µg/L	2.64 µg/L	14.04 µg/L	11.59 µg/L

5.9.3 Vegetation and other food sources

No data were provided on concentrations of fenamidone on foliar crops immediately after application. Thus, in the absence of these data, concentrations of fenamidone on vegetation and insects resulting from direct over-spray were estimated using a nomogram developed by the USEPA from the data of Hoerger and Kenaga (1972) and Kenaga (1973), (Table 5.9.3) (see also Appendix IV, Table 7).

Table 5.9.3 Maximum EECs in diets of birds and mammals

Organism	Maximum EEC
	Fenamidone (mg a.i./kg dw diet)
Bobwhite quail	210.1
Mallard duck	40.6
Rat	605.4
Mouse	601.8
Rabbit	905.2

6.0 Effects on non-target species

6.1 Effects on terrestrial organisms

The toxicity of fenamidone was studied with earthworms, honey bees, a predatory mite as well as with a parasitoid wasp. The reported 14-day LC_{50} for earthworms was 25 mg a.i./kg dw of substrate whereas the NOEC was 8 mg a.i./kg. The toxicity of the transformation products RPA 412636 and RPA 412708 to earthworms was also evaluated. The NOEC values were > 1000 mg a.i. kg dw and 556 mg a.i. kg dw for RPA 412636 and RPA 412708, respectively. In bees the 96-h LD_{50} based on contact was reported as 74.8 µg a.i./bee and the 96-h NOEL was 7.48 µg a.i./bee which classifies this material as relatively non-toxic to bees. The 96-hour LC_{50} of fenamidone to bees is > 159.8 µg a.i./bee and the 96-hour NOEC is 79.2 µg a.i./bee. These values would also classify fenamidone as relatively non-toxic to honey bees. Data on the toxicity to beneficial predators and parasites was generated using a formulated product at rates for vine crops which are significantly lower than those for potatoes. Despite the lower rates, predatory mites showed significant mortality at the one-fold application rate which would indicate that these beneficial organisms would suffer a negative impact if they were on the crop being treated. The predatory mites showed no significant reproductive effects as a result of exposure to fenamidone. Parasitoid wasps also showed negative impacts as a result of exposure to fenamidone. There was 100% mortality of parasitoids when exposed to one-fold field rate and three-fold field rate, whereas no significant mortality occurred at the 7.5% drift rate. There were significant effects on reproduction for the parasitoid at the 7.5% drift rate.

Studies on the acute oral toxicity, acute dietary toxicity and reproductive toxicity to birds were reviewed. Fenamidone is classified as practically non-toxic to bobwhite quail on an acute oral basis based on the LD_{50} of >2000 mg a.i./kg bw. The single-dose acute oral NOEL was 2000 mg a.i./kg bw. The acute dietary toxicity of fenamidone to bobwhite quail and mallard ducks was assessed and the 8-day oral LD_{50} was determined to be > 5200 mg a.i./kg dw of diet for both species and the 8-day NOEL for fenamidone based on food consumption and body weight was 5200 and 2600 mg a.i./kg diet for the bobwhite quail and mallard duck, respectively. According to the USEPA classification, fenamidone would be classified as practically non-toxic to bobwhite quail and mallard duck on an acute dietary basis. In the reproduction toxicity studies, the NOEC of fenamidone was 1125 and 1500 mg a.i./kg dw diet for the mallards and bobwhites, respectively. For bobwhite quail, there were no sublethal effects observed and the NOEC is the highest concentration to which the birds were exposed. In the mallard ducks, the NOEC was based on a decrease in the 14 day old hatchling weights at the highest concentration tested. No other sublethal effects were reported.

Following oral dosing in rats, fenamidone was rapidly absorbed, distributed, and excreted. The feces and urine were both major routes of excretion. Biliary excretion data indicated that systemic absorption of fenamidone was high. Tissue distribution and bioaccumulation were minimal. Acute oral studies with the technical and end-use product

on Sprague Dawley rats determined fenamidone to have low toxicity with an LD_{50} of >5000 mg/kg bw and 2028 mg/kg bw for active ingredient and one for the formulated end-use product, respectively. The lowest no observed adverse effect levels (NOAEL) reported in short-term dietary studies (≤3months) 29.68 mg/kg bw/day (equi. to 500 mg/kg diet) and 35.39 mg/kg bw/day (equi. to 500 mg/kg diet) for male and female Sprague Dawley rats, respectively. A similar assessment was performed for the 3-month dietary studies with mice. The most sensitive NOAEL in mice was 1064.3/1375.17 mg/kg bw/day (equi. to 5000 mg a.i./kg dw) in male and female mice, respectively. From a two-generation reproductive study with rats, the most sensitive NOEC was 63.76/68.61 mg/kg bw/day (equi. to 60.0 mg a.i./kg dry weight) for male and female rats, respectively. There was no evidence of oncogenic/carcinogenic potential in the species tested (rodents) and no evidence of neurotoxicity in rats after acute and short-term exposure to fenamidone.

The acute oral toxicity of the major transformation products RPA 412636 (S-enantiomer of RPA 717879) and RPA 412708 (S-enantiomer of RPA 408056) was also evaluated. The acute oral LD_{50} values for Sprague Dawley rats are 1520 and 176 mg/kg bw for RPA 412636 and RPA 412708, respectively. This would classify RPA 412636 and RPA 412708 as having slight toxicity and high toxicity to mammals, respectively. In short-term dietary studies (3 months) with RPA 412636, the NOEL values were 6.4 mg/kg bw/day (equi. to 100 mg/kg diet) and 7.7 mg/kg bw/day (equi. to 100 mg/kg diet) for male and female Sprague Dawley rats, respectively.

The effects of EXP 10623A, a formulated product containing 51.7% fenamidone, on the seed germination, seedling emergence and vegetative vigour of 6 species of dicot and 4 species of monocot plants was studied. The most sensitive species in the Tier 1 emergence was lettuce (*Lactuca sativa*) with 20% less emergence than formulation blank, 19% inhibition in shoot length, 18% inhibition in shoot length, 32% inhibition in shoot dry weight, and a 39% inhibition in shoot dry weight. Tier II results with this species established an NOEC of 1200 g a.i./ha (the highest concentration tested and the maximum seasonal application rate) for emergence, shoot length, and shoot dry weight. EC_{50} and EC_{25} values were greater than the maximum seasonal application rate of 1200 g a.i/ha. These results indicate that fenamidone is non-toxic to non-target plant species at the maximum label rate.

Summaries of the environmental toxicity of fenamidone to terrestrial organisms are presented in Appendix IV, Table 6.

6.2 Effects on aquatic organisms

Studies on the toxicity of fenamidone (RPA 407213) and two of its transformation products, RPA 412636 (S-enantiomere of RPA 717879) and RPA 412708 (S-enantiomere of RPA 408056), were reviewed for a variety of freshwater and marine organisms. Fenamidone was found to be highly toxic to *Daphnia magna* under acute exposure, with a 48-h EC_{50} of 0.18 mg a.i./L. Chronic exposure of fenamidone over 21 days significantly reduced daphnid length and reproductive output at 0.029 mg a.i./L.

Studies submitted for freshwater fish show that fenamidone is acutely toxic to both coldwater and warmwater fish, while the transformation products RPA 412636 and RPA 412708 are generally non-toxic. Rainbow trout (*Oncorhynchus mykiss*) exhibited a highly toxic response to acute fenamidone exposure (96-h LC_{50} = 0.74 mg a.i./L). Sublethal effects seen in trout included lethargy, muscular contractions and erratic swimming. Bluegill sunfish (*Lepomis macrochirus*) were similarly susceptible to fenamidone toxicity (96-h LC_{50} = 0.74 mg a.i./L), and all fish that exhibited erratic swimming and moribund behaviour were dead by the next observation period. Acute exposure of rainbow trout to RPA 412636 and RPA 412708 failed to elicit mortality up to the highest tested concentrations (NOEC = 34.4 and 98 mg a.i./L, respectively). Significant sublethal effects, however, were observed at RPA 412708 levels of 24 to 98 mg a.i./L (i.e., pigmentation disorders, erratic swimming and lethargy).

Fenamidone exposure to three groups of freshwater algae (green algae, diatoms and blue-green algae) was reviewed. Fenamidone failed to inhibit cellular growth in green algae (*Pseudokirchneriella subcapitata),* diatoms (*Navicula pelliculosa*), or blue-green algae (*Anabaena flos-aquae*) up to the highest tested concentrations of 0.73, 0.90, or 0.94 mg a.i./L, respectively. The fenamidone transformation products RPA 412636 and RPA 412708 were similarly found not to exhibit any growth inhibiting effects in green algae (*Scenedesmus subspicatus*), up to the highest exposure levels of 33.5, and 18.7 mg a.i./L, respectively. In a 14-day acute toxicity study, fenamidone was found not to inhibit frond production in the freshwater floating plants, duckweed (*Lemna gibba*), at the test concentration of 0.88 mg a.i./L.

Three studies were reviewed on the effects of fenamidone toxicity to marine invertebrates. Fenamidone was very highly toxic to mysid shrimp (*Mysidopsis bahia*), with a 96-h LC_{50} of 0.069 mg a.i./L, and a NOEC based on mortality and sublethal effects of 0.047 mg a.i./L. Sublethal effects observed in mysids included erratic swimming behaviour, loss of equilibrium, and lethargy. The Eastern oyster (*Crassostrea virginica*) was also susceptible to acute exposure of fenamidone (96-h EC_{50} = 0.120 mg a.i./L). Significant reductions in shell deposition were observed at the lowest tested fenamidone concentration of 0.055 mg a.i./L, resulting in a 96-h EC_{10} of 0.027 mg a.i./L. Chronic exposure of fenamidone over a 28-day period significantly reduced reproductive success in the marine mysid *M. bahia* at 0.019 mg a.i./L, with a corresponding NOEC of 0.0095 mg a.i./L. Other sublethal effects from chronic fenamidone exposure included a decrease in growth (i.e., length and body weight) in females.

One study on fenamidone toxicity to a marine fish, the sheepshead minnow (*Cyprinidon variegatus*), was reviewed. Fenamidone was moderately toxic to sheepshead minnows (96-h LC_{50} = 2.5 mg a.i./L; NOEC based on mortality = 1.1 mg a.i./L). At concentrations greater than 1.6 mg a.i./L, some fish exhibited erratic swimming and complete or partial loss of equilibrium.

The effects of acute fenamidone exposure to the marine diatom *Skeletonema costatum* were reviewed. Over a 5-day period, fenamidone significantly inhibited cell growth

(density), at concentrations above 0.012 mg a.i./L. The 5-d EC_{50} was calculated to be 0.075 mg a.i./L, suggesting that marine algae may be more susceptible to fenamidone exposure than freshwater algae.

Summaries of the environmental toxicity of fenamidone to aquatic organisms are presented in Appendix IV, Table 7.

6.3 Effects on biological methods of sewage treatment

As data are not required, no data were submitted.

6.4 Risk characterization

Risk assessment integrates the exposure and ecotoxicology data to estimate the potential for adverse effects. The PMRA currently conducts a deterministic risk assessment of pest control products. Environmental risk is characterized using the margin of safety (MOS) method, which is the ratio of the toxicity endpoint to the EEC. Unless otherwise stated, the degree of risk to terrestrial and aquatic organisms was classified according to the following index developed by the Environmental Assessment Division, Pest Management Regulatory Agency:

Margin of Safety (MOS)	Risk Qualifier
≥ 10	Negligible risk
1 to < 10	Low risk
0.1 to < 1	Moderate risk
0.01 to < 0.1	High risk
0.001 to < 0.01	Very high risk
< 0.001	Extremely high risk

PMRA, 2002

The submitted toxicity studies were conducted using the parent compound alone or using the transformation products. Therefore, the terrestrial and aquatic risk assessments are based on toxicity of the parent compound or the transformation products.

6.4.1 Environmental behaviour

Results from laboratory and field studies indicate that fenamidone is non-persistent in aerobic soil. Terrestrial organisms will be exposed to fenamidone in the soil as well as from the consumption of contaminated vegetation. Results from laboratory and field studies do not indicate that fenamidone or its major transformation products are likely to

leach to groundwater, however, groundwater modelling (Section 5.9.2) did indicate that both fenamidone and RPA 717879 are likely to leach into groundwater.

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.

6.4.2 Terrestrial organisms

A summary table of the risks to terrestrial organisms is provided in Appendix IV, Table 8.

Earthworms: One scientifically valid and acceptable toxicity study with earthworms was submitted for fenamidone. The NOEC was 8 mg a.i./kg soil. The EEC of fenamidone in soil (0.13 mg a.i./kg soil) is below the NOEC. The margin of safety is 61.5, therefore, fenamidone will not pose any appreciable risk to earthworms at the proposed application rate.

One scientifically valid and acceptable toxicity study with earthworms was submitted for the transformation product RPA 412636 (S-enantiomere of RPA 717879). The NOEC was >1000 mg a.i./kg soil. The EEC of RPA 412636, assuming 100% transformation and no degradation in soil would be 0.533 mg a.i./kg soil which is below the NOEC. The margin of safety is in excess of 1876, therefore, RPA 412636 will not pose any appreciable risk to earthworms at the proposed application rate.

One scientifically valid and acceptable toxicity study with earthworms was submitted for the transformation product RPA 412708 (S-enantiomere of RPA 408056). The NOEC was 556 mg a.i./kg soil. The EEC of RPA 412708, assuming 100% transformation and no degradation in soil would be 0.533 mg a.i./kg soil which is below the NOEC. The margin of safety is 1043, therefore, RPA 412636 will not pose any appreciable risk to earthworms at the proposed application rate.

Bees: One scientifically valid and acceptable acute contact/oral toxicity study with honey bees was submitted. According to the classification scheme of Atkins *et al*. (1981), fenamidone is relatively non-toxic to bees.

The acute contact LD_{50} for honey bees was >74.8 µg a.i./bee, which is equivalent to >83.8 kg a.i./ha. The maximum seasonal application rate of 1.2 kg a.i./ha is lower than the LD_{50}. The margin of safety is 70, therefore, fenamidone will not pose any appreciable risk to honey bees at the proposed application rate.

Predators and parasites: One scientifically valid and acceptable study on the toxicity of fenamidone to beneficial predators was submitted. Specific endpoints were not calculated, however toxicity was observed at a rate equivalent to 133 g a.i./ha and no toxicity was seen at a rate of 9.98 g a.i./ha. The maximum seasonal application rate for potatoes is 1200 g a.i./ha and is higher than the rate producing toxic effects in predatory mites. The margin of safety based on these endpoints is 0.0083 and indicates that there is very high risk to beneficial predators associated with the use of fenamidone at the proposed rates for potatoes.

One scientifically valid and acceptable study on the toxicity of fenamidone to beneficial parasites was submitted. Specific endpoints were not calculated, however significant reproductive effects were observed at a rate equivalent to 7.5% drift rate equivalent to 9.98 g a.i./ha. The maximum seasonal application rate for potatoes is 1200 g a.i./ha and is higher than the rate producing toxic effects in parasitic wasps. Since no concentration was used that produced no adverse effects, the margin of safety has been determined based on the lowest application rate. The margin of safety based on these endpoints is < 0.008 and indicates that there is at least a very high risk to beneficial parasites associated with the use of fenamidone at the proposed rates for potatoes.

Birds: Wild birds, such as bobwhite quail (*Colinus virginianus*) and mallard duck (*Anas platyrhynhcos*), could be exposed to residues of fenamidone as a result of the consumption of sprayed vegetation and(or) contaminated prey. The EECs of fenamidone in the diets of the bobwhite quail and mallard duck are 210 and 40.6 mg a.i./kg dry weight, respectively. Individual risk assessments were carried out for acute oral exposure to bobwhite quail, acute dietary exposure to bobwhite quail and mallard duck, and chronic exposure for reproductive effects with both avian species.

One acceptable toxicity study was submitted on the acute oral exposure of wild birds to fenamidone. In an acute oral study with bobwhite quail, the LD_{50} was >2000 mg a.i./kg bw while the NOEL was 2000 mg a.i./kg bw. The average body weight per individual (BWI) of the control group in the study was 103.5 g and the food consumption (FC) was 0.014 kg dw/ind/d. Therefore, the daily intake of fenamidone (DI = FC × EEC) was 2.94 mg a.i./ind/d. Expressed on a per individual basis, the $LD_{50\ (ind)}$ and $NOEL_{(ind)}$ were >207 and 207 mg a.i./ind, respectively. Based on the predicted daily intake of the active ingredient and the $LD_{50\ (ind)}$, the number of days of intake of fenamidone by a bobwhite quail in the wild that is equivalent to the dose administered by intubation that killed 50% of the individuals in the laboratory population is > 70 d. Similarly, based on the predicted daily intake and the $NOEL_{(ind)}$, the maximum number of days of intake of fenamidone by a wild bobwhite quail, equivalent to the dose administered by intubation that had no observed effect on the laboratory population is 70 d. These values indicate that the application of fenamidone at the maximum proposed label rate will not pose any appreciable risk to wild bird populations, such as the bobwhite quail, that are acutely exposed to fenamidone.

The LD_{50}s from separate acute dietary studies with bobwhite quail and mallard duck were both greater than 5200 mg a.i./kg diet. According to the USEPA classification scheme, fenamidone is considered practically non-toxic when birds are acutely exposed. The NOECs were 5200 and 2600 mg a.i./kg dw diet for bobwhite quail and mallard duck, respectively. As the EECs in the diet of the bobwhite quail and the mallard duck are expected to be 210 mg a.i./kg dry weight and 40.6 mg a.i./kg dry weight, respectively, the margins of safety for bobwhite quail and mallard duck are 24.76 and 64.04, respectively. Thus, fenamidone is considered to pose a negligible dietary risk to bobwhite quail and mallard ducks at the proposed maximum application rate.

Two chronic studies were submitted that examined reproductive effects in bobwhite quail and mallard duck. For bobwhite quail, the NOEC was 1500 mg a.i./kg diet, whereas the NOEC for mallard ducks was 1125 mg a.i./kg diet. For bobwhite quail, the NOEC exceeds the EEC in the diet of 210 mg a.i./kg diet resulting in a margin of safety of 7.1. For mallard duck, the NOEC also exceeds the EEC in the diet of 40.6 mg a.i./kg diet, resulting in a margin of safety of 27.7. The margins of safety indicate a low and negligible risk of reproductive effects occurring in bobwhite quail and mallard duck, respectively, following long-term dietary exposure to fenamidone.

Wild mammals: Wild mammals could be exposed to residues of fenamidone as a result of the consumption of sprayed vegetation and(or) contaminated prey. Assuming no transformation, the EECs of fenamidone in the diets of rats and mice were 605.4 and 601.8 mg a.i./kg dry weight, respectively.

For rats, a BWI of 0.35 kg and a food consumption (FC) of 0.06 kg dry weight per individual rat was used (EAD default values). Therefore, the daily intake (DI = FC × EEC) of fenamidone is 36.3 mg a.i./ind/d. Two acute oral toxicity studies were reviewed by HED: one for the active ingredient and one for the formulated end-use product. The LD_{50}s in these studies were 2028 and > 5000 mg a.i./kg bw for the active ingredient and for the formulated end-use product, respectively. Expressed on a per individual basis, the $LD_{50\ (ind)}$s (LD_{50} × BWI) are 709.8 and 1750 mg a.i./ind for the active ingredient and end-use product studies, respectively. As NOELs were not available for either study, one-tenth of the LD_{50} was used as the NOEL. The calculated NOELs are, therefore, 202.8 and 500 mg a.i./kg bw and the $NOEL_{(ind)}$s (NOEL × BWI) are 70.98 and 175 mg a.i./ind for the active ingredient and end-use product studies, respectively.

Using the data from the oral toxicity study with the active ingredient, the daily intake, and the LD_{50} of individual rats, it would take more than 19.5 days of continuous feeding ($LD_{50\ (ind)}$ ÷ DI) for a wild rat to attain a dose equivalent to that administered by gavage in the laboratory that killed 50% of the laboratory population. From study with the end-use product, it would take more than 48.2 days of continuous feeding for a wild rat to attain a dose equivalent to that administered by gavage in the laboratory that killed 50% of the laboratory population.

As the NOELs used in the risk assessment are one-tenth of the LD_{50}s, the maximum number of days of intake of fenamidone by a wild rat to attain a dose equivalent to that administered by gavage in the laboratory that had no-observable effect on the laboratory population is also one-tenth of the number of days of intake to accumulate a dose equivalent to that administered by gavage that killed 50% of the laboratory population. Thus, from the active ingredient study, the maximum number of days of intake to reach the laboratory dosage that had no observable effect is 1.95 days. Similarly, from the end-use product study, the maximum number of days of intake is 4.8 days.

Based on the above assessments, application of fenamidone at the maximum proposed label rate will not pose an acute risk to populations of wild mammals that are exposed to fenamidone on vegetation in their diet.

In the short-term dietary studies (< 3 months) with rats, the lowest NOEL was 500 mg a.i./kg dw diet (3-month study with rats). Using an EEC of 605.4 mg a.i./kg dw, the margin of safety is 0.82, which indicates a moderate risk to rats.

A similar assessment was performed for the 3-month dietary studies with mice. The most sensitive NOEC was 5000 mg a.i./kg dw for both male and female mice. Using an EEC of 601.8 mg a.i./kg dw, the margin of safety is 8.3, which indicates a low risk to mice.

From reproductive studies with rats, the most sensitive NOEC was 60.0 mg a.i./kg dry weight. Using an EEC of 605.4 mg a.i./kg dw the margin of safety is 0.10, which indicates a moderate reproductive risk to rats.

Acute oral and dietary studies were also conducted using some of the major transformation products of fenamidone.

An acute oral study was conducted exposing Sprague Dawley rats to RPA 412636 (s-enantiomer of RPA 717879). The LD_{50} was determined to be 1520 mg/kg bw. Data on the transformation of fenamidone on vegetation were not available, however the aerobic biotransformation study of fenamidone in soil found that a maximum of 35% of the parent compound will transform to RPA 412636. Using this value as a default on vegetation would equate to an EEC of 211.89 mg/kg dw of diet. Expressed on a per individual basis, the $LD_{50\ (ind)}$ ($LD_{50} \times$ BWI) is 532 mg/ind. As NOELs were not available for either study, one-tenth of the LD_{50} was used as the NOEL. The calculated NOEL is therefore 152 mg/kg bw and the $NOEL_{(ind)}$ (NOEL × BWI) is 53.2 mg/ind.

Using the data from the oral toxicity study with the transformation product RPA 412636, the daily intake, and the LD_{50} of individual rats, it would take more than 41.8 days of continuous feeding ($LD_{50\ (ind)} \div$ DI) for a wild rat to attain a dose equivalent to that administered by gavage in the laboratory that killed 50% of the laboratory population. Using the NOEL as the endpoint the maximum number of days of intake to reach the laboratory dosage that had no observable effect is 4.18 days. This would indicate that the application of fenamidone at the maximum proposed label rate will not pose an

appreciable acute risk to populations of wild mammals that are exposed to the transformation product RPA 412636 on vegetation in their diet.

A similar study was conducted using the transformation product RPA 412708 (s-enantiomer of RPA 408056). The LD_{50} was determined to be 176 mg/kg bw. Data on the transformation of fenamidone on vegetation were not available, however the aerobic biotransformation study of fenamidone in soil found that a maximum of 17.3% of the parent compound will transform to RPA 412708, which would equate to an EEC of 104.73 mg/kg dw of diet. Expressed on a per individual basis, the $LD_{50\ (ind)}$ (LD_{50} × BWI) is 61.60 mg/ind. As NOELs were not available for either study, one-tenth of the LD_{50} was used as the NOEL. The calculated NOEL is therefore 17.6 mg/kg bw and the $NOEL_{(ind)}$ (NOEL × BWI) is 6.16 mg/ind.

Using the data from the oral toxicity study with the transformation product RPA 412708, the daily intake, and the LD_{50} of individual rats, it would take more than 9.8 days of continuous feeding ($LD_{50\ (ind)}$ ÷ DI) for a wild rat to attain a dose equivalent to that administered by gavage in the laboratory that killed 50% of the laboratory population. Using the NOEL as the endpoint, the maximum number of days of intake to reach the laboratory dosage that had no observable effect is 1 day. This would indicate that the application of fenamidone at the maximum proposed label rate will not pose an appreciable acute risk to populations of wild mammals that are exposed to the transformation product RPA 412708 on vegetation in their diet.

A 3-month dietary study was also conducted in which Sprague Dawley rats were exposed to RPA 412636. The NOAEL value determined from the results of this study was 100 ppm, which expressed on a per individual basis, the $NOAEL_{(ind)}$ is 35 mg/ind. The aerobic biotransformation study estimates that a maximum of 35% of the parent compound will transform to RPA 412636, which would equate to an EEC of 211.89 mg/kg dw of diet. Thus the margin of safety for this transformation product is 0.17, indicating a moderate risk.

Based on the studies with mammals, fenamidone may pose dietary and reproductive risks to mammals in the wild.

Non-target terrestrial plants: One seedling germination/emergence and vegetative vigour study was submitted and reviewed. The Tier II results established an EC_{50} for emergence, shoot length and dry weight of > 1200 g a.i./ha. The EEC for fenamidone is 1200g a.i./ha and therefore the margin of safety for terrestrial plants is in excess of 1.0. These results indicate that there is a low risk to terrestrial plants resulting from the use of fenamidone at the proposed label rates for potatoes.

Summary of risk to terrestrial organisms: An assessment of the environmental safety associated with the use of fenamidone has identified some areas of concern for terrestrial organisms, primarily beneficial invertebrate species and mammals (Appendix IV, Table 8). Using the proposed pattern of six applications per year at a maximum rate of

1.20 kg a.i./ha, fenamidone poses a very high risk to both predatory and parasitic arthropods. It should be noted that the exposures for beneficial insects were conducted at rates that are representative of vine crops and consequently are nine-fold lower than the proposed rates for potatoes. It should also be noted that, in the case of the parasitic arthropod, the lowest concentration tested yielded an adverse effect and therefore the actual risk may be underestimated.

There is also a moderate risk to wild mammals (rats) via short-term (3 months) dietary exposure as well as a moderate risk of reproductive effects in mammals. There was also an acute dietary risk from exposure to the transformation product RPA 412708. A short-term (3 month) dietary risk from exposure to the transformation product RPA 412636 was also identified. No short-term dietary study was conducted with RPA 412708.

The data for terrestrial plants indicates that at the highest allowable seasonal application rate, fenamidone will at most pose a low risk to non-target terrestrial plants.

6.4.3 Aquatic organisms

As for terrestrial organisms, the submitted toxicity studies for aquatic organisms were conducted using the parent and some major transformation products. However, due to the low toxicity of the transformation products in relation to the parent and the rapid partitioning of parent and transformation products to sediments, it is felt that mitigation measures based on the risk assessment of fenamidone will be protective of any risk associated with the transformation products. Therefore, the aquatic risk assessment will be limited to the parent compound. A summary table of the risks to aquatic organisms is provided in Appendix IV, Table 9.

Non-target freshwater invertebrates: One acceptable study was submitted on the acute toxicity of fenamidone to *Daphnia magna*. The 48-h EC_{50} was 0.19 mg a.i./L. Therefore, according to the USEPA classification scheme, fenamidone is classified as highly toxic to daphnids. The EEC of fenamidone in water (0.212 mg a.i./L) is above the 48-h NOEC of 0.11 mg a.i./L from the acute study. The MOS is 0.52, therefore fenamidone will pose a moderate acute risk to pelagic freshwater invertebrates at the proposed application rate. Note, however, that this result cannot be generalized to all freshwater invertebrates as fenamidone partitions to sediment where it may accumulate.

One valid study was submitted to illustrate the chronic toxicity of fenamidone to *Daphnia magna*. In a chronic life cycle toxicity test, 21-d NOEC and LOEC for number of young per adult and adult growth was 0.0125 mg a.i./L.

Non-target marine invertebrates: One acceptable study was submitted on the acute toxicity of fenamidone to *Mysidopsis bahia*, a pelagic marine crustacean. The 96-h LC_{50} was 0.069 mg a.i./L. Therefore, according to the USEPA classification scheme, fenamidone is classified as very highly toxic to mysids. The EEC of fenamidone in water (0.212 mg a.i./L) is above the 96-h NOEC of 0.047 mg a.i./L. The margin of safety is

0.22, therefore, fenamidone poses a moderate risk to mysids at the proposed application rate.

A study on the acute toxicity of fenamidone to the Eastern oyster, *Crassostrea virginica*, was accepted. Based on the 96-h EC_{10} of 0.027 mg a.i./L, fenamidone is classified as highly toxic to this marine mollusk according to the USEPA classification scheme. Based on the EEC of fenamidone in water (0.212 mg a.i./L) and the 96-h EC_{10} of 0.027 mg a.i./L, the margin of safety is 0.13, therefore fenamidone will pose a moderate acute risk to *C. virginica* at the proposed application rate.

One acceptable study was submitted on the chronic toxicity of fenamidone to *Mysidopsis bahia*, a pelagic marine crustacean. The 28-d NOEC was determined to be 0.0095 mg a.i./L.

As for freshwater organisms, the results for mysids and mollusks cannot be generalized to all marine invertebrates as fenamidone partitions to sediment where it may accumulate and benthic species may be exposed.

Freshwater fish: Two acceptable studies were submitted on the acute toxicity of fenamidone to freshwater fish. For coldwater fish (*Onchorynchus mykiss*, rainbow trout), the 96-h LC_{50} was 0.74 mg a.i./L. Therefore, according to the USEPA classification scheme, fenamidone is classified as highly toxic to coldwater fish. The EEC of fenamidone in water (0.212 mg a.i./L) is less than the 96-h NOEC of 0.35 mg a.i./L for rainbow trout. The margin of safety is 1.7, therefore, fenamidone poses a low risk to coldwater fish at the proposed application rate.

For warmwater fish (*Lepomis macrochirus*, bluegill sunfish), the 96-h LC_{50} was 0.74 mg a.i./L. Therefore, according to the USEPA classification scheme, fenamidone is classified as highly toxic to warmwater fish. The EEC of fenamidone in water (0.212 mg a.i./L) is below the 96-h NOEC of 0.57 mg a.i./L for bluegill sunfish resulting in a margin of safety of 2.7. Therefore, fenamidone poses a low risk to warmwater fish at the proposed application rate.

Marine/Estuarine fish: One acceptable study on the toxicity to marine/estuarine fish (*Cyprinodon variegatus*, sheepshead minnow) was submitted. The 96-h LC_{50} was 2.5 mg a.i./L. Therefore, according to the USEPA classification scheme, fenamidone is classified as moderately toxic to marine/estuarine fish. The EEC of fenamidone in water (0.212 mg a.i./L) is below the 96-h NOEC of 1.1 mg a.i./L for sheepshead minnow resulting in a margin of safety of 5.2. Therefore, fenamidone poses a low risk to marine/estuarine fish at the proposed application rate.

Freshwater algae: Three studies on the phytotoxicity of fenamidone to freshwater algae were submitted and reviewed. The empirical 5-d EC_{50} for the green algal species *Pseudokirchneriella subcapitata*, was determined to be > 0.73 mg a.i./L. The NOEC in this study was 0.73 and was greater than the EEC of fenamidone in water

(0.212 mg a.i./L) with a resulting margin of safety of 3.4. Fenamidone is therefore classified as posing a low risk to freshwater green algae when applied at the maximum proposed label rates.

The empirical 72-h EC_{50} for the green algal species *Anabaena flos-aquae* was determined to be > 0.94 mg a.i./L. The NOEC in this study was 0.94 mg a.i./L and was greater than the EEC of fenamidone in water (0.212 mg a.i./L) with a resulting margin of safety of 4.4. Fenamidone therefore is classified as posing a low risk to freshwater green algae when applied at the maximum proposed label rates.

The empirical 5-d EC_{50} for the freshwater diatom *Naviculla pellicosa* was determined to be > 0.90 mg a.i./L. The 5-d NOEC was determined to be 0.90 mg a.i./L and is greater than the EEC for fenamidone of 0.212 mg a.i./L resulting in a margin of safety of 4.3. Therefore fenamidone is classified as posing a low risk to freshwater diatoms when applied at the maximum proposed label rate.

Marine algae: One study on the toxicity of fenamidone to marine algae was submitted and reviewed. The 5-d EC_{50} for the marine diatom *Skeletonema costatum* was determined to be 0.075 mg a.i/L. The 5-d NOEC was 0.012 mg a.i./L which is considerably lower than the EEC for fenamidone of 0.212 mg a.i/L and resulting in a margin of safety of 0.057. This would classify fenamidone as posing a high risk to marine diatoms when applied at the proposed maximum label rate.

Aquatic vascular plants: One toxicity study with an aquatic vascular plant was submitted and reviewed. The empirical 14-d EC_{50} for the aquatic macrophyte, *Lemna gibba*, was determined to be >0.88 mg a.i./L. The 14-d NOEC was 0.88 mg a.i./L which results in a margin of safety of 4.2 when using an EEC of 0.212 mg a.i./L. This classifies fenamidone as posing a low risk to freshwater vascular plants when applied at the proposed maximum label rate for potatoes.

Summary of risk to aquatic organisms: Multiple areas of concern have been identified for aquatic species following an assessment of the environmental safety associated with the use of fenamidone (Appendix IV, Table 9). Using the proposed pattern of six applications per year at a maximum rate of 1.20 kg a.i./ha, fenamidone poses a low acute risk to marine and freshwater fish, freshwater algae and vascular plants. There is a moderate risk of effects in freshwater and marine crustaceans as well as in marine mollusks following exposure to fenamidone. The only identified organism at high risk from exposure is marine algae.

The risk classification to benthic invertebrates should be interpreted with caution as the risk from exposure to fenamidone in sediment has not been assessed. Thus, the actual risks to benthic species may be greater than those which are presented. Although no data were submitted on the risks to benthic species, this risk may be expected to exceed that of the pelagic species that were reviewed due to the rapid partitioning and persistence of fenamidone in sediments.

6.5 Risk mitigation

Environmental concerns: Based on the data submitted and on the existing data requirements for Use Site Categories 13 and 14, an assessment of the environmental safety associated with the use of fenamidone has been conducted. Application of fenamidone using the proposed pattern of six applications per year at a maximum rate of 1.2 kg a.i./ha will pose a potential risk to mammals, beneficial insects, freshwater and saltwater invertebrates, as well as marine algae. The risk to freshwater benthic invertebrates could not be assessed and these data are required as the parent compound and transformation products partition to sediments where they remain persistent.

Label statements and buffer zones: Based on the proposed application rates, buffer zones to protect sensitive aquatic habitats are recommended to mitigate risks. The following label amendements are required for the technical grade active ingredient and the end-use product.

Fenamidone Technical fungicide
No changes to the label are recommended at this time.

Reason 500 SC Fungicide
The proposed labels for the technical grade active ingredient and end-use product state the following under “Environmental Precautions”:

> “This product is toxic to fish, aquatic invertebrates, and marine/estuarine organisms. Do not apply where runoff is likely to occur. Runoff from treated areas may be hazardous to aquatic organisms in neighbouring areas. Do not contaminate water supplies, ponds, lakes, streams and irrigation ditches by direct application, spray drift or when cleaning and rinsing spray equipment or containers.
> - Do not apply this product through any type of irrigation system.
> - DO NOT apply by air.
> - A buffer zone of 15 metres should be observed around bodies of water in order to protect aquatic organisms from drift from treated areas. Provincial buffer zones that are greater than 15 metres should be respected.”

should be replaced with the following:

> “Toxic to fish and other aquatic organisms. Do not apply where runoff is likely to occur. Runoff from treated areas may be hazardous to aquatic organisms in neighbouring areas. Observe buffer zones specified under “Directions for use”.

This product may be harmful to beneficial predatory or parasitic arthropods. The best available application technique, which minimises off-target drift, should be used to reduce effects on beneficial arthropods in the field boundary."

Under the section entitled "Directions for use" in "section 9: Application precautions", add the following statements:

"DO NOT apply by air.
Do not apply this product through any type of irrigation system.

Field sprayer:
Do not apply during periods of dead calm or when winds are gusty.

Overspray and drift to sensitive habitats must be avoided. A buffer zone of 8 metres is required between the downwind point of direct application and the closest edge of estuarine/marine habitats. Do not contaminate aquatic habitats when cleaning and rinsing spray equipment or containers."

7.0 Efficacy

7.1 Effectiveness

7.1.1 Intended use

Reason 500 SC is a flowable concentrate fungicide, containing 500 g/L fenamidone which is proposed for control of late blight on potatoes. Apply when plants are 15–20 cm high or when disease threatens at 7–10 day interval. The proposed application rate is 400 mL/ha when applied alone or 200 mL when applied in a tank mix with Dithane DG at 1.25 kg/ha or Bravo 500 at 1.25 L/ha. By active ingredient, the proposed rates are:

Active ingredient	Application rate	
	product/ha	gram a.i./ha
fenamidone alone	400 mL	200
fenamidone + mancozeb	200 mL + 1250 g	100 + 935
fenamidone + chlorothalonil	200 mL + 1250 mL	100 + 625

7.1.2 Mode of action

Fenamidone belongs to the class of chemical imidazolinones which is part of the Quinone outside Inhibitors (QoI) fungicide group (fungicide group 11). It inhibits mitochondrial respiration by blocking electron transfer at Complex III level. Specifically, fenamidone is an inhibitor of the Qo (quinone outside) site within the electron transport

system. When used as a preventative, protectant fungicide, fenamidone inhibits direct germination of sporangia, zoospore mobility, zoospore encystment and cyst germination on plant surface.

7.1.3 Nature of the pest problem

Late blight is one of the most devastating diseases in potato production worldwide. The causal agent, *Phytophthora infestans*, survives mainly in abandoned potato plant material in fields, cull piles and gardens. All parts of crops are susceptible. Symptoms first appear as pale green water-soaked spots, often beginning at the leaf tips or edges. The circular or irregularly shaped lesions are often surrounded by a pale yellowish green border that merges with the healthy tissue. Lesions enlarge rapidly and turn brown or purplish black. During periods of high humidity, lesions may be bordered with a white mould growth on the underside of the leaf. In dry weather, infected leaf tissue turns brown and quickly dries up. Infected stems and petioles turn brown to black and entire vines may become blackened. In addition to blighting foliage, the fungus can infect potato tubers. Affected tubers first show brownish blotch on the outer edge before harvest. The disease continues to develop after the crop is harvested causing the potatoes to rot in storage. Late blight may result in total plant loss or death from early infection and severe reduction of the yield.

7.1.4 Effectiveness against pest

Results were submitted from 19 field trials conducted in Canada, the US, Brazil, France, the UK and Spain between 1994 and 1999. Reason 500 SC was compared with a commercial standard and an untreated check. Crops were evaluated for disease severity by rating the percent foliage infection and yield.

Fenamidone alone:
Five studies showed a significant difference between fenamidone and the check in disease severity. The data also showed that fenamidone provided the same level of control as the commercial standards, 90% disease severity control for fenamidone alone vs. 93% and 89% for mancozeb and chlorothanil respectively.

Three Canadian studies compared the proposed rate with 0.5 and 0.75 of the proposed rate. Of these, two studies showed that the proposed rate provided higher level of disease control, one study showed no significant difference between the proposed rate (200 g a.i./ha) and 0.5 of the proposed rate (100 g a.i./ha). Nine foreign studies showed that the proposed rate consistently provided higher level of disease severity control than 0.5 and 0.75 of the proposed rate, i.e., 63.9% control at 0.5× rate (100 g a.i./ha), 71.4% control at 0.75× rate (150 g a.i./ha), and 79.4% control at the proposed rate (200 g a.i./ha).

A review of the data supports the proposed claim that fenamidone alone at the rate of 200 g a.i./ha for control of late blight on potatoes.

Tank mixed with chlorothalonil or mancozeb:
Five studies showed a significant difference between the tank mixture and the check. The data showed that tank mixture provided the same level of control as the commercial standards, i.e., fenamidone + chlorothalonil provided 92% control and fenamidone + mancozeb provided 94% control vs. 93% and 89% control for mancozeb and chlorothalonil applied at approximately twice the tank mix rates.

Three studies compared fenamidone alone with tank mixture. The data showed that the tank mixture provided higher disease severity control than fenamidone alone. i.e., 96% control by fenamidone + mancozeb and 95% control by fenamidone + chlorothalonil vs. 90% control by fenamidone alone.

A review of the data supports the proposed claim for control of late blight on potatoes by tank mixing fenamidone with mancozeb or chlorothalonil at the rate of Reason 200 mL/ha + Dithane DG 1.25kg/ha or Reason 200 mL/ha + Bravo 1.25 L/ha.

Application interval:
Six studies compared fenamidone alone applied at 7-day intervals with 10-day intervals under high disease pressure. The data showed that the 7-day interval consistently provided higher disease severity control than the 10-day interval (76.8% vs. 55.9% control).

Three studies compared fenamidone alone applied at 7-day interval with 10-day interval under low to moderate disease pressure. The data showed that the 10-day application interval provided adequate late blight control under low to moderate disease pressure.

A review of the data supports the proposed claim of fenamidone alone or tank mixed with chlorothalonil or mancozeb with a 7-day application interval under high disease pressure and 10 days between applications under low disease pressure.

7.2 Phytotoxicity to target plants (including different cultivars), or to target plant products (OECD 7.4)

No independent crop tolerance studies were conducted. However, most studies had notes about phytototoxicity and yield data which showed no adverse effects. Yield was obtained from all Canadian studies and tuber yields were significantly higher compared to the check plots and comparable to the commercial standards.

7.3 Observations on undesirable or unintended side effects

N/A

7.4 Economics

Not assessed.

7.5 Sustainability

7.5.1 Survey of alternatives

The major alternative fungicide active ingredients currently registered for control of the pests on the proposed crops include, but are not necessarily limited to, the following:

Pest	Crop	Available alternative active ingredient
Late blight	Potatoes	Inorganics (copper hydroxide, copper oxychloride, copper sulphate), triazines (anilazine), phthalimides (captan), cinnamic acids (dimethomorph), acylalanines (metalaxyl-m), carbamates (propamocarb), dithio-carbamate (zineb, mancozeb, maneb, metiram), chloronitriles (chlorothalonil), cyanoacetamide oxime (cymoxanil), benzamides (zoxamide), methoxy-carbamates (pyraclostrobin), oxazolidinediones (famoxadone)

7.5.2 Compatibility with current management practices including IPM

A number of disease management practices, in addition to chemical control, are available to growers. For control of late blight on potatoes, it is essential to employ early management strategies to minimize the introduction of inoculum into the field and to monitor blight development using disease prediction models relevant to the geography and regular field monitoring. As a foliar fungicide, Reason 500 SC is compatible with these practices.

7.5.3 Contribution to risk reduction

Reason 500 SC fits well into IPM strategies due to its strong activity on diseases. It is a potential alternative to some of the older fungicides currently used for control of late blight on potatoes.

7.5.4 Information on the occurrence or possible occurrence of the development of resistance

Fenamidone, the active ingredient of Reason 500 SC, is a Group 11 fungicide (QoI fungicide). The resistance biotypes may dominate the fungal population if Group 11 fungicides are used repeatedly in the same field. Other resistance mechanisms that are not linked to site of action, but specific for individual chemicals, such as enhanced metabolism, may also exist. Appropriate resistance-management strategies should be followed.

An appropriate resistance management section for group 11 fungicides has been developed in consultation with the North American QoI (NAQoI) Working Group for another QoI group fungicide, Headline, and will be used for Reason 500 SC.

GROUP	11	FUNGICIDE

Resistance management recommendations:

For resistance management, Reason 500 SC contains a Group 11 fungicide (fenamidone). Any fungal population may contain individuals naturally resistant to this product and other Group 11 fungicides. The resistance biotypes may dominate the fungal population if these fungicides are used repeatedly in the same field. Other resistance mechanisms that are not linked to site of action, but specific for individual chemicals, such as enhanced metabolism, may also exist. Appropriate resistance-management strategies should be followed.

To delay fungicide resistance:

1. A maximum of six applications per year.

2. Alternate with fungicides having a different mode of action other than group 11 after each application of Reason 500 SC.

7.6 Conclusions

The claim for control of late blight on potatoes is acceptable as follow:
Apply Reason 500 SC at 400 mL per hectare when applied alone or as a tank mix with Dithane DG at 200 mL + 1.25 kg per hectare or Bravo 500 at 200 mL + 1.25 L per hectare. Application of Reason 500 SC for control of late blight should begin when plants are 15–20 cm high or when disease threatens (whichever comes first). Apply a fungicide having a different mode of action within 7–10 days after each application of Reason 500 SC. When Reason 500 SC is applied alone, use the shorter spray interval when conditions favour disease development. Under severe disease conditions, it is recommended to use a tank mix of Reason 500 SC with Dithane DG or Bravo 500 and the shorter spray interval. Follow the recommended spray interval for each fungicide application before proceeding with the next application. Ensure that the area to be treated is covered uniformly. Do not apply Reason 500 SC, alone or in a tank mix, more than six times in a year.

8.0 Toxic Substances Management Policy considerations

During the review of Fenamidone Technical fungicide and Reason SC Fungicide, the PMRA has taken into account the federal Toxic Substances Management Policy[1] and has followed its Regulatory Directive DIR99-03[2]. It has been determined that this product does not meet TSMP Track-1 criteria:

- Fenamidone does not meet the criteria for persistence in water and soil but exceeds the criteria in sediment. Its values for half-life in water (up to 32 days), soil (up to 18 days) are below the TSMP Track-1 cut-off criteria for water (≥182 days) and soil (≥182 days). The half-life in anaerobic sediment (up to 1115 days) exceeds the TSMP Track-1 cut-off criteria for sediment (≥365 days). Although data on the persistence in air were not available, the vapour pressure and Henry's Law constant indicate that fenamidone will not volatilize from water or moist soil under field conditions, thus long-range atmospheric transport of fenamidone is not likely to occur.

- Fenamidone is not bioaccumulative. The octanol–water partition coefficient (log K_{ow}) is 2.8, which is below the TSMP Track-1 cut-off criterion of ≥5.0.

- Fenamidone is toxic to certain non-target organisms thus, fenamidone meets the TSMP criterion for toxicity.

- Fenamidone (technical grade) does not contain any by-products or microcontaminants that meet the TSMP Track-1 criteria. Impurities of toxicological concern are not expected to be present in the raw materials nor are they expected to be generated during the manufacturing process.

The formulated product does not contain any formulants that are known to contain TSMP Track-1 substances. Two major transformation products (RPA 717879 and RPA 408056) have been identified as potentially meeting the TSMP Track-1 criteria based on their persistence and toxicity. Octanol–water partition coefficients are required for these major transformation products to determine if the compounds meet the criterion for bioaccumulation. Should these major transformation products meet the TSMP criterion for bioaccumulation, further data will be requested to address the TSMP.

---

1 The federal Toxic Substances Management Policy is available through Environment Canada's Web site at: www.ec.gc.ca/toxics

2 The PMRA's Strategy for Implementing the Toxic Substances Management Policy, DIR99-03, is available through the Pest Management Information Service: Phone 1-800-267-6315 within Canada or 1-613-736-3799 outside Canada (long distance charges apply); Fax (613) 736-3798; E-Mail pminfoserv@hc-sc.gc.ca or through our Web site at www.hc-sc.gc.ca/pmra-arla

As the four TSMP Track-1 criteria for anthropogenicity, persistence, bioaccumulation, and toxicity are not all met for the active ingredient, fenamidone, the PMRA has determined that fenamidone does not qualify as a TSMP Track-1 chemical and is not subject to virtual elimination.

9.0 Regulatory decisions

9.1 Regulatory decisions (OECD 3.2 and 3.3)

Fenamidone Technical Fungcide has been granted temporary registration for use on potatoes, pursuant to Section 17 of the Pest Control Products Regulations, subject to the following conditions:

- Submission of batch analytical data from full scale production
- Submission of analytical standards
- Information on the presence of free N-phenyl anilines in plant metabolism studies
- Information on the formation of aniline and substituted aniline in soil
- Submission of octanol/water partitioning data for 2 major transformation products
- Submission of sediment toxicity data with a sediment dwelling species

List of abbreviations

a.i.	active ingredient
ADI	acceptable daily intake
ARfD	acute reference dose
BCF	bioconcentration factor
bw	body weight
CAS	Chemical Abstracts Service
CEPA	*Canadian Environmental Protection Act*
CV	coefficient of variation
d	day(s)
DFR	dislodgeable foliar residue
DNA	deoxyribonucleic acid
DT_{50}	dissipation time 50%
EC_{25}	concentration effective against 25% of test organisms
EC_{50}	median effective concentration
ECD	electron capture detection
EEC	expected environmental concentration
EP	end-use product
EXPRES	Expert System for Pesticide Regulatory Evaluation and Simulation
FOB	functional observational battery
GAP	good agricultural practice
GC	gas chromatography
GIT	gastrointestinal tract
GST-P	glutatione S-transferase, placental form
h	hour(s)
ha	hectare(s)
HAFT	highest average field trial
HPLC	high performance liquid chromatography
ILV	independent laboratory validation
IPM	integrated pest management
K_{oc}	organic carbon adsorption coefficient
K_{ow}	octanol–water partition coefficient
LADD	lifetime average daily dose
LC	liquid chromatography
LC_{50}	median lethal concentration
LD_{50}	median lethal dose
LI	leaching index
LOAEL	lowest observed adverse effect level
LOD	limit of detection
LOQ	limit of quantitation
LP	leaching potential
MAS	maximum average score
M/L/A	mixer/loader/applicator
MOE	margin of exposure
MRL	maximum residue limit

MRM	multiresidue method
MS	mass spectrometry
nm	nanometre
NOAEL	no observed adverse effect level
NOEC	no observed effect concentration
NOEL	no observed effect level
OC	organic carbon content
PAI	pure active ingredient
pH	potential hydrogen
PHED	Pesticide Handlers' Exposure Database
PHI	pre-harvest interval
pK_a	dissociation constant
PMRA	Pest Management Regulatory Agency
ppb	parts per billion
ppm	parts per million
Q_1*	cancer estimate risk number
PIS	primary irritation score
r	correlation coefficient
r^2	coefficient of determination
R^2	regression coefficient
RAC	raw agricultural commodity
RfD	reference dose
ROC	residue of concern
RP	reversed phase
SGGT	serum γ-glutamyl transferase
SPE	solid phase extraction
TC	transfer coefficient
TGAI	technical grade of active ingredient
TSMP	Toxic Substances Management Policy
$t_{½}$	half-life
US	United States
USEPA	United States Environmental Protection Agency
UV	ultraviolet

References

From environmental assessment:

Atkins, E. L., D. Kellum and K. W. Atkins. 1981. Reducing Pesticide Hazards to Honey Bees: Mortality Prediction Techniques and Integrated Management Strategies. University of California Division of Agricultural Sciences. Leaflet 2883, 22 p.

Fletcher, J. S., J. E. Nellessen and T. G. Pfleeger. 1994. Literature review and evaluation of the EPA food-chain (Kenaga) nomogram, an instrument for estimating pesticide residues on plants. *Environmental Toxicology and Chemistry* **13**:1383–1391.

Harris, L. E. 1975. *Guide for Estimating Toxic Residues in Animal Feeds Or Diets*. EPA-540/9-75-019. (NTIS reference # PB243748). USEPA, Washington, D.C.

Hoerger, F. and E. E. Kenaga. 1972. Pesticide residues on plants: correlation of representative data as a basis for estimation of their magnitude in the environment. *In* (Coulston, F. and F. Korte, eds.) *Environmental Quality and Safety—Chemistry, Toxicology and Technology. Vol I: Global Aspects of Chemistry, Toxicology and Technology as Applied to the Environment*. Georg Thieme Publishers, Stuttgart, and Academic Press, New York, pp 9–28.

Kenaga, E. E. 1973. Factors to be considered in the evaluation of the toxicity of pesticides to birds in their environment. *In* (Coulston, F. and F. Korte, eds.) *Environmental Quality and Safety—Global Aspects of Chemistry, Toxicology and Technology as Applied to the Environment. Vol. II*. Georg Thieme Publishers, Stuttgart, and Academic Press, New York, pp 166–181.

Kennedy, J. M. and R. E. Talbert. 1977. Comparative persistence of dinitroaniline type herbicides on the soil surface. *Weed Science* **25**:373–381.

McCall, J. P., D. A. Laskowski, R. L. Swann and H. J. Dishburger. 1981. Measurement of sorption coefficients of organic chemicals and their use in environmental fate analysis. pp. 89–109. *In Test protocols for environmental fate and movement of toxicants.* Proceedings of a symposium. Association of Official Analytical Chemists. 94th Annual Meeting, October 21–22, 1980. Washington, D.C.

Spector, W. S. 1956. *Handbook of Biological Data.* W.B. Saunders Co., Philadelphia, PA.

Urban, D. J. and N. J. Cook, 1986. *Hazard Evaluation Division, Standard Evaluation Procedure, Ecological Risk Assessment*. EPA 540/9-85-001. USEPA, Washington, D.C.

USEPA. 1975. Volatilization Studies. *Guidelines for Registering Pesticides in the United States.* 40 FR 123: 26889–26891. USEPA, Washington, D.C.

Appendix I Methods of Analysis

Table 1 Analytical methods for analysis of the active substance as manufactured

Product	Analyte	Method type	Linearity range	Recovery (%)	RSD (%)	LOQ (%)	Method
Technical	Fenamidone	HPLC	0.25–0.75 g/L	100–100.7	0.3		Accepted
	R-isomer	Chiral HPLC	1–100 mg/L	101	17.8	0.13	Accepted
Technical	Major impurities	HPLC	0.01–0.14	93–100	1.9–12.6	<0.002	Accepted

Table 2 Methods for formulation analysis

Product	Analyte	Method ID	Method type	Linearity range (g/L)	Mean recovery (%) (n)	RSD (%) (n)	Method
Reason 500 SC	Fenamidone	F-1062-11-00	HPLC	0.1–1.0	98.7 ± 1 (n=6)	0.6	Accepted

Table 3 Methods for environmental residue analysis

Summary of method validation data							
Matrix	Method code	Method type	Analyte	LOQ	Mean % recovery (n)	Mean % RSD	Method
Soil	98W13195	HPLC/MS/MS	Fenamidone	10 ppb	86.6 (143)	12	Acceptable
			RPA 408056		106 (143)	10	Acceptable
			RPA 406012		85.9 (143)	14	Acceptable
			RPA 410914		77.6 (143)	15	Acceptable
			RPA 717879		102.6 (142)	11	Acceptable
			RPA 409446		81.3 (25)	22	Acceptable
			RPA 410995		75.1 (25)	21	Acceptable
Sediment	A waiver was requested and granted based on the premise that the methods for soil may be acceptable for use for sediments						Acceptable
Water: Mineral water	98-218	GC/TID	Fenamidone	0.1 ppb	100 (5)	3	Acceptable
			RPA 405862		106 (5)	3	Acceptable
			RPA 408056		103 (5)	4	Acceptable
			RPA 717879		98 (5)	5	Acceptable

Summary of method validation data							
Matrix	Method code	Method type	Analyte	LOQ	Mean % recovery (n)	Mean % RSD	Method
Water: Tap water	98-218	GC/TID	Fenamidone	0.1 ppb	93 (5)	8	Acceptable
			RPA 405862		95 (5)	8	Acceptable
			RPA 408056		93 (5)	9	Acceptable
			RPA 717879		98 (5)	10	Acceptable
Water: Surface (Rhône river) water	98-218	GC/TID	Fenamidone	1 ppb	95 (5)	4	Acceptable
			RPA 405862		100 (5)	2	Acceptable
			RPA 408056		87 (5)	3	Acceptable
			RPA 717879		96 (5)	7	Acceptable
Crops* (potato)	45683	HPLC-MS-MS	Fenamidone	20 ppb	100 (5)	7.8	Acceptable
			RPA 405862		97 (5)	7	Acceptable
			RPA 408056		96 (5)	8	Acceptable
			RPA 717879		90 (5)	8	Acceptable
Animal biota**	AR 178-98	GC/TID, GC/MSD	Fenamidone	50 ppb	80 (5)	9	Acceptable
			RPA 405862		82 (5)	11	Acceptable
			RPA 717879		94 (5)	8	Acceptable

* Refers to potato tubers, cucumbers, head lettuce, green onions, tomato fruit, paste and puree, spinach leaves, wheat forage, wheat hay, wheat grain, wheat straw and processed wheat fractions—bran, flour, middlings, shorts and germ. Example data for potato tubers

** Example data for beef meat

Appendix II Toxicology

Table 1 Toxicology summary table

METABOLISM—TECHNICAL

Radiolabelled fenamidone was rapidly absorbed, distributed and excreted following oral administration in rats. Total 96-hour recoveries of the radioactivity were high for all groups (96.47%–106.74% of the administered dose). Biliary excretion data indicated that systemic absorption was approximately 90% to 95% following a single oral low dose of either C-phenyl-[U-^{14}C]-fenamidone or N-phenyl-[U-^{14}C]-fenamidone, and a part of the radioactivity excreted via the bile could be reabsorbed (enterohepatic circulation) and subsequently re-excreted via the urine.

After dosing with N-phenyl-[U-^{14}C]-fenamidone, elimination via the feces was greater than via the urine for males. Urinary excretion was similar to, or greater than, via the feces for females. Fecal elimination accounted for 64.3% (single low dose) and 52.0% (repeat low dose) of the administered dose (AD) for males, and 49.6% (single low dose) and 44.7% (repeat low dose) of the AD for females, respectively. Urinary excretion for males accounted for 26.6% (single low dose) and 40.6% (repeat low dose) of the AD, and for females accounted for 40.5% (single low dose) and 46.5% (repeat low dose) of the AD.

After dosing with C-phenyl-[U-^{14}C]-fenamidone, elimination via the feces was greater than via the urine for both sexes. For females, a higher level of radioactivity was eliminated in the feces after single low and repeated low dosing, whereas the level of radioactivity was similar between single and repeated low dosing in males. Fecal elimination accounted for 80.7% (single low dose), 84.7% (repeat low dose) and 83.7% (single high dose) of the AD for males, and 52.1% (single low dose), 60.5% (repeat low dose) and 91.0% (single high dose) of the AD for females, respectively. Urinary excretion for males accounted for 12.8% (single low dose), 11.4% (repeat low dose) and 10.6% (single high dose) of the AD, and for females accounted for 39.9% (single low dose), 31.3% (repeat low dose) and 13.0% (single high dose) of the AD.

Blood kinetic experiments revealed that at 3 mg/kg bw, peak concentrations of radioactivity in the blood occurred at 4 hours post-dosing, both sexes, and at 300 mg/kg bw, peak concentrations of radioactivity in the blood occurred at 8 hours and 24 hours, for males and females, respectively. The T_{max} extrapolated values were higher for females in the high-dose group, and longer for the high-dose group vs. the low-dose group. The t 1/2 elim was estimated to be ~103 hours in the high dose group and ~61 to 73 hours for the low dose group.

Tissue distribution and bioaccumulation of fenamidone were minimal; <0.66% of the administered dose was recovered in tissues 7 days after oral administration for all dosing groups. Highest levels of radioactivity were found in the blood, liver, kidneys, thyroid and spleen.

Metabolism of fenamidone was extensive as shown by the numerous metabolites characterized and isolated in the feces, bile and urine (i.e., 22 metabolites isolated from urine and bile, and 24 metabolites isolated from feces). In addition to fenamidone, Phase I metabolites (hydroxylation, oxidation and reduction products) and Phase II metabolites (conjugation) were isolated. The major metabolites of fenamidone were RPA 409352, RPA 409361, RPA 408056 and RPA 717879. There were no significant differences in the total metabolite profile among all dose groups for both male and female rats, although the quantities of some metabolites varied between males and females, and between the dose groups. A dose-related difference in metabolism was evident; the higher amount of unmetabolized parent compound in the feces of the high-dose group, compared to the low-dose and repeated-dose groups, indicates that saturation of the metabolic pathway may be occurring at the high dose.

STUDY	SPECIES/STRAIN AND DOSES	NOAEL and LOAEL mg/kg bw/day	TARGET ORGAN/SIGNIFICANT EFFECTS/COMMENTS
ACUTE STUDIES—TECHNICAL			
Oral	Rat—Sprague Dawley, 700, 850, 1000 and 5000 mg/kg bw, 5/sex/group; 2000 mg/kg bw, 5 females only.	LD_{50}: males, > 5000 mg/kg bw females = 2028 mg/kg bw (982-4186).	**750 and 800 mg/kg bw:** No treatment-related findings. **1000, 2000 and 5000 mg/kg bw:** Reduced motor activity, white/soft/mucoid feces, hunched posture, tremors, bradypnea, soiled fur, staggering gait, prostration, piloerection, dyspnea, palpebral ptosis and absent righting reflex. Recovery was complete by day 3. **2000 and 5000 mg/kg bw:** Treatment-related mortality, females only, i.e., 2/5 and 5/5 females, respectively. **LOW TOXICITY**
Dermal	Rat—Sprague Dawley, 5/sex; 2000 mg/kg bw	LD_{50}> 2000 mg/kg bw	No treatment-related findings. No skin irritation. **LOW TOXICITY**

STUDY	SPECIES/STRAIN AND DOSES	NOAEL and LOAEL mg/kg bw/day	TARGET ORGAN/SIGNIFICANT EFFECTS/COMMENTS
Inhalation, 4-hour, nose-only.	Rat—Sprague Dawley, 5/sex/group; 0 or 2.1 mg/L	LC_{50} > 2.1 mg/L	MMAD = 2.5 µm, GSD = 1.97. General clinical signs of toxicity were evident during dosing (exaggerated respiratory movements) and post-dosing (lethargy, uncoordinated movement of the limbs, noisy respiration, hunched posture, gasping, decreased food and water consumption). Complete recovery was evident for all animals by study day 2. **LOW TOXICITY**
Skin irritation	Rabbit—New Zealand White, 6 males; 500 mg dose.	MAS = 0.00/8.0	**NON-IRRITATING**
Eye irritation	Rabbit—New Zealand White, 6 males; 100 mg dose.	MIS = 3.33/110	**MINIMALLY IRRITATING**
Skin sensitization (Maximization method of Magnusson and Kligman)	Guinea pig—Dunkin-Hartley; 10/sex in test group, 5/sex in positive and negative control groups. Test material administered 100% for induction and challenge. Positive control 2,4-dinitrochlorobenzene.	Test material did not elicit any dermal reactions. No evidence of sensitization. Positive control was sensitizing—demonstrating responsiveness of assay.	**NOT A SENSITIZER**
ACUTE STUDIES—FORMULATION (REASON 500 SC FUNGICIDE)			
Oral	Rat—Sprague Dawley, 5/sex; 5000 mg/kg bw	LD_{50} > 5000 mg/kg bw	Soft/mucoid stools, decreased activity and congested breathing. Complete recovery by study day 2. **LOW TOXICITY**
Dermal	Rabbit—New Zealand White, 5/sex; 5000 mg/kg bw	LD_{50}> 5000 mg/kg bw	Very slight to well-defined erythema, edema and white staining of the test site, desquamation, superficial lightening of the test site, focal eschar formation, focal blanching and dermal irritation outside of the test area. First observed on study day 1 with almost complete recovery by day 11. **LOW TOXICITY**
Inhalation, 4-hour, nose-only.	Rat—Sprague Dawley, 5/sex; 0.9 mg/L	LC_{50} > 0.9 mg/L	MMAD = 2.7 µm, GSD = 2.31 µm. Red material around the nose. Complete recovery by day 1. Dark red areas on the lungs and pale kidneys for 1 female, and dark red areas on the testes of 1 male. **LOW TOXICITY**
Skin Irritation	Rabbit—New Zealand White, 4 males, 2 females; 0.5 mL dose	MIS = 1.5/8.0	Very slight erythema and very slight edema, observed within 1 hour, with complete recovery by 24 hours (edema) and 48 hours (erythema). **SLIGHTLY IRRITATING**

STUDY	SPECIES/STRAIN AND DOSES	NOAEL and LOAEL mg/kg bw/day	TARGET ORGAN/SIGNIFICANT EFFECTS/COMMENTS
Eye irritation	Rabbit—New Zealand White, 3/sex; 0.1mL dose	MIS = 17.0/110	Conjunctivitis, noted 1 hour post-dosing, cleared by 72 hours in all animals. Iritis noted 1 hour post-dosing, with complete resolution in all eyes by 24 hours. Corneal opacity affecting >75% of the surface area was noted in one animal, with complete recovery by 48 hours. In addition, the cornea had a slightly dulled appearance in 2 animals at 1 hour only **MILDLY IRRITATING** **Label recommendation:** **CAUTION EYE IRRITANT**
Skin sensitization (Modified Buehler method)	Guinea pig—Hartley; 10/sex in test group, 5/sex in positive and negative control groups. Test material administered 100% for induction and challenge. Positive control DNCB.	Test material did not elicit any dermal reactions. No evidence of sensitization. Positive control was sensitizing—demonstrating responsiveness of assay.	**NOT A SENSITIZER**
ACUTE STUDIES—Metabolites			
Oral; RPA 410193	Rats—Sprague Dawley, 5/sex, 5000 mg/kg bw	LD_{50}> 5000 mg/kg bw	No treatment-related findings. **LOW TOXICITY**
Oral; RPA 412636	Rats—Sprague Dawley; 5/sex/dose, 500, 1000 and 2000 mg/kg bw.	LD_{50}: males, not calculated. females, not calculated. Combined 1520 (1154-2043) mg/kg bw with 95% confidence intervals.	Treatment-related mortality was observed in the 1000 and 2000 mg/kg bw groups. Clinical findings were body weight loss, sedation, piloerection and lateral recumbancy at all dose levels; dyspnea and coma in the 1000 and 2000 mg/kg bw groups. Complete recovery in all groups by day 7. **SLIGHTLY TOXIC** **Label recommendation is not required**
Oral; RPA 412708	Rats—Sprague Dawley, 5/sex/dose; 25, 100, 150 and 200 mg/kg bw	LD_{50}: males, not calculated. females, not calculated. Combined 176 (0-99999) mg/kg bw.	Treatment-related mortality was observed in the 150 and 200 mg/kg bw groups. General clinical signs of toxicity were noted for all animals in the 100, 150 and 200 mg/kg bw groups. Findings were sedation, hypoactivity, lateral recumbancy, piloerection and dyspnea. Complete recovery by day 4. **HIGHLY TOXIC** **Label recommendation is not required**
SHORT TERM—TECHNICAL			
28-day dermal	Rats—Sprague Dawley, 10/sex/group; 0 and 1000 mg/kg bw/day	**Systemic toxicity** LOAEL could not be determined since there were no adverse, treatment-related systemic effects. NOAEL = 1000 mg/kg bw/day. **Dermal toxicity** LOAEL could not be determined since there were no treatment-related dermal effects. NOAEL = 1000 mg/kg bw/day.	**Systemic findings:** **1000 mg/kg bw/day:** No adverse treatment-related effects. **Dermal findings:** No treatment-related dermal effects at any dose level tested.

STUDY	SPECIES/STRAIN AND DOSES	NOAEL and LOAEL mg/kg bw/day	TARGET ORGAN/SIGNIFICANT EFFECTS/COMMENTS
28-day dietary	Rats—Sprague Dawley; 10/sex/group; 0, 500, 5000 and 10 000 ppm (equal to 0, 38.60, 389.01 and 1203.44 mg/kg bw/day for males, and 0, 41.53, 404.63 and 1193.57 mg/kg bw/day for females).	LOAEL = 389.01/404.63 mg/kg bw/day. NOAEL = 38.60/41.53 mg/kg bw/day.	**38.60 mg/kg bw/day:** No adverse, treatment-related effects. ≥ **389.01/404.63 mg/kg bw/day:** Decreased body-weight gain (males); decreased food intake; slightly decreased HCT and Hb; decreased glucose; increased cholesterol (males); increased liver weight; enlarged spleen (males); hepatocyte hypertrophy; hypertrophy/hyperplasia of splenic germinative follicle of the white pulp. **1203.44/1193.57 mg/kg bw/day:** Slightly decreased RBC count; increased bilirubin (males); increased spleen weight.
3-month dietary	Mouse—C57; 10/sex/group; 0, 50, 200, 1000 and 5000 ppm (equal to 0, 11.31, 44.49, 220.17 and 1064.25 mg/kg bw/day for males, and 0, 13.70, 54.13, 273.86 and 1375.17 mg/kg bw/day for females).	LOAEL could not be determined since there were no treatment-related systemic effects. NOAEL = 1064.3/1375.17 mg/kg bw/day.	**11.31/13.70, 44.49/54.13, 220.17/273.86 and 1064.25/1375.17 mg/kg bw/day:** No adverse, treatment-related effects.
3-month dietary	Rat—Sprague Dawley; 10/sex/group; 0, 50, 150, 500 and 5000 ppm (equal to 0, 2.94, 8.95, 29.68 and 305.48 mg/kg bw/day for males, and 0, 3.40, 10.55, 35.39 and 337.19 mg/kg bw/day for females).	LOAEL = 305.48/337.19 mg/kg bw/day. NOAEL = 29.68/35.39 mg/kg bw/day.	**2.94/3.40, 8.95/10.55 and 29.68/35.39 mg/kg bw/day:** No treatment-related findings. **305.48/337.19 mg/kg bw/day:** Decreased body-weight gain and food intake; slightly decreased RBC, HCT and Hb; decreased thymus weight (males); increased thyroid weight (males); hepatocyte macro/microvacuolation; bile duct hyperplasia; prominent splenic germinal centres and renal extramedullary hematopoiesis.
3-month dietary	Rat—Sprague Dawley, 10/sex/group; 0, 60, 150, 1000 and 5000 ppm (equal to 0, 4.05, 10.41, 68.27 and 343.93 mg/kg bw/day for males and 0, 4.81, 12, 83.33 and 380.68 mg/kg bw/day for females).	LOAEL = 343.93/380.68 mg/kg bw/day. NOAEL = 68.27/83.33 mg/kg bw/day.	**4.05/4.81, 10.41/12 and 83.33 (females) mg/kg bw/day:** No treatment-related findings. **68.27 mg/kg bw/day:** Ground glass cytoplasm in hepatocytes (males; an adaptive effect so not considered adverse in the absence of any other findings). **343.93/380.68 mg/kg bw/day:** Decreased body-weight gain and food intake; increased cholesterol; decreased thymus weight (males); increased thyroid weight (males); increased liver weight (females); dark livers; ground glass cytoplasm in hepatocytes (adaptive effect).
28-day oral, gelatin capsules	Dog—Beagle, 3/sex/group; 0, 3, 10 and 100 mg/kg bw/day.	LOAEL could not be determined since there were no adverse, treatment-related findings. NOAEL = 100 mg/kg bw/day.	**3, 10 and 100 mg/kg bw/day:** No adverse, treatment-related findings,
3-month oral, gelatin capsules	Dog—Beagle, 4/sex/group; 0, 10, 100 and 500 mg/kg bw/day.	LOAEL = could not be determined since there were no adverse, treatment-related findings. NOAEL = 500 mg/kg bw/day.	**10 and 100 mg/kg bw/day:** No treatment-related findings. **500 mg/kg bw/day:** No adverse, treatment-related findings.

STUDY	SPECIES/STRAIN AND DOSES	NOAEL and LOAEL mg/kg bw/day	TARGET ORGAN/SIGNIFICANT EFFECTS/COMMENTS
1-year oral, gelatin capsules	Dog—Beagle, 4/sex/group, 10, 100 and 1000 mg/kg bw/day.	LOAEL = 1000 mg/kg bw/day. NOAEL = 100 mg/kg bw/day.	**10 mg/kg bw/day:** No treatment-related effects. **100 mg/kg bw/day:** Increased liver weight (females; non-adverse since no corresponding clinical chemistry or histopathological findings). **1000 mg/kg bw/day:** Increased alkaline phosphatase; increased liver weight; hepatic biliary proliferation.
SHORT TERM—Metabolites			
3-month dietary, RPA 410193	Rat—Sprague Dawley, 10/sex/group; 0, 150, 1500 and 15000 ppm (equal to 0, 9.38, 93.32 and 977.94 mg/kg bw/day for males, and 0, 11.45, 114.94 and 1089.72 mg/kg bw/day for females).	LOAEL = 93.32/114.94 mg/kg bw/day NOAEL = 9.38/11.45 mg/kg bw/day.	**9.38/11.45 mg/kg bw/day:** Decreased thymus weight (not adverse since no corresponding histopathology). **93.32/114.94 mg/kg bw/day:** Increased cholesterol (males); increased liver weight (males); enlarged livers (males); hepatocellular hypertrophy; decreased thymus weight; increase in severity of thymus involution (females). **977.94/1089.72 mg/kg bw/day:** Increased cholesterol and triglycerides; marginally decreased RBC, HCT, Hb and MCHC; marginally increased MCV (females); increased liver weight; enlarged livers; hepatocellular hypertrophy; decreased thymus weight; increase in severity of thymus involution.
3-month dietary, RPA 412636	Rat—Sprague Dawley, 10/sex/group; 0, 100, 500 and 2500 ppm (equal to 0, 6.4, 32.9 and 162.2 mg/kg bw/day for males and 0, 7.7, 39.1 and 196.1 mg/kg bw/day for females).	LOAEL = 32.9/39.1 mg/kg bw/day NOAEL = 6.4/7.7 mg/kg bw/day.	**6.4/7.7 mg/kg bw/day:** There were no treatment-related findings. **32.9/39.1 mg/kg bw/day:** Increased liver weight (males); enlarged livers (males); hepatocyte hypertrophy; hepatocyte vacuolation (males). **162.2/196.2 mg/kg bw/day:** Increased cholesterol; increased liver weight; decreased thymus weight; increased adrenal weight (males); enlarged livers (males); prominent lobulation in the liver; hepatocyte hypertrophy; hepatocyte vacuolation; hypertrophy in adrenal gland (males); colloid depletion and agglomeration, and increase in follicular epithelial height in the thyroid (males); increase in severity of thymus involution (males); increase in severity of eosinophilic droplets in renal proximal tubules (males).

STUDY	SPECIES/STRAIN AND DOSES	NOAEL and LOAEL mg/kg bw/day	TARGET ORGAN/SIGNIFICANT EFFECTS/COMMENTS
CHRONIC TOXICITY/ONCOGENICITY—TECHNICAL			
80-week dietary	Mouse—C57 mice, 65/sex/group; 0, 70, 350, 3500 and 7000 ppm (equal to 0, 9.5, 47.5, 525.5 and 1100.2 mg/kg bw/day for males, and 0, 12.6, 63.8, 690.5 and 1392.3 mg/kg bw/day for females.	**Chronic effects** LOAEL = 525.5/690.5 mg/kg bw/day. NOAEL = 47.5/63.8 mg/kg bw/day. **Oncogenicity** No evidence of treatment-related oncogenicity.	**9.5/12.6 and 47.5/63.8 mg/kg bw/day:** No adverse, treatment-related effects. **525.5/690.5 and 1100.2/1392.3 mg/kg bw/day:** Increased platelet count (females); decreased food efficiency; increased liver weight; clear cell foci (females), increased pleomorphism with or without increased cytoplasmic eosinophilia and occasional giant cells and eosinophilic globules within the cytoplasm of hepatocytes. No treatment-related oncogenic effects at any dose level tested.
2-year dietary	Rat—Sprague Dawley, 70/sex/group; 0, 60, 150 and 1000 ppm (equal to 0, 2.83, 7.07 and 47.68 mg/kg bw/day for males, and 0, 3.63, 9.24 and 60.93 mg/kg bw/day for females). NOTE: An additional group at the dose level of 8000 ppm was terminated by study day 20 due to severe physical distress.	**Chronic effects** LOAEL = 47.68/60.93 mg/kg bw/day. NOAEL = 7.07/9.24 mg/kg bw/day. **Oncogenicity** No evidence of treatment-related oncogenicity.	**2.83/3.63 mg/kg bw/day:** No treatment-related effects. **7.07/9.24 mg/kg bw/day:** No adverse, treatment-related findings. **47.68/60.93 mg/kg bw/day:** Increased thyroid weight; enlarged liver and thyroids (males); thyroid follicular cell hypertrophy/hyperplasia; colloid basophilia; increased follicular diameter (males); and increased liver weight. No treatment-related oncogenic effects at any dose level tested.
2-year dietary; supplementary study.	Rats—Sprague Dawley, 70/sex/group; 0 and 5000 ppm (equal to 0 and 260.13 mg/kg bw/day for males, and 0 and 335.10 mg/kg bw/day for females). An additional 15/rats/sex/group were treated for 52 weeks followed by a 3-month recovery period.	**Chronic effects** LOAEL = 260.13/335.10 mg/kg bw/day. NOAEL = could not be determined. **Oncogenicity** No evidence of treatment-related oncogenicity.	**260.13/335.10 mg/kg bw/day:** Decreased body-weight gain (females); decreased food intake (females); increased liver weight; increased thyroid weight (males); enlarged thyroids; foamy hepatocyte cytoplasm and eosinophilic inclusions (males); hepatocyte hypertrophy (females); hypertrophy/hyperplasia of the thyroid follicular cells; hepatocyte vacuolation; colloid basophilia; increased follicle diameter; diffuse C-cell hyperplasia (males). **After a 3-month recovery period:** Partial recovery of body weight, males only; slightly increased thyroid weight (males only); foamy hepatocyte cytoplasm (1 male). No treatment-related oncogenic effects at any dose level tested.

STUDY	SPECIES/STRAIN AND DOSES	NOAEL and LOAEL mg/kg bw/day	TARGET ORGAN/SIGNIFICANT EFFECTS/COMMENTS
REPRODUCTION/DEVELOPMENTAL TOXICITY—TECHNICAL			
Two-generation dietary, one litter per generation	Rat—Sprague Dawley, 28/sex/group; 0, 60, 1000 and 5000 ppm (equal to 0, 3.90, 63.76 and 328.35 mg/kg bw/day for males, and 0, 4.04, 68.61 and 353.20 mg/kg bw/day for females).	**Parental toxicity** LOAEL = 328.35/353.20 mg/kg bw/day. NOAEL = 63.76/68.61 mg/kg bw/day.	**3.90/4.04 mg/kg bw/day:** No treatment-related effects. **63.76/68.61 mg/kg bw/day:** No adverse, treatment-related findings. **328.35/353.20 mg/kg bw/day:** Slightly lower body weight and body-weight gain (F_0 and F_1 males and females); decreased food intake (F_1 males and females); decreased food efficiency (F_0 males and females); increased liver and spleen weights (F_0 and F_1 males and females; histopathology not conducted).
		Reproductive toxicity LOAEL could not be determined since there were no treatment-related effects at any dose level tested. NOAEL = 328.35/353.20 mg/kg bw/day.	No treatment-related effects at any dose level tested.
		Offspring toxicity LOAEL = 328.35/353.20 mg/kg bw/day. NOAEL = 63.76/68.61 mg/kg bw/day. No evidence of increased susceptibility of rat pups.	**3.90/4.04 mg/kg bw/day:** No treatment-related effects. **63.76/68.61 mg/kg bw/day:** No adverse, treatment-related effects. **328.35/353.20 mg/kg bw/day:** Lower pup body-weight gain, F_1 litters.
Teratogenicity oral gavage	Female rats—Sprague Dawley, 25/group; 0, 25, 150 or 1000 mg/kg bw/day.	**Maternal toxicity** LOAEL = 1000 mg/kg bw/day NOAEL = 150 mg/kg bw/day	**25 and 150 mg/kg bw/day:** No treatment-related effects. **1000 mg/kg bw/day:** Decreased body-weight gain and decreased food intake during the dosing period.
		Developmental toxicity LOAEL = 1000 mg/kg bw/day NOAEL = 150 mg/kg bw/day	**25 and 150 mg/kg bw/day:** No treatment-related effects. **1000 mg/kg bw/day:** Slightly lower fetal body weight; increased incidence of incomplete ossification of the parietal bone and hyoid body; slightly increased incidence of unossified 5th sternebrae and incomplete ossification of the 6th sternebrae.
		Teratogenicity LOAEL could not be determined since there were no treatment-related findings. NOAEL = 1000 mg/kg bw/day. No evidence of increased susceptibility of rat fetuses to in utero exposure.	No treatment-related teratogenic effects noted at any dose level tested.

STUDY	SPECIES/STRAIN AND DOSES	NOAEL and LOAEL mg/kg bw/day	TARGET ORGAN/SIGNIFICANT EFFECTS/COMMENTS
Range-finding: Teratogenicity oral gavage	Female rabbits—New Zealand White, 8/group; 0, 25, 75, 200 and 500 mg/kg bw/day.	NOAEL/LOAELs were not established, since this range-finding study was conducted to determine dose levels to be used in the main rabbit developmental study. The 200 and 500 mg/kg bw/day dose levels exceeded the maximum tolerated dose. Hence, dose levels chosen for the main rabbit developmental study were 0, 10, 30 and 100 mg/kg bw/day.	**25 and 75 mg/kg bw/day:** No treatment-related effects. **200 mg/kg bw/day:** Loss in body weight, decreased food intake, abortion (3/8), 100% post-implantation loss (2/8), lower fetal body weight (↓ 40%). **500 mg/kg bw/day:** Mortality (2/8), abortions (6/8), loss in body weight, lower food intake.
Teratogenicity oral gavage	Female rabbits—New Zealand White, 30/group; 0, 10, 30 and 100 mg/kg bw/day.	**Maternal toxicity** LOAEL=30 mg/kg bw/day NOAEL=10 mg/kg bw/day **Developmental toxicity** LOAEL could not be determined since there were no adverse treatment-related effects. NOAEL=100 mg/kg bw/day **Teratogenicity** LOAEL could not be determined since there were no treatment-related findings. NOAEL=100 mg/kg bw/day. No evidence of increased susceptibility of rabbit fetuses to in utero exposure.	**10 mg/kg bw/day:** No treatment-related effects. **30 mg/kg bw/day:** Increased liver weight (↑ 18.9%; histopathology not conducted). **100 mg/kg bw/day:** Increased liver weight (↑ 36.6%; histopathology not conducted). No treatment-related developmental effects noted at any dose level tested. No treatment-related teratogenic effects noted at any dose level tested.
STUDY	**SPECIES/STRAIN or CELL TYPE**	**DOSES EMPLOYED**	**SIGNIFICANT EFFECTS/COMMENTS**
MUTAGENICITY—TECHNICAL			
Reverse gene mutation assay	*S. typhimurium*, strains TA98, TA100, TA102, TA1535 and TA1537.	**Assay 1:** 50, 100, 250, 500, 1000 and 2500 µg/plate, ± S9. **Assay 2:** 50, 100, 250, 500 and 1000 µg/plate, +S9; 10, 25, 50, 100, 250, 500 and 1000 µg/plate, -S9.	**Negative** (± S9)
Chromosome aberration assay	Human lymphocyte cultures, in vitro.	**Assay 1:** 2.907, 4.152, 5.932, 8.474, 12.11, 17.29, 24.70, 35.29, 50.42, 72.03, 102.9, 147.0, 210.0 and 300.0 µg/mL **Assay 2:** 71.19, 94.94, 126.6, 168.8, 225.0 and 300.0 µg/mL, +S9. 0.9514, 1.268, 1.691, 2.255, 3.007, 4.009, 5.345, 7.127, 9.503, 12.67, 16.89, 22.53, 30.03, 40.05, 53.39, 71.19, 94.92, 126.6, 168.8, 225.0 and 300.0 µg/mL, -S9.	**Positve** (± S9)

STUDY	SPECIES/STRAIN or CELL TYPE	DOSES EMPLOYED	SIGNIFICANT EFFECTS/COMMENTS
Gene mutation assay	L5178Y mouse lymphoma cell cultures, in vitro.	**Assay 1:** 0, 12.5, 25, 50, 75, 100, 125 and 150 µg/mL, -S9; 0, 3.125, 6.25, 12.5, 25. 37.5 and 50 µg/mL, +S9. **Assay 2:** 0, 50, 75, 100, 125, 150, 175 and 200 µg/mL, -S9; 0, 6.25, 12.5, 18.75, 25, 31.25, 37.5 and 43.75 µg/mL, +S9.	**Negative** (-S9) **Positive** (+S9)
Micronucleus assay	CD-1 mouse bone marrow cells	0, 500, 1000 and 2000 mg/kg bw/day.	**Negative**
Unscheduled DNA synthesis assay, in vitro	Primary rat hepatocyte cultures	**Assay 1:** 0.064, 0.32, 1.6, 8.0, 40, 200, 1000 and 5000 µg/mL. **Assay 2:** 1.25, 2.5, 5, 10, 20 and 30 µg/mL.	**Negative**
Unscheduled DNA synthesis assay, in vivo	Wistar rats, males	800 and 2000 mg/kg bw.	**Negative**
MUTAGENICITY—RPA 410193			
Reverse gene mutation assay	*S. typhimurium*, strains TA98, TA100, TA102, TA1535 and TA1537; *E. Coli*, strain WP2 uvrA.	**Assay 1:** 8, 40, 200, 1000 and 5000 µg/plate, ± S9. **Assay 2:** 312.5, 625, 1250, 2500 and 5000 µg/plate, ± S9. There was unacceptably high cytotoxicity in the presence of S-9 mix only. Therefore, assay 2 was repeated at dose levels of 62.5, 125, 250, 500 and 1000 µg/plate for strains TA98, TA100 and TA1537, and at dose levels of 125, 250, 500, 1000 and 2000 µg/plate for strains TA1535 and WP2 uvrA.	**Negative**
Gene mutation assay	L5178Y mouse lymphoma cells.	**Assay 1:** 50, 100, 200, 400 and 800 µg/mL, ± S9. **Assay 2:** 100, 200, 400 and 800 µg/mL, ± S9.	**Negative**
Micronucleus assay	CD-1 mouse bone marrow cells.	0, 500, 1000 or 2000 mg/kg bw/day.	**Negative**

STUDY	SPECIES/STRAIN or CELL TYPE	DOSES EMPLOYED	SIGNIFICANT EFFECTS/COMMENTS
MUTAGENICITY—RPA 412636			
Reverse gene mutation assay	*S. typhimurium*, strains TA98, TA100, TA102, TA1535 and TA1537; *E. Coli*, strain WP2 uvrA.	**Assay 1:** 8, 40, 200, 1000 and 5000 µg/plate, ± S9. **Assay 2:** 312.5, 625, 1250, 2500 and 5000 µg/plate, ± S9.	**Negative**
Gene mutation assay	L5178Y mouse lymphoma cells.	**Assay 1:** 100, 200, 400, 800 and 1600 µg/mL, ± S9. **Assay 2:** 400, 800, 1200 and 1600 µg/mL, ± S9.	**Negative**
Micronucleus assay	CD-1 mouse bone marrow	0, 75, 150 and 300 mg/kg bw/day.	**Negative**
MUTAGENICITY—RPA 412708			
Reverse gene mutation assay	*S. typhimurium*, strains TA98, TA100, TA102, TA1535 and TA1537; *E. Coli*, strain WP2 uvrA.	**Assay 1:** 8, 40, 200, 1000 and 5000 µg/plate, ± S9. **Assay 2:** 51.2, 128, 320, 800, 2000 and 5000 µg/plate, ± S9.	**Negative**
Micronucleus assay	CD-1 mouse bone marrow	0, 37.5, 75.0 and 150 mg/kg bw/day.	**Negative**
NEUROTOXICITY (acute and subchronic)			
Acute oral	Rat—Sprague Dawley, 10/sex/group; 0, 125, 500 and 2000 mg/kg bw.	**Systemic toxicity** **Males:** LOAEL = 2000 mg/kg bw NOAEL = 500 mg/kg bw **Females:** LOAEL = 500 mg/kg bw NOAEL = 125 mg/kg bw **Neurotoxicity** LOAEL could not be determined since there were no treatment-related neurotoxic effects noted at any dose level tested. NOAEL=1000 mg/kg bw.	**125 mg/kg bw:** No treatment-related effects. **500 mg/kg bw:** Mucus in the feces; soiling/staining of the fur (females); and unsteady gait (females). **1000 mg/kg bw:** Increased urination (females); soiling/staining of the fur; mucus in the feces; hunched posture (females); unsteady gait (females); decreased rectal temperature (females). No treatment-related neurotoxic effects at any dose level tested.
3-month dietary	Rat—Sprague Dawley, 10/sex/group; 0, 150, 1000 and 5000 ppm (equal to 0, 11.2, 73.5 and 392.3 mg/kg bw/day for males, and 0, 12.7, 83.4 and 414.2 mg/kg bw/day for females).	**Systemic toxicity** LOAEL=392.3/414.2 mg/kg bw/day NOAEL=73.5/83.4 mg/kg bw/day **Neurotoxicity** LOAEL could not be determined since there were no treatment-related neurotoxic effects noted at any dose level tested. NOAEL=392.3/414.2 mg/kg bw/day.	**11.2/12.7 and 73.5/83.4 mg/kg bw/day:** No treatment-related effects. **392.3/414.2 mg/kg bw/day:** Decreased body-weight gain; lower food intake. No treatment-related neurotoxic effects at any dose level tested.

STUDY	SPECIES/STRAIN or CELL TYPE	DOSES EMPLOYED	SIGNIFICANT EFFECTS/COMMENTS

Recommendation for ADI: For the general population, 0.071 mg/kg bw/day based on the lowest NOAEL of 7.07 mg/kg bw/day in the rat combined chronic/oncogenicity study, using a 100-fold uncertainty factor, i.e, 10× for interspecies differences and 10× for intraspecies differences.

Recommendation for ARfD: No acute endpoints of concern were identified, and so an ARfD is not required.

There was no indication of increased susceptibility of rat pups in the rat reproductive toxicity study.

There was no indication of increased susceptibility of rat or rabbit fetuses to in utero exposure in the developmental toxicity studies.

There was no evidence of oncogenic/carcinogenic potential of fenamidone in rodents.

There was no evidence of neurotoxicity in rats after acute and short-term exposure to fenamidone.

Appendix III Residues

Table 1 Integrated food residue chemistry summary

DIRECTIONS FOR USE OF FENAMIDONE		
Crop	**Pest**	**a.i.**
Potatoes	Late blight on potato caused by *Phytophthora infestans*.	200 g a.i./ha × 6 for a total of 1200 g a.i./ha/season. PHI of 14 days. 100 g a.i./ha × 6 in tankmix with Dithane DG (mancozeb) or Bravo 500 (chlorothalonil) at 1.25 kg/ha at 7 to 10 day intervals.

PHYSICOCHEMICAL PROPERTIES	
Water solubility, @ 20°C (mg/L) 99.6% purity	7.8
Solvent solubility @ 25°C (g/L)	acetone (250); acetonitrile (86.1); dichloromethane (330); ethyl acetate (105.7); n-heptane (0.3); toluene (40.1); methanol (43.1); n-octanol (9.7)
Octanol/water partition coefficient (Log K_{ow})	2.8
Dissociation constant (pKa) at 20°C	No substituent which could be easily ionizable in water.
Vapour pressure at 25°C (99.6% purity)	3.4×10^{-7} Pa
Relative density at 20°C g/mL (99.6% purity)	1.285
Melting point (99.6% purity) °C	136.8
UV/Visible absorption spectrum	medium λ (nm) ϵ 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 200-99 (milk)	AR 188-98 (tissues)
Type	Data gathering and enforcement	Data gathering and proposed enforcement	
Analytes	fenamidone, RPA 717879, RPA 408056, RPA 405862	fenamidone, RPA 408056, RPA 717879	
Instrumentation	HPLC-MS/MS	GC-TID	GC-TID (other); GC-MSD (liver)
LOQ	0.02 ppm for each analyte	0.01 ppm	0.05 ppm
Standard	external bracketing standards	external bracketing standards	

Parameters	Plant matrices	Animal matrices	
ILV	Average recoveries for fenamidone in potatoes were 106 ± 5.7%; RPA 717879 (93 ± 9.7%); RPA 405862 (93 ± 7.9%); RPA 408056 (97 ± 6.2%) indicating reliability.	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/ cleanup	Aqueous acetonitrile or accelerated solvent extraction (ASE) with cleanup using HR-P polymeric solid phase extraction cartridge (SPE) and an amino SPE cartridge.	Aqueous acetonitrile extraction with cleanup on C-18 SPE.	Aqueous acetonitrile extraction with cleanup using HR-P polymeric SPE and an amino SPE cartridge.
Radiovalidation	Extraction efficiency in potato tubers (0.021 ppm and 0.023 pm) from the metabolism studies compare well with the extraction of the proposed residue analytical method using ASE extraction (0.025 ppm).	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 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 × 3 at 15-day intervals		454 g a.i./ha × 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 ^{14}C-residues were in the haulm (73–78%; 5.9–6.6 ppm), peel (47–66%; 0.032–0.12 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	**C-phenyl-^{14}C**	**N-phenyl-^{14}C**	**C-phenyl-^{14}C**	**N-phenyl-^{14}C**
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	—
Turnip root	—	RPA 408056 C	RPA 408056 C	RPA 717879 RPA 408056 C	RPA 717879	RPA 717879
Barley chaff	RPA 408056 C	RPA 717879 RPA 408056 C	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 408056 C RPA 717879	—	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 h 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**	**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

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.

CROP FIELD TRIALS- Potatoes

In Canada (1998), eleven trials were conducted in Zones 1, 1A, 5, 5B, 7A, 12 and 14. In the United States (1999), eighteen trials were conducted in Zones 1, 2, 3, 5, 5A, 7, 10 and 11.

Commodity	Total rate g a.i./ha	PHI (days)	Analyte	Residue levels (ppm)					
				n	Min.	Max.	HAFT	Mean	SDEV
Potato tubers	1200	14	Fenamidone	58	<0.02	<0.02	<0.02	<0.02	—
Potato tubers	1200	14	RPA 408056	58	<0.02	<0.02	<0.02	<0.02	—
Potato tubers	1200	14	RPA 405862	58	<0.02	<0.02	<0.02	<0.02	—
Potato tubers	1200	14	RPA 717879	58	<0.02	<0.02	<0.02	<0.02	—

MAXIMUM RESIDUE LIMITS

Potatoes	0.02 ppm

FIELD ACCUMULATION IN ROTATIONAL CROPS—SPINACH, RADISH, WHEAT

Two trials (WA and CA) with EXP 10623A 50SC at 200 g a.i./ha × 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	RPA 405862	RPA 717879
Spinach leaf	28/30	< 0.02	< 0.02	< 0.02	0.095 ± 0.034
	201/234	< 0.02	< 0.02	< 0.02	< 0.02
Radish tops	28/30	< 0.02	< 0.02	< 0.02	0.020 ± 0.018
	201/234	< 0.02	< 0.02	< 0.02	0.017 ± 0.007
Radish roots	28/30	< 0.02	< 0.02	< 0.02	0.018 ± 0.015
	201/234	< 0.02	< 0.02	< 0.02	< 0.02
Wheat forage	28/30	< 0.02	< 0.02	< 0.02	0.017 ± 0.012
	201/234	< 0.02	< 0.02	< 0.02	0.045 ± 0.045
Wheat hay	28/30	< 0.02	< 0.02	< 0.02	0.026 ± 0.023
	201/234	< 0.02	< 0.02	< 0.02	0.220 ± 0.231
Wheat straw	28/30	< 0.02	< 0.02	< 0.02	0.047 ± 0.048
	201/234	< 0.02	< 0.02	< 0.02	0.114 ± 0.131
Wheat grain	28/30	< 0.02	< 0.02	< 0.02	0.024 ± 0.026
	201/234	< 0.02	< 0.02	< 0.02	< 0.02

FIELD ACCUMULATION IN ROTATIONAL CROPS—WHEAT					
A supplemental study, involving 22 trials, was conducted in Zones 2, 4, 5, 7, 8, 10 and 11 on wheat as a rotational crop following soil treatment at 1200 g a.i./ha/season with EXP10623A 50SC.					
Commodity	**Replant interval**	**Mean residue levels (ppm)**			
		Fenamidone	**RPA 408056**	**RPA 405862**	**RPA 717879**
Wheat forage	30	< 0.02	< 0.02	0.048 ± 0.02	0.023 ± 0.013
Wheat hay	30	< 0.02	< 0.02	< 0.02	0.061 ± 0.074
Wheat grain	30	< 0.02	< 0.02	< 0.02	< 0.02
Wheat straw	30	< 0.02	< 0.02	< 0.02	0.035 ± 0.037

PROCESSING STUDIES									
Commodity	**PHI (days)**	**Mean residue levels (ppm)**							
		Fenamidone		**RPA 408056**		**RPA 405862**		**RPA 717879**	
Potato tubers	14	<0.02	N/A	<0.02	N/A	<0.02	N/A	<0.02	N/A
Potato flakes	14	<0.02	≤1	0.03	1.6	<0.02	≤1	0.023	1.1
Potato chips	14	<0.02	≤1	<0.02	≤1	<0.02	≤1	<0.02	≤1
Potato wet peels	14	0.05	2.3	<0.02	≤1	<0.02	≤1	<0.02	≤1

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

Table 2 Overview of plant/animal metabolism studies and risk assessment

PLANT STUDIES—Potatoes			
ROC FOR ENFORCEMENT **Potatoes** **Rotational crops**		Fenamidone Not determined; no N-phenyl data provided.	
ROC FOR RISK ASSESSMENT **Potatoes** **Rotational crops**		Fenamidone Fenamidone	
METABOLIC PROFILE IN DIVERSE CROPS		Not applicable since only potatoes were evaluated.	
ANIMAL STUDIES—Lactating goat			
ROC FOR ENFORCEMENT		Fenamidone	
ROC FOR RISK ASSESSMENT		Fenamidone If MRLs established on meat/milk/eggs, include RPA 717879 for use expansion on feed items.	
METABOLIC PROFILE IN ANIMALS		Only lactating goats were examined.	
FAT SOLUBLE RESIDUE		YES	
DIETARY RISK from food and water			
Chronic non-cancer dietary risk **ADI = 0.071 mg/kg bw/day** **EEC = 60.3 µg a.i./L**	**POPULATION**	**ESTIMATED RISK (% of ADI)**	
		Food (MRLs)	**Food + EEC**
	All infants < 1 yr old	0.1	5.9
	Children 1 to 2 yrs	3	5.6
	Children 3 to 5 yrs	4.5	7
	Children 6 to 12 yrs	4.8	6.5
	Youths 13 to 19 yrs	4.8	6.1
	Adults 20 to 49 yrs	5.8	7.5
	Adults 50+ yrs	5	6.8
	Females 13 to 49 yrs	6	7.7
	Total population	5.2	7

Appendix IV Environmental Assessment

Table 1 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}:7.3 d (sandy loam) DT_{50}: 8.2 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 degradation 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 K_{oc}: 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 sandy loam:31.66 loam: 21.05 Silt loam: 33 sediment: 15	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 degradation established) Slightly persistent to persistent

Table 2 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
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:17.4 d sediment: 85.9 d system: 67.2 d **sandy silt loam system** water: 5.1 d sediment: N/A system:136.4	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

Property	Test material	DT_{50}	Comments
Biotransformation in anaerobic water/sediment systems	Fenamidone	**clay system** water: 6.3 d sediment: N/A system: 1115 d	Not a major transformation pathway. Fenamidone rapidly partitions to the sediment where it is persistent.

Table 3 Parameters used for PRZM-EXAMS and LEACHM water modelling (Level I—screening assessment)

Item		Value
Name of the crop that uses the maximum label rate		**Potatoes**
Maximum allowable rate per year		1.2 kg a.i./ha
Maximum number of applications per year		6
Minimum interval between application		applications 14 d apart
Timing of applications		first application on July 1
Method of application		Spray boom
Solubility in water at pH 7		7.8 mg/L
Vapour pressure		2.6 × 10-9 mmHg
Henry's Law constant		4.3×10^{-9} atm·m^3/mol
K_{ow}		630.95
Hydrolysis half-life	**pH 4**	41.7
	pH 5	221.8
	pH 7	411
	pH 9	27.6
Phototransformation half-life in soil		N/A
Aerobic soil biotransformation DT_{50}		7.8 d
Aerobic aquatic biotransformation DT_{50}		118.6 d
Anaerobic aquatic biotransformation DT_{50}		1115 d (in sediment)

Item	Value
Adsorption K_d	Silt loam (US): 2.43 Sandy loam (US): 5.93 Loam (UK): 6.89 Silt loam (UK): 4.93 sediment (UK): 8.9
Adsorption K_{oc}	Silt loam (US): 486 Sandy loam (US): 494 Loam (UK): 313 Silt loam (UK): 259 sediment (UK): 387

Table 4 Maximum EEC of fenamidone in vegetation and insects following direct over-spray

Matrix	EEC (mg a.i./kg fw)[a]	Fresh/dry weight ratios	EEC (mg a.i./kg dw)
Short range grass	256.8	3.3	847.5
Leaves and leafy crops	134.4	11	1478.4
Long grass	117.6	4.4	517.4
Forage crops	144	5.4	777.6
Small insects	62.4	3.8	237.1
Pods with seeds	12.8	3.9	50.1
Large insects	10.6	3.8	40.6
Grain and seeds	10.7	3.8	40.6
Fruit	10.1	7.6	122.2

[a] Based on correlations reported in Hoerger and Kenaga (1972) and Kenaga (1973) and modified according to Fletcher *et al*. (1994)

[b] Fresh/dry weight ratios from Harris (1975)

[c] Fresh/dry weight ratios from Spector (1956)

Table 5 Maximum EECs in diets of birds and mammals

Organism	Matrix	Maximum EEC (mg a.i./kg dw diet)
Bobwhite quail	30% small insects 15% forage crops 55% grain	210.1
Mallard duck	30% large insects 70% grain	40.6
Rat	70% short grass 20% grain/seeds 10% large insects	605.4
Mouse	25% short grass 50% grain/seeds 25% leaves and leafy crops	601.8
Rabbit	25% short grass 25% leaves and leafy crops 25% long grass 25% forage crops	905.2

Table 6 Summary of effects of fenamidone on terrestrial organisms

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity[a]
Invertebrates				
Earthworm	Acute	RPA 407213	LC_{50}: 25 mg a.i./kg dw NOEC: 8 mg a.i./kg dw	
	Acute	RPA 412636	LC_{50}> 1000 mg a.i./kg dw NOEC> 1000 g a.i./kg dw	Non-toxic up to 1000 mg a.i./kg dw
	Acute	RPA 412708	LC_{50}> 1000 mg a.i./kg dw NOEC: 556 mg a.i./kg dw	Non-toxic up to 1000 mg a.i./kg dw
Bee	Oral	RPA 407213	LC_{50}> 159.8 µg a.i./bee NOEL:79.2 µg a.i./bee	
	Contact	RPA 407213	LD_{50}:74.8 µg a.i./bee NOEL <3.3 µg a.i./bee	Relatively non-toxic
	Brood/hive	Not applicable	—	No data
Predatory arthropod	Contact	EXP 10623A	Specific endpoints were not determined; the test materials were toxic to predatory mites	No data
Parasitic arthropod	Contact	Not applicable	Specific endpoints were not determined; the test materials were toxic to parasitic wasps	No data
Birds				
Bobwhite quail	Acute	RPA 407213	LD_{50}: >2000 mg a.i./kg bw NOEL: 2000 mg a.i./kg bw	Practically non-toxic
	Dietary	RPA 407213	LC_{50}>5200 mg a.i./kg diet NOEC:5200 mg a.i./kg diet	Practically non-toxic
	Reproduction	RPA 407213	LOEC> 1500 mg a.i./kg diet NOEC: 1500 mg a.i./kg diet	—

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity[a]
Mallard duck	Acute	Not applicable	–	No data
	Dietary	RPA 407213	LC_{50}>5200mg a.i./kg diet NOEC: 2600 mg a.i./kg diet	Practically non-toxic
	Reproduction	RPA 407213	LOEC: 1500 mg a.i./kg diet NOEC: 1125 mg a.i./kg diet	—
Mammals				
Rat	Acute	RPA 407213	Oral LD_{50}: 2028 mg a.i./kg bw	Low oral toxicity
		Formulated product	Oral LD_{50}: >5000 mg a.i./kg dw	Low oral toxicity
		RPA 412636	Oral LD_{50}: 1520 mg a.i./kg bw	Slight oral toxicity
		RPA 412708	Oral LD_{50}: 176 mg a.i./kg bw	High oral toxity
	Short-term dietary	RPA 407213	NOAEL: 500 mg a.i./kg dw	
		RPA 412636	NOAEL: 100.0 mg a.i./kg dw	
	Two-generation reproduction	RPA 4072123	NOAEL: 60 mg a.i./kg dw	
Mouse	Short-term dietary	RPA 407213	NOAEL: >5000.0 mg a.i./kg dw	
Vascular plants				
Vascular plant	Tier II Seedling emergence	EXP 10623A	EC_{25} >1200 g a.i./ha EC_{50} >1200 g a.i./ha	No data
	Tier II Vegetative vigour (shoot length and dry weight)	EXP 10623A	EC_{25} >1200 g a.i./ha EC_{50} >1200 g a.i./ha	No data

[a] Atkins *et al.* (1981) for bees and USEPA classification for others, where applicable

Table 7 Summary of effects of fenamidone on aquatic organisms

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity[a]
Freshwater species				
Daphnia magna	Acute	RPA 407213	$EC_{50:}$ 0.18 mg a.i./L NOEC: 0.11 mg a.i./L	Highly toxic
	Chronic	RPA 407213	LOEC: 0.029 mg a.i./L NOEC: 0.0125 mg a.i./L	—
Rainbow trout (*Oncorhynchus mykiss*)	Acute	RPA 407213	LC_{50}: 0.74 mg a.i./L NOEC: 0.35 mg a.i./L	Highly toxic
		RPA 412636	LC_{50}: >34.4 mg a.i./L NOEC: 34.4 mg a.i./L	Slightly toxic (note: classification due to highest tested concentration being <100 mg a.i./L)
		RPA 412708	LC_{50}: >98 mg a.i./L NOEC: 12.3 mg a.i./L	Slightly toxic to practically non-toxic
Bluegill sunfish (*Lepomis macrochirus*)	Acute	RPA 407213	LC_{50}: 0.74 mg a.i./L NOEC: 0.57 mg a.i./L	Highly toxic
Freshwater alga	Acute	RPA 407213	*Pseudokirchneriella subcapitata* (formerly *Selenastrum capricornutum*) (green algae) EC_{50} (120 h): >0.73 mg a.i./L NOEC: 0.73 mg a.i./L	—
		RPA 412636	*Scenedesmus subspicatus* (green algae) EC_{50} (72 h): >33.5 mg a.i./L NOEC (72 h): 33.5 mg a.i./L	

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity[a]
		RPA 412708	*Scenedesmus subspicatus* (green algae) EC_{50} (72 h): >18.7 mg a.i./L NOEC (72 h): 18.7 mg a.i./L	
		RPA 407213	*Navicula pelliculosa* (diatom) EC_{50} (120 h): >0.90 mg a.i./L NOEC (120 h): 0.90 mg a.i./L	
		RPA 407213	*Anabaena flos-aquae* (blue-green alga) EC_{50} (120 h): >0.94 mg a.i./L NOEC (120 h): 0.94 mg a.i./L	
Vascular plant (*Lemna gibba)*	Dissolved	RPA 407213	EC_{50} (14 d): >0.88 mg a.i./L NOEC (14 d): 0.88 mg a.i./L	No data
	Over-spray	Not applicable	—	No data
Marine species				
Crustacean Mysid shrimp (*Mysidopsis bahia*)	Acute	RPA 407213	LC_{50}: 0.069 mg a.i./L NOEC: 0.047 mg a.i./L	Very highly toxic
	Chronic	RPA 407213	NOEC (reproductive success): 0.0095 mg a.i./L	—
Mollusc Eastern oyster (*Crassostrea virginica*)	Acute	RPA 407213	EC_{50}: 0.120 mg a.i./L EC_{10}: 0.027 mg a.i./L (surrogate value for NOEC)	Highly toxic
	Chronic	Not applicable	—	No data
Fish Sheepshead minnow (*Cyprinidon variegatus*)	Acute	RPA 407213	LC_{50}: 2.5 mg a.i./L NOEC: 1.1 mg a.i./L	Moderately toxic
	Salinity challenge	Not applicable	—	No data

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity[a]
Marine alga *Skeletonema costatum* (diatom)	Acute	RPA 407213	EC_{50} (120 h): 0.075 mg a.i./L NOEC (120 h): 0.012 mg a.i./L	—

[a] USEPA classification, where applicable

Table 8 Risk to terrestrial organisms

Organism	Exposure	Endpoint value	EEC	MOS	Risk
Invertebrates					
Earthworm	Acute to fenamidone	8 mg a.i./kg soil	0.13 mg a.i./kg soil	61.5	Negligible risk
	Acute to RPA 412636	> 1000 mg a.i./kg soil	0.533 mg a.i./kg soil	>1876	Negligible risk
	Acute to RPA 412708	556 mg a.i./kg soil	0.533 mg a.i./kg soil	1043	Negligible risk
Bee	Oral	No data	N/A	N/A	No data
	Contact	>83.80 kg a.i./ha	1.20 kg a.i./ha	70	Negligible risk
	Brood/hive	No data	N/A	N/A	No data
Predatory arthropod	Contact	9.98 g a.i./ha	1.20 kg a.i./ha	0.008	Very high risk
Parasitic arthropod	Contact	< 9.98 g a.i./ha	1.20 kg a.i./ha	< 0.008	Very high risk
Birds					
Bobwhite quail	Acute	>2000 mg a.i./kg bw	210.10 mg a.i./kg bw	70 days*	Negligible risk
	Dietary	5200 mg a.i./kg dw	210.10 mg a.i./kg dw	24.76	Negligible risk
	Reproduction	1500 mg a.i./kg dw	210.10 mg a.i./kg dw	7.1	Low risk
Mallard duck	Acute	No data	N/A	N/A	No data
	Dietary	2600 mg a.i./kg dw	40.60 mg a.i./kg dw	64.04	Negligible risk
	Reproduction	1125 mg a.i./kg dw	40.60 mg a.i./kg dw	27.7	Negligible risk

Organism	Exposure	Endpoint value	EEC	MOS	Risk
Mammals					
Rat	Acute to fenamidone	202.80 mg a.i./kg bw	605.40 mg a.i./kg dw	1.95 days†	Negligible risk
	Acute to RPA 412636	152 mg a.i./kg bw	211.89 mg a.i./kg dw	4.18 days	Negligible risk
	Acute to RPA 412708	176 mg a.i./kg bw	104.73 mg a.i./kg dw	0.485 days	Acute risk
	Dietary	500 mg a.i./kg dw	605.40 mg a.i./kg dw	0.82	Moderate risk
	Dietary to RPA 412636	100 mg a.i./kg dw	211.89 mg a.i./kg dw	0.47	Moderate risk
	Reproduction	60 mg a.i./kg dw	605.40 mg a.i./kg dw	0.1	Moderate risk
Mouse	Acute	N/A	N/A	N/A	N/A
	Dietary	5000 mg a.i./kg dw	601.80 mg a.i./kg dw	8.3	Low risk
	Reproduction	Not applicable	N/A	N/A	No data
Vascular plants					
Vascular plant	Seedling emergence	> 1200 g a.i./ha	1200 g a.i./ha	> 1	Low risk
	Vegetative vigour	> 1200 g a.i./ha	1200 g a.i./ha	>1	Low risk

* For bobwhite quail acute oral toxicity (DACO 9.6.2.1), food consumption (FC) was 0.014 kg dw/ind/day, body weight per individual (BWI) was 0.103 kg bw/ind, daily intake (DI = FC × EEC) was 2.94 mg a.i./ind/day, $NOEL_{(ind)}$ (=NOEL × BWI) was 300 mg a.i./ind. The number of days for a wild population to reach the NOEL in the laboratory population was calculated as $NOEL_{(ind)}$ / DI.

† For rat acute oral toxicity, food consumption (FC) was 0.06 kg dw/ind/day, body weight per individual (BWI) was 0.35 bw/ind, daily intake (DI = FC × EEC) was 36.3 mg a.i./ind/day, $NOEL_{(ind)}$ (=NOEL × BWI) was 175 mg a.i./ind. The number of days for a wild population to reach the NOEL in the laboratory population was calculated as $NOEL_{(ind)}$ / DI.

Table 9 Risk to aquatic organisms

Organism	Exposure	Endpoint value	EEC	MOS	Risk
Freshwater species					
Daphnia magna	Acute	0.11 mg a.i./L	0.212 mg a.i./L	0.52	Moderate
	Chronic	0.0125 mg a.i./L	–	N/A	No classification
Rainbow trout	Acute	0.35 mg a.i./L	0.212 mg a.i./L	1.7	Low risk
	Chronic	No data	N/A	N/A	No data
Bluegill sunfish	Acute	0.57 mg a.i./L	0.212 mg a.i./L	2.7	Low risk
	Chronic	No data	N/A	N/A	No data
Fathead minnow (Study rejected)	Chronic (early life stage toxicity)	No data	N/A	N/A	
Freshwater green algae	Acute	0.73 mg a.i./L	0.212 mg a.i./L	3.4	Low Risk
Freshwater green algae	Acute	0.94 mg a.i./L	0.212 mg a.i./L	4.4	Low Risk
Freshwater diatom	Acute	0.90 mg a.i./L	0.212 mg a.i./L	4.3	Low Risk
Vascular plant	Dilution	0.88 mg a.i./L	0.212 mg a.i./L	4.2	Low Risk
Marine species					
Crustacean	Acute	0.069 mg a.i./L	0.212 mg a.i./L	0.22	Moderate
Crustacean	Chronic	0.0095 mg a.i./L	N/A	N/A	No data
Mollusk	Acute	0.027 mg a.i./L	0.212 mg a.i./L	0.13	Moderate
Sheepshead minnow	Acute	1.10mg a.i./L	0.212 mg a.i./L	5.2	Low Risk
Marine algae	Acute	0.012	0.212	0.057	High Risk