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humaine et l'environnement

Proposed Re-evaluation Decision

PRVD2026-04

Fenamidone and Its Associated End-use Product

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Proposed re-evaluation decision for fenamidone and associated end-use product

Under the authority of the *Pest Control Products Act*, all registered pesticides must be re-evaluated by Health Canada to ensure that they continue to meet current health and environmental standards and continue to have value. The re-evaluation considers data and information from pesticide manufacturers, published scientific reports and other regulatory agencies. Health Canada applies internationally accepted risk assessment methods as well as current risk management approaches and policies.

Fenamidone is a preventative, protectant fungicide registered to manage diseases in a variety of field crops, vegetables, and specialty crop. Currently registered products containing fenamidone can be found in the Pesticide Product Information Database and in Appendix I. Appendix II lists all uses for which fenamidone is presently registered. All uses were supported by the registrant at the time of re-evaluation initiation and were therefore considered in the health and environmental risk assessments and value assessment of fenamidone.

This document presents the proposed re-evaluation decision for fenamidone, including the proposed amendments (risk mitigation measures) to protect human health and the environment, as well as the Science evaluation on which the proposed decision is based. All products containing fenamidone that are registered in Canada are subject to this proposed re-evaluation decision. This document is subject to a 90-day public consultation period,¹ during which the public (including the pesticide manufacturers and stakeholders) may submit written comments and additional information to Pesticides Regulatory Directorate Publications. The final re-evaluation decision will be published after taking into consideration the comments and additional information received during the consultation period that are directly related to this proposed re-evaluation decision.

Proposed re-evaluation decision for fenamidone

Health Canada, under the authority of the *Pest Control Products Act*, has conducted all evaluations considered necessary with respect to the health and environmental risks and value of fenamidone based on available scientific information in accordance with subsection 16(6) of the *Pest Control Products Act*. Based on these evaluations, Health Canada is proposing for public consultation, pursuant to section 28 of the *Pest Control Products Act*, the continued registration of uses of fenamidone and the associated end-use product registered for sale and use in Canada under section 21 of the *Pest Control Products Act*.

With respect to human health, dietary (food and drinking water), occupational (handler and postapplication), and non-occupational (bystander) risks were shown to be acceptable when fenamidone is used according to proposed conditions of registration, which includes new mitigation measures such as restricted-entry intervals (up to 4 days) and additional personal protective equipment for specific workers during planting of treated potato seed pieces.

¹ “Consultation statement” as required by subsection 28(2) of the *Pest Control Products Act*.

The environmental risk assessment found that the risks to the environment were shown to be acceptable when fenamidone is used according to proposed conditions of registration, which includes new mitigation measures such as additional precautionary label statements and spray buffer zones.

When used as a seed piece treatment on potato seeds infected with late blight, fenamidone increases levels of emergence and may prevent the spread of late blight spores when handling and planting seed pieces. The ability to tank mix fenamidone provides users with the ability to increase the spectrum of diseases controlled with a single seed treatment application. With the exception of potatoes, tomatoes, and turnip greens, fenamidone was registered for use on all other labelled crops under the User Requested Minor Use Label Expansion program, and as such is important to the minor use community.

Risk mitigation measures

Registered pesticide product labels include specific directions for use. Directions include risk mitigation measures to protect human health, the environment and ensure the product has acceptable value which must be followed by law. The proposed label amendments including the revised/updated label statements and/or mitigation measures, as a result of the re-evaluation of fenamidone, are summarized below. Refer to Appendix IX for details.

Human health

Risk mitigation:

- To protect workers during mixing/loading/application, the following risk-reduction measures are proposed:
 - Require that workers wear additional personal protective equipment (PPE) when in the back of planters during planting of treated potato seed pieces.
- To protect workers entering treated sites, the following risk-reduction measures are proposed:
 - Require the minimum restricted-entry interval (REI) of 12 hours.
 - Increase the REIs for some postapplication activities in some crops.

Label improvements to meet current standards:

- Due to updates of the crop groups nomenclature, the label statement “Brassica leafy greens” is proposed to be replaced by “Leafy vegetables”.
- Updates to personal protective equipment and REI label statements as per current labelling standards.
- Add statement to clarify that fenamidone is registered for outdoor application only.
- Require an additional statement specific to potato seed piece treatment to promote best management practices to minimize human exposure from spray drift or spray residues resulting from drift.

Environment

Risk mitigation:

- To protect the environment, the following risk-reduction measures are proposed:
 - Precautionary label statements to inform users of toxicity to aquatic organisms and beneficial arthropods.
 - Advisory statement to minimize risk to beneficial arthropods.
 - A spray buffer zone of 1 m is required to protect sensitive aquatic habitats from spray drift.
 - Best management label statement to reduce the runoff entering sensitive aquatic habitats.

International context

Fenamidone is currently acceptable for use in other Organisation for Economic Co-operation and Development (OECD) member countries, including New Zealand, Colombia, and the United States. As announced on 18 December 2020, the European Union (EU) prohibited all uses of fenamidone based on human health and environmental concerns in 2019 (Commission Implementing Regulation (EU) 2018/1043). Following a preliminary analysis of the EU regulatory decision, and pursuant to subsection 17(7) of the *Pest Control Products Act*, the scope of the re-evaluation of products containing fenamidone was expanded to include all the aspects of concern identified in the EU decision and a special review was not initiated. Therefore, this re-evaluation addresses the following aspects of concern identified in the EU decision on fenamidone:

1. Potential for genotoxicity.
2. Potential for groundwater leaching by metabolite RPA 412708.
3. Potential risk to aquatic organisms from exposure to the metabolite acetophenone.

Next steps

Upon publication of this proposed re-evaluation decision, the public, including the registrants and stakeholders are encouraged to submit additional information that could be used to refine risk assessments during the 90-day public consultation period.

Health Canada will accept written comments and additional information on this proposal up to 90 days from the date of publication of this document (“consultation period”). Comments and additional information on the proposed decision can be submitted during the consultation period to Health Canada through Pesticides Regulatory Directorate Publications, or the Public Engagement Portal (Public Engagement Portal forms - Consultation Comment). For more information or if you have questions, contact Health Canada’s Pesticides Information Service.

Before making a re-evaluation decision on fenamidone under section 21 of the *Pest Control Products Act*, the comments and additional information received during the consultation period that are directly related to this proposed decision, such as comments directed to the science evaluation, will be taken into consideration in preparation of the final re-evaluation decision

document. A science-based approach will be applied in making a final decision on fenamidone. In accordance with subsection 28(5) of the *Pest Control Products Act*, Health Canada will then publish a final re-evaluation decision document, which will include the decision, the reasons for it, a summary of the comments received directly related to the proposed re-evaluation decision during the consultation period, and Health Canada's response to these comments.

Refer to Appendix I for details on specific products impacted by this proposed decision.

Other information

The relevant confidential test data on which the proposed decision is based (in the References section of this document) are available for public inspection, upon application, in Pesticides Regulatory Directorate's Reading Room. For more information, please contact Health Canada's Pesticides Information Service.

Additional scientific information

The following additional data may be submitted during the consultation for consideration during the final decision phase:

Value

Risks were shown to be acceptable for most uses at the minimum restricted-entry interval (REI) of 12 hours. For some uses and activities, longer REIs (up to 4 days) were required to mitigate risks. Most REIs are likely to be agronomically feasible. Feedback is requested regarding the feasibility of the REIs for the following crops and activities:

- Hand set irrigation: basil, spinach, baby spinach, carrot, brassica leafy greens, edible podded legume vegetables, succulent shelled pea and bean, ginseng, turnip greens.
- Scouting: edible podded beans, succulent shelled pea and bean.

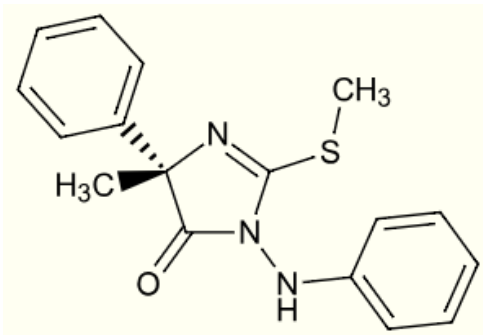
Science evaluation

1.0 Introduction

Fenamidone is a preventative, protectant fungicide registered to manage diseases in a variety of field crops, vegetables, and specialty crop. For all crops, it is foliar applied by ground application (field sprayer) and is also registered for aerial application and as a seed piece treatment on potato (use-site category 10). Its pesticidal mode of action involves inhibition of complex III of the mitochondrial electron transport chain. Currently registered products containing fenamidone can be found in the Pesticide Product Information Database and in Appendix I.

2.0 Technical grade active ingredient

2.1 Identity

Common name	Fenamidone
Function	Fungicide
Chemical family	Imidazolinone
Chemical name	
1 International Union of Pure and Applied Chemistry (IUPAC)	(<i>S</i>)-1-anilino-4-methyl-2-(methylthio)-4-phenylimidazolin-5-one
2 Chemical Abstracts Service (CAS)	(5 <i>S</i>)-3,5-dihydro-5-methyl-2-(methylthio)-5-phenyl-3-(phenylamino)-4 <i>H</i> -imidazol-4-one
CAS registry number	161326-34-7
Molecular formula	C ₁₇ H ₁₇ N ₃ OS
Structural formula	
Molecular weight	311.4
Purity of the technical grade active ingredient	99%
Registration number	27461

2.2 Physical and chemical properties

Property	Result
Vapour pressure at 25°C	3.4×10^{-4} mPa
Ultraviolet (UV) / visible spectrum	Media λ_{max} (nm) ϵ (L* mol^{-1} * cm^{-1}) Neutral 202.5 18470 230 9148 Acidic 203 25138 230 15734 Alkaline 228.538838 Does not absorb at $\lambda > 300$ nm in acidic, neutral or basic media.
Solubility in water at 20°C	7.8 mg/L
n-Octanol/water partition coefficient	$\log K_{\text{ow}} = 2.8$ $\log K_{\text{ow}} = 2.8$ at 20°C
Dissociation constant	From the structure there is no substituent which could be easily ionizable in water.

3.0 Human health assessment

3.1 Toxicology summary

Fenamidone is an imidazolinone fungicide which inhibits complex III of the mitochondrial respiratory chain to decrease oxidative phosphorylation, leading to reduced adenosine triphosphate (ATP) production in plants. A detailed review of the toxicology database for fenamidone, and its metabolites, was conducted. The database is complete, consisting of the full array of toxicity studies currently required for hazard assessment purposes. In addition, several studies were available for metabolites RPA 410193, RPA 412636 and RPA 412708, as well as an immunotoxicity study and mechanistic studies for unchanged fenamidone. The majority of studies were carried out in accordance with international testing protocols and Good Laboratory Practices (GLP). The toxicology assessment also considered information available in the published scientific literature up to July 2023. The database is considered adequate to characterize the potential health hazards associated with fenamidone and its metabolites.

Phenyl-radiolabelled fenamidone was rapidly absorbed in rats following an oral gavage exposure. The peak plasma concentration was reached within 4 hours in both sexes following a single low dose. However, following a single high dose, the peak plasma concentration was different between sexes where the peak concentration was reached within 8 hours for males and within 24 hours for females. The blood, liver, kidneys, thyroid, and spleen showed the highest tissue concentrations of radiolabel in rats. The thyroid, in particular, displayed a high tissue to plasma ratio, indicating equilibrium in favour of the thyroid with respect to plasma. Clearance from the thyroid was slower than from other organs. Radiolabelled fenamidone did not accumulate in tissues and there was minimal retention of radiolabel after 7 days.

Feces were the predominant route for excretion for both sexes, irrespective of position of the radiolabel. Females excreted more fenamidone in the urine than males. Biliary excretion data indicated that absorption of fenamidone was extensive, with approximately 90–95% of the administered dose (AD) recovered in the bile and urine. Biliary studies further indicated that fenamidone was readily reabsorbed via enterohepatic circulation and subsequently excreted in the urine. Following high-dose administration, a greater proportion of unchanged fenamidone was recovered in feces, suggesting saturation of absorption kinetics.

Fenamidone was extensively metabolized in rat, with up to 24 metabolites identified following a single low- or high-dose, or repeated low-dose exposure. Metabolism occurred predominantly via oxidation, reduction, hydrolysis, and conjugation reactions, including glucuronidation and sulfation. Major rat metabolites ($\geq 10\%$ of AD) included racemic RPA 409361 and RPA 408056. Minor rat metabolites included racemic RPA 409352 (8% of AD) and RPA 717879 (3% of AD). The relative proportion of metabolites differed slightly between sexes, and dose levels.

Fenamidone was of low acute oral, dermal and inhalation toxicity in rats. In rabbits, fenamidone was minimally irritating to the eye and non-irritating to the skin. In guinea pigs, fenamidone was not a skin sensitizer when assessed by the Maximization test method. The metabolites RPA 410193 (S-Enantiomer of RPA 405862), RPA 412636 (S-Enantiomer of RPA 717879) and RPA 412708 (S-Enantiomer of RPA 408056) were of low, slight and high oral acute toxicity, respectively.

Short-term dietary toxicity studies conducted with fenamidone were available for mice, rats, and dogs. Following administration of fenamidone, the major target organs included the liver, thyroid, and nervous system. The liver effects were predominantly observed in rodents and included increased liver weights, hepatocellular hypertrophy and enlargement, and changes in liver enzyme levels. Overall, dogs were less sensitive than rodents with respect to liver effects, with treatment-related effects such as increased liver weight, alkaline phosphatase (ALP) and biliary proliferation only observed at the limit dose of testing. Effects on the thyroid and nervous system were not observed in dogs. Two metabolites, RPA 410193 and RPA 412636 showed similar toxicity to fenamidone with respect to liver, thyroid and thymus effects based on results from short-term toxicity studies. In 14-day mechanistic studies assessing liver proliferation and enzyme induction, fenamidone, RPA 410193 and RPA 412636 were shown to induce the cytochrome CYP450 enzymes 7-benzyloxyresorufin O-dealkylase (BROD) and 7-pentoxyresorufin O-dealkylase (PROD), leading to liver cell proliferation. Both metabolites were more potent CYP450 inducers than fenamidone.

Increased thyroid weights were observed following administration of fenamidone in multiple short-term and long-term oral toxicity studies in rats but not in mice or dogs. Thyroid follicular cell hypertrophy and hyperplasia were observed in 2-year oral rat carcinogenicity studies (PMRA No. 777112, 777124), with no evidence of progression to thyroid tumours. The metabolites RPA 410193 and RPA 412636 were also shown to promote thyroid hypertrophy in short-term toxicity studies in rats (PMRA No. 777165, 777156). In long-term studies in rodents, liver and thyroid effects were similar to those observed in the short-term studies. In rats, the thyroid effects after chronic exposure occurred at lower doses than in the short-term oral toxicity studies and increased kidney weights were observed starting at the mid-dose level.

The registrant proposed a potential mode of action (MOA) for the thyroid effects noted in the database (increased thyroid weight, follicular cell hypertrophy and hyperplasia) which they claim were secondary to liver enzyme induction. The key events of the proposed MOA include metabolic liver enzyme induction (for example, cytochrome P450, uridine glucuronosyl transferase (UDP-GT)), leading to perturbations in thyroid hormone levels, interaction with the hypothalamic-pituitary axis, resulting in chronic stimulation of the thyroid by thyroid stimulating hormone (TSH). Mechanistic studies summarized below were submitted in support of this MOA and to demonstrate that the observed thyroid effects in rats are not biologically relevant to the human health assessment. Two in vitro toxicity studies were also submitted to exclude other potential MOAs implicated in thyroid hormone synthesis. These included an in vitro sodium/iodide symporter (NIS) assay, and an in vitro thyroid peroxidase (TPO) assay.

In a mechanistic combined 7- and 90-day dietary toxicity study in rats assessing liver enzyme induction (PMRA No. 3486357), UDP-GT activities towards triiodothyronine (T3) and thyroxine (T4) were statistically significantly increased. Such increases would be expected to lead to reduced plasma thyroid hormones levels via enhanced biliary clearance. However, despite statistically significant increases in liver metabolic activation and increased UDP-GT activities towards T3 and T4, no meaningful changes in serum T3, T4 or TSH levels were observed across multiple studies and timepoints, ranging from 7–90 days. Furthermore, any changes in thyroid hormone levels following administration of fenamidone lacked both time- and dose-concordance therefore were not toxicologically significant.

In a different 90-day toxicity oral study in rats following administration of the metabolite RPA 410193 (PMRA No. 777165), a slight decrease in serum T4 levels and a slight increase in TSH were observed at a single timepoint. No changes in serum thyroid hormone levels were observed in a similar study with metabolite RPA 412636 (PMRA No. 777156). Although both metabolites were significantly more potent liver CYP450 inducers than the parent fenamidone on a per weight basis, there was no compelling evidence of any biologically relevant alterations in serum thyroid hormone levels following dosing with either metabolite.

In an in vitro TPO inhibition assay using rat thyroid microsomes, fenamidone was not an inhibitor of rat TPO when tested up to the highest non-precipitating concentration. In an in vitro NIS inhibition assay using a Fischer rat thyroid follicular cell line (FRTL-5), a concentration-dependent decrease in both iodide uptake and cellular ATP content was observed, suggesting that fenamidone may impair thyroid iodide uptake, potentially through disruption of the ATP-mediated sodium-potassium gradient. No changes in cell viability were observed in a correlative Resazurin assay, and no morphological alterations were noted by light microscopy, indicating an absence of cytotoxicity in FRTL-5 cells following fenamidone exposure. Consequently, an indirect mode of action for NIS inhibition mediated by perturbations in cellular ATP status, cannot be ruled out. Although fenamidone did not interact directly with the sodium-iodide symporter, inhibition of the symporter due to alternative mechanisms such as decreased ATP levels cannot be ruled out.

Overall, the evidence showed a lack of concordance of key events with the proposed MOA, as liver effects observed in rats were not consistently followed by thyroid effects, and in some cases thyroid effects occurred at lower doses than those inducing liver effects. Fenamidone was not an inhibitor of rat TPO; however, inhibition of TPO in other species (for example, human) was not evaluated and the potential inhibition of the sodium-iodide symporter cannot be ruled out. Overall,

there was no compelling evidence to support the proposed MOA and the claim that the thyroid effects were secondary to liver enzyme induction. The thyroid follicular cell hypertrophy and hyperplasia observed in rats are considered toxicologically relevant endpoints for use in the human health assessment.

In a short-term repeat-dose dermal toxicity study in rats (PMRA No. 777108), no treatment-related local effects were observed. Systemic effects occurred only at the limit dose and were limited to slight decreases in body weight gain and body weight in males.

Potential for genotoxicity was one of the aspects of concern identified in the 2018 EU decision and this was considered as part of the re-evaluation. In both dietary long-term mice and rat toxicity studies, there was no evidence of treatment-related oncogenicity at any dose level. A standard battery of in vitro genotoxicity assays, including bacterial reverse gene mutation assays, a chromosome aberration assay, mammalian forward gene mutation assays, as well as in vivo micronucleus and unscheduled DNA synthesis assays, were available. Fenamidone was negative for reverse mutations in vitro, with or without metabolic activation. Fenamidone was also negative for inducing unscheduled DNA synthesis in hepatocytes in vitro. However, fenamidone was positive for mutagenicity in the presence of metabolic activation in mouse lymphoma cells in vitro. Results from this study showed predominantly small mutant colonies suggesting a clastogenic response. Fenamidone was also positive in both the presence and absence of metabolic activation in human lymphocytes in vitro, also suggesting a clastogenic response. However, the clastogenic effects observed in mammalian cells in vitro were not expressed in vivo as results obtained in an in vivo mouse bone marrow micronucleus assay were negative for genotoxicity. Further, fenamidone did not induce DNA damage and repair in the liver of rats from an in vivo unscheduled DNA synthesis assay. There was bone marrow exposure as evidenced by an inversion of the polychromatic/normochromatic erythrocyte (PCE/NCE) ratio in the in vivo micronucleus assay. Based on these considerations, the clastogenic response observed in the in vitro studies does not present a toxicological concern. Overall, based on the weight of evidence from a standard battery of genotoxicity tests, fenamidone is not considered genotoxic.

Metabolites RPA 410193, RPA 412636 and RPA 412708 did not show genotoxic potential based on results from an in vitro bacterial reverse gene mutation assay and an in vivo micronucleus assay in mouse bone marrow. RPA 410193 and RPA 412636 were negative in an in vitro mammalian forward gene mutation assay.

A literature search and screen was conducted to identify published studies relevant to the human health effects assessment, up to July 2023, with no limit on the publication start date. Two studies by van der Stel et al. (2020; 2022) reported that fenamidone perturbed mitochondrial membrane potential, reduced the oxygen consumption rate, and increased rate of glycolysis in cultured human hepatocytes, all indicative of limited capability for oxidative phosphorylation and respiration as a result of electron transport chain (ETC) inhibition. In a non-guideline in vitro study by Pearson et al. (2016) examining transcriptional changes in cortical neuron-enriched cultures in mice, fenamidone clustered together with other chemicals that showed concordance with the aging human brain and various neurological disorders involving dopamine pathways. None of the studies in the toxicology database tested the ability of fenamidone to specifically target dopaminergic neurons. However, neurological effects observed in the toxicology database were limited to decreased brain weight in adults and pups and changes in brain morphometrics in pups, with no apparent neuropathological findings and no effect on functional or behavioural

parameters that might indicate dopaminergic toxicity. Further, a non-guideline in vitro study by Delp et al. (2021) reported that fenamidone was not a dopaminergic neurotoxicant when tested up to 100 μ M, despite promoting mitochondrial dysfunction at the same concentration.

Fenamidone was considered negative in 16 of 17 assays from the developmental neurotoxicity in vitro battery (DNT-IVB). In the rat cortical neuronal network formation assay, there was no evidence of selective activity across the 17 endpoints assessed; however, cytotoxic activity was observed in one of the two cytotoxicity endpoints measured in cortical primary cells. The half-maximal activity concentration (AC₅₀) fell within the ToxCast cytotoxicity “burst” window, indicating that the cytotoxicity observed in the rat cortical neuronal assay was in the same general concentration range associated with broad cellular toxicity/stress across many ToxCast assays, rather than at concentrations suggestive of selective neuronal sensitivity. Similarly, in an in vitro study conducted in mature neuronal networks, fenamidone disrupted activity; however, the reported AC₅₀ values for these effects were above the ToxCast cytotoxicity-burst potency, again indicating that these effects did not occur at concentrations suggestive of selective neuronal sensitivity relative to other cell types.² Fenamidone has also been shown to cause cytotoxicity in other cell types including human epithelial cells and hepatocytes [van der Stel et al. (2020, 2022)]. Cytotoxicity and cell death at high concentrations are biologically plausible given that fenamidone can disrupt mitochondrial function and deplete ATP, which is needed to sustain cellular metabolic processes. Taken together, this suggests that fenamidone causes generalized cellular toxicity rather than selective neurotoxicity in these in vitro models.²

The neurotoxic potential of fenamidone was also examined in vivo in several studies conducted in rats in the toxicology database. In an acute oral neurotoxicity study in adult rats, no evidence of selective neurotoxicity was observed. Although clinical signs of toxicity and decreased locomotor activity were observed, these effects were attributed to overt systemic toxicity that occurred at doses above the limit dose of testing.

Potential evidence of neurotoxicity was noted in a 90-day dietary neurotoxicity study in Sprague-Dawley rats (PMRA No. 777153) where a significant decrease in absolute brain weight in high dose males was observed in the presence of reduced body weight. Although high dose females also had reduced body weight, there were no concomitant changes in their brain weights. The changes in absolute brain weights in high dose males were not correlated with alterations in brain lengths, widths, or relative brain weights. The absolute brain weight reduction noted in this study is not expected to be secondary to body weight effects, given that adult rats tend to maintain stable brain weight despite overall adult body weight fluctuations.³ While two 90-day dietary toxicity studies (PMRA No. 777094, 777096), also conducted in Sprague-Dawley rats, showed no changes in brain weight at similar dose levels as those used in the 90-day neurotoxicity study (PMRA No. 777153) and despite showing similar body weight reductions, decreased offspring brain weights (F1 adult and F2 pups) were observed in the 2-generation reproductive toxicity study in Sprague-Dawley rats (PMRA No. 777132). Consequently, while the evidence available offers conflicting results, the potential for neurotoxicity in adult rats cannot be ruled out.

² USEPA Bioactivity ToxCast Summary:
<https://comptox.epa.gov/dashboard/chemical/invitrodb/DTXSID2034590>

³ Garman, Robert H., et al. "Methods to identify and characterize developmental neurotoxicity for human health risk assessment. II: neuropathology." *Environmental health perspectives* 109.Suppl 1 (2001): 93.

In a dietary rat DNT study with Wistar rats (PMRA No. 3197478), there was no evidence of adverse findings observed in dams up to the highest dose tested (HDT). Sensitivity of the young was observed, as evidenced by decreased body weight during the pre- and early post-weaning periods as well as statistically significant changes in brain morphometrics at the HDT on postnatal day (PND) 21 and 75. Brain morphometric analyses were, however, limited to the control and high-dose groups and as a result this study was considered acceptable with limitations.⁴ In male pups tested at the high dose, there were statistically significant increases in the frontal cortex size on PND 21 and 75, and in the cerebellum measurements on PND 75, which may suggest an effect on the developing nervous system. A statistically significant increase in the caudate putamen measurements was noted in PND 21 males as well; however, the methodology used in this study to assess this parameter may be less reliable. As such, this effect, while noted, was considered equivocally related to treatment. There were no treatment-related changes in brain morphology findings in female offspring or on the assessed neurobehavioural parameters in either sex. While changes in brain morphometric findings were observed in male Wistar pups in the rat DNT study, there was no concomitant change in pup brain weights from this strain. However, decreased pup brain weights were observed in the 2-generation reproductive toxicity study in Sprague-Dawley rats (PMRA No. 777132) and in adult Sprague-Dawley rats in a 90-day sub-chronic neurotoxicity study (PMRA No. 777153), suggesting the potential for strain differences, with Sprague-Dawley rats being more sensitive than Wistar rats.

In a dose range-finding 1-generation dietary reproductive toxicity study in rats (PMRA No. 1065312), decreased offspring body weights from postnatal day (PND) 4 onwards were noted starting at the lowest dose tested, with reduced viability and decreased survival to PND 21 observed in offspring at the highest dose tested. The onset of maternal toxicity was evident starting at the mid-dose (decreased body weight and body weight gain during gestation), with body weight loss potentially related to reduced palatability reported during the pre-mating period at the high dose.

A 2-generation dietary reproductive toxicity study in rats (PMRA No. 777132) was conducted according to OECD Test Guideline (TG) 416 (1983 version) and is currently considered acceptable with limitations. The study showed no treatment-related reproductive effects. In parental (P) and F1 generation females, decreased body weight was observed at the highest dose. F1 females also displayed decreased absolute brain weights and decreased body weight gain starting at the mid-dose. In offspring, decreased body weight and body weight gain as well as decreased brain weights were observed at maternally toxic doses. No increased sensitivity of the young was observed. Ovarian follicle counts and thyroid weights were not assessed in this study; however, the level of concern for these missing parameters is low, given the assessment of developmental neurotoxicity and lack of observed effects on reproductive tissues and related developmental landmarks across studies.

Developmental toxicity studies were available in which pregnant rats and rabbits were administered fenamidone via gavage. These studies were conducted according to OECD TG 414 (1981) and are currently considered acceptable with limitations. In the rat (PMRA No. 777136), maternal effects were observed at the limit dose and included body weight loss in the first days of dosing (GD 6-9), decreased body weight gain and decreased food consumption. Developmental effects in rats were also observed at the limit dose and included decreased fetal body weight, and

⁴ Information Note : *Determining Study Acceptability for use in Pesticide Risk Assessments*

slightly increased incidences of unossified fifth sternebrae and incomplete ossification of the parietal bone and hyoid body. In the main rabbit developmental toxicity study (PMRA No. 777137), treatment-related effects were not observed in fetuses at any dose while maternal toxicity was characterized by notable increases in liver weight. The dose range-finding developmental toxicity study in rabbits (PMRA No. 1065314) provides qualitative context of potential fetal toxicity at higher doses, including increased post-implantation loss, abortions, and decreased fetal body weight in the presence of maternal toxicity. Given the older study protocol, both rat and rabbit developmental toxicity studies lacked a thyroid hormone assessment. Further, the rat developmental toxicity study did not measure anogenital distance and had a shorter duration of exposure compared to updated protocols. However, the level of concern for these missing parameters was low, given the assessment of developmental neurotoxicity, and lack of observed effects on endocrine tissues and related developmental landmarks across the available toxicology database.

In a 28-day dietary immunotoxicity study in rats (PMRA No. 3197496) there was evidence of immune system dysregulation based on a statistically significant decrease in the anti-sheep red blood cell (anti-SRBC) response and an increase in spleen weight at the high dose. These changes occurred in the presence of systemic toxicity as evidenced by decreased body weight, body weight gain, and food consumption, and an increase in thymus atrophy and small thymus.

The identification of fenamidone and select metabolites is presented in Appendix III, Table 1. The toxicological reference values for use in the human health risk assessment are summarized in Appendix III, Table 2. Results of the toxicology studies conducted on laboratory animals with fenamidone and select metabolites are summarized in Appendix III, Table 3.

3.1.1 *Pest Control Products Act* hazard characterization

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

With respect to the completeness of the toxicity database as it pertains to the toxicity in infants and children, the database contains the full complement of required studies including oral gavage developmental toxicity studies in rats and rabbits, and a dietary 2-generation reproductive toxicity study in rats. In addition, a dietary DNT study in rats, a dose range-finding 1-generation dietary reproductive toxicity study in rats, a dose range-finding gavage developmental toxicity study in rabbits, and results from a DNT IVB were available. While some studies were conducted according to older test guidelines and are therefore missing updated assessment parameters, the level of concern for limitations in these study outputs was low given the full weight of evidence available on the most sensitive target (in other words, brain development). As such, the overall database was considered sufficient to characterize the potential pre- and post-natal toxicity of fenamidone.

There was no evidence of increased sensitivity of the young or treatment-related malformations in the developmental toxicity studies in the rat or rabbit or in the reproductive toxicity study in rats. In the guideline rat developmental toxicity study, slightly increased incidences of incomplete ossification and marginal decreases in body weight were noted in pups at the limit dose of testing and in the presence of maternal toxicity. In the rabbit, no developmental effects were noted up to the highest dose tested in the main study, while maternal toxicity at this dose was characterized by a notable increase in liver weights as well as decreased body weight gain and food consumption during gestation. The dose range-finding developmental toxicity study in rabbits conducted at higher dose levels reported a qualitative increase in post-implantation loss and decreased fetal weight at dose levels also reporting maternal toxicity. Since post-implantation loss was not observed at any dose tested in the main study, and given significant protective margin afforded by the relevant point of departure for risk assessment, the overall level of concern is low.

In a dose range-finding 1-generation reproductive toxicity study in rats, decreased offspring body weights were noted starting at the lowest dose tested from PND 4 onwards, with reduced viability and decreased survival to PND 21 reported at the highest dose tested. The serious offspring effects at the high dose occurred in the presence of maternal toxicity, including body weight loss during premating, as well as decreased body weight despite increased food consumption during the first week of pregnancy. Reproductive toxicity was noted with decreased pup body weight at birth. In the more comprehensive 2-generation reproductive toxicity study in Sprague-Dawley rats, decreases in offspring body weight were observed in both generations starting at the mid-dose along with decreased absolute brain weights. At the same dose, maternal toxicity was primarily defined by decreased absolute brain weight in F1 adult females. No treatment-related reproductive effects were observed in this study.

In a DNT study in Wistar rats, there was evidence of increased sensitivity of the young, as neurotoxicity was observed in offspring in the absence of overt maternal toxicity. Although there were slight decreases in body weight in dams during lactation days (LDs) 0–21 at the highest dose tested, these effects were marginal and were not considered adverse. At the highest dose tested, body weights were decreased pre- and post-weaning in both sexes. In males, changes in brain morphometrics were observed, including increases in the size of the frontal cortex (PND 21 and 75) and cerebellum (PND 75). Increases in the size of the caudate putamen (PND 21) were also observed in high dose males, however these effects were considered equivocally related to treatment due to limitations with respect to the reliability of the caudate putamen measurements. Although changes in brain morphometric measurements were observed, there were no treatment-related effects on functional or behavioural assessment parameters in offspring and there was no effect on offspring brain weights at any timepoint.

Some residual uncertainty remains with respect to the possible effects of fenamidone on the brain morphometry of the developing young, given that brain samples of offspring in the low- and mid-dose groups of the DNT study did not undergo morphometric analyses. Furthermore, the weight of evidence for fenamidone suggests that Wistar rats may be less sensitive to neurotoxicity than Sprague-Dawley rats. These concerns are addressed with the retention of the *Pest Control Products Act* (PCPA) factor as noted below.

Overall, the database is adequate for determining the potential for serious effects and sensitivity of the young. The decreased brain weight noted in F2 offspring in the 2-generation reproductive toxicity study in rats was considered serious in nature and occurred in the presence of maternal toxicity. On this basis, a threefold PCPA factor is retained for scenarios for which this endpoint is used to establish the point of departure for risk assessment. The change in brain morphometrics noted in offspring in the rat DNT study was considered serious in nature and occurred in the absence of maternal toxicity. On this basis, a 10-fold PCPA factor is retained for scenarios in which this endpoint is used to establish the point of departure for risk assessment. This PCPA factor was also considered adequate to address potential strain differences and residual uncertainty regarding the lack of morphometric analysis at lower dose levels in the DNT study. For all other scenarios, the PCPA factor can be reduced to onefold.

3.2 Dietary exposure and risk assessment

In a dietary exposure assessment, Health Canada determines how much of a pesticide residue may be ingested with the daily diet. Exposure to fenamidone from potentially treated imported foods is also included in the assessment. Dietary exposure assessments are age-specific and incorporate the different eating habits of the population at various stages of life (infants, children, adolescents, adults and seniors). For example, the assessments take into account differences in children's eating patterns, such as food preferences and the greater consumption of food relative to their body weight when compared to adults. Dietary risk is then determined by the combination of the exposure and the toxicity assessments. High toxicity may not indicate high risk if the exposure is low. Similarly, there may be risk from a pesticide with low toxicity if the exposure is high.

Health Canada considers limiting use of a pesticide when exposure exceeds 100% of the reference dose. Health Canada's Science Policy Note SPN2003-03, Assessing Exposure from Pesticides, A User's Guide, presents detailed acute, chronic and cancer risk assessment procedures.

Canadian maximum residue limits (MRLs) are established for fenamidone for a range of plant and animal commodities. Residues in all other agricultural commodities, including those approved for treatment in Canada but without specific MRLs, are regulated under Subsection B.15.002 (1) of the Food and Drugs Regulations, which requires that residues do not exceed 0.1 ppm. A complete list of MRLs specified in Canada can be found on Health Canada's MRL Database, an online query application that allows users to search for specified MRLs, regulated under the *Pest Control Products Act*, both for pesticides or food commodities.

The acute, chronic, and cancer dietary exposure and risk assessments for fenamidone considered the registered food uses identified in the use pattern table (see Appendix IV). Potential residues on foods imported to Canada were also considered. Sufficient information was available to assess the dietary exposure and risk to fenamidone for the uses considered in the re-evaluation. Acute and chronic dietary exposure and risk assessments were conducted using the Dietary Exposure Evaluation Model - Food Commodity Intake Database™ (DEEM-FCID™, Version 4.02, 05-10-c) program, which incorporates consumption data from the National Health and Nutrition Examination Survey, What We Eat in America (NHANES/ WWEIA) 2005–2010 available through the Centers for Disease Control and Prevention's (CDC) National Center for Health Statistics (NCHS).

Further details on the consumption data are available in Science Policy Note SPN2014-01, *General Exposure Factor Inputs for Dietary, Occupational and Residential Exposure Assessments*.

Canadian MRLs for fenamidone and the current residue definition for enforcement are available in the Pesticides section of the Canada.ca. The current residue definition in plant commodities is the parent fenamidone, and in the animal commodities it is the sum of parent fenamidone and the metabolite RPA 717879. As a result of the re-evaluation, no changes to the enforcement residue definition is proposed. Similarly, no changes to the established MRLs are proposed.

3.2.1 Determination of acute reference dose (ARfD)

To estimate acute dietary risk for all populations, the developmental no observed adverse effect level (NOAEL) of 93 mg/kg bw/day from the DNT study in rats was selected for risk assessment. At the lowest observed adverse effect level (LOAEL) of 429 mg/kg bw/day, increases in the size of the frontal cortex (PND 21 and 75) and cerebellum (PND 75) were observed in male pups. These effects could result from a single exposure and are therefore relevant to an acute risk assessment. Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability were applied. As discussed in the *Pest Control Products Act* hazard characterization section, the full 10-fold PCPA factor was retained. The composite assessment factor (CAF) is therefore 1000.

The ARfD (all populations) is calculated according to the following formula:

$$\text{ARfD} = \frac{\text{NOAEL}}{\text{CAF}} = \frac{93 \text{ mg/kg bw/day}}{1000} = 0.09 \text{ mg/kg bw of fenamidone}$$

The ARfD provides a margin greater than 1600 to the NOAEL for body weight loss (GD 6–9) in dams tested at the limit dose in the rat developmental toxicity study. It also provides a margin of greater than 1300 to the NOAEL for unsteady gait and clinical signs of toxicity which occurred within hours of dosing in the acute neurotoxicity study in adult rats.

3.2.2 Acute dietary exposure and risk assessment

The acute dietary risk was calculated considering the highest ingestion of fenamidone that would be likely on any one day, and using food and drinking water consumption and food and drinking water residue values. The expected intake of residues is compared to the ARfD, which is the dose at which an individual could be exposed on any given day and expect no adverse health effects. When the expected intake of residues is less than the ARfD, the acute dietary exposure is acceptable.

Acute dietary exposure and risk assessments for food and drinking water were conducted for all population subgroups. The acute analysis was conducted using the highest average residue values taken from existing field trials and MRLs. Refinements such as percent crop treated in food handling establishments and statistical import and domestic production were available but not used in the risk assessment, as they were not required for refinement.

Drinking water contribution to the exposure was accounted for by direct incorporation of the appropriate estimated environmental concentration (EEC), obtained from water modelling (see Section 3.3), into DEEM. Experimental and default processing factors were used for the estimation of residues in processed commodities.

The acute dietary risk assessment was conducted for the general population and all population subgroups. The acute dietary (food and drinking water) exposure estimates for fenamidone, at the 95th percentile, ranged for all population subgroups from 24–42% of the ARfD with the most exposed population subgroup being the children 1–2 years of age (see Appendix IV, Table 1.1). The primary source of exposure were the leafy vegetables.

3.2.3 Determination of acceptable daily intake (ADI)

To estimate risk following repeated dietary exposure for all populations, the offspring NOAEL of 5.2 mg/kg bw/day from the 2-generation dietary reproductive toxicity study in rats was selected. At the LOAEL of 84 mg/kg bw/day, decreased body weight (both generations) and body weight gain (F2 generation only) were observed in offspring, and decreased brain weights were observed in F2 generation female offspring. Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability were applied. As discussed in the *Pest Control Products Act* hazard characterization section, a threefold PCPA factor was retained. The CAF is therefore 300.

The ADI (all populations) is calculated according to the following formula:

$$\text{ADI} = \frac{\text{NOAEL}}{\text{CAF}} = \frac{5.2 \text{ mg/kg bw/day}}{300} = 0.02 \text{ mg/kg bw/day of fenamidone}$$

The ADI provides margins of greater than 800 to the NOAEL for decreased brain weight in the 90-day neurotoxicity study in rats and greater than 1300 to the NOAEL for the observed immunotoxicity (decreased anti-SRBC IgM response) in the 28-day immunotoxicity study in rats.

Although a lower point of departure from the 2-year carcinogenicity study in rats was available, it was not selected as it would have resulted in a higher, and therefore less protective, ADI after applying the standard CAF of 100.

3.2.4 Chronic dietary exposure and risk assessment

The chronic dietary risk from food and drinking water was calculated using the average consumption of different foods and drinking water and the average residue values on those foods and in drinking water. The estimated exposure was then compared to the ADI. When the estimated exposure is less than the ADI, the chronic dietary exposure is acceptable.

The chronic assessment was conducted using median residue values taken from field trials and MRLs. Refinements such as percent crop treated in food handling establishments and statistical import and domestic production were available but not used in the risk assessment, as they were not required for refinement.

Drinking water contribution to the exposure was accounted for by direct incorporation of the appropriate EEC, obtained from water modelling (see Section 3.3), into DEEM. Experimental and default processing factors were used for the estimation of residues in processed commodities.

The chronic dietary exposure estimates from food and drinking water ranged for all population subgroups from 12–28% of the ADI with the most exposed population subgroup being the children 1–2 years of age (see Appendix IV, Table 1.2). The primary source of exposure were the leafy vegetables.

3.2.5 Cancer assessment

There was no evidence of treatment-related tumourigenicity in rats or mice and therefore, a cancer risk assessment was not required.

3.3 Exposure from drinking water

Residues of fenamidone in potential drinking water sources were estimated from modelling, as described below.

3.3.1 Concentrations in drinking water

EECs were calculated using the Pesticide in Water Calculator model (PWC, version 2.0). Modelling for surface water used a standard Level 1 scenario, a small reservoir adjacent to an agricultural field. EECs in groundwater were calculated by selecting the highest EEC from a set of standard scenarios representing different regions of Canada. All scenarios were run for 50 years.

A conservative use pattern was modelled at Level 1 and the modelling used initial application dates from March 11 to October 20 (see Table 1 in this section). Given the modelled use pattern, the Level 1 EECs can allow for future use expansion into other crops using single applications of no more than 300 g a.i./ha with minimum interval of 5 days and cumulative yearly applications of no more than 900 g a.i./ha applied by ground sprayer or seed treatment.

Table 1 Level 1 EECs of combined residues of fenamidone and nine of its transformation products (RPA 412636, RPA 412708, RPA 411639, RPA 413255, RPA 221607, RPA 221701, RPA 410193, RPA 418915, RPA 413350) in potential sources of drinking water.

Use pattern	Groundwater (µg a.i./L)		Surface Water (µg a.i./L)		
	Acute ¹	Chronic ²	Daily ³	Yearly ⁴	Overall ⁵
Cabbage 3 application × 300 g a.i./ha/application (5 day interval) for a total of 900 g a.i./ha/year	1337	1241	74	12	7.7

EECs = estimated environmental concentrations

¹ The highest (peak) simulated average concentration (µg a.i./L) in 1 m below the water table.

² The temporal average concentration (µg a.i./L) in the 1 m below the water table over the post-breakthrough simulation period.

³ 90th percentile of the highest 1-day average concentration from each year.

⁴ 90th percentile of yearly average concentrations.

⁵ Average of all yearly average concentrations.

3.3.2 Drinking water exposure and risk assessment

The exposure from drinking water residue estimates were determined to be up to 15% of the ARfD and up to 4.5% of the ADI, for the acute and chronic assessment, respectively.

In the aggregate food and drinking water assessment, drinking water residue estimates were combined with food residue estimates, with EEC point estimates incorporated directly in the dietary (food and drinking water) assessments. Please refer to Sections 3.2.2 and 3.2.4 for details.

3.4 Occupational and non-occupational exposure and risk assessment

Occupational and non-occupational (for example, residential) risk is estimated by comparing potential exposures with the most relevant endpoint from toxicology studies to calculate a margin of exposure (MOE). This is compared to a target MOE incorporating uncertainty factors protective of the most sensitive subpopulation. If the calculated MOE is less than the target MOE, it does not necessarily mean that exposure will result in adverse effects, but mitigation measures to reduce risk would be required.

3.4.1 Toxicological reference values

3.4.1.1 Short-, intermediate- dermal and inhalation

For short-, intermediate-, and long-term occupational exposures via the dermal and inhalation routes, the offspring NOAEL of 5.2 mg/kg bw/day from the 2-generation reproductive toxicity study in rats was selected for the risk assessment. Starting at 84 mg/kg bw/day, decreased body weight (both generations) and body weight gain (F2 generation only) were observed in offspring, and decreased brain weights were observed in F2 female offspring. In the absence of a suitable route-specific study, an oral toxicity study was selected for the inhalation risk assessment. Although a 28-day dermal toxicity in rats was available for the dermal risk assessment, it was not designed to address the endpoint of concern (decreased pup brain weights), thus necessitating the use of an oral toxicity study for risk assessment.

The target margin of exposure (MOE) for these scenarios is 300, which includes uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability, and a factor of threefold applied for the reasons outlined in the *Pest Control Products Act* hazard characterization section. The selection of this study and target MOE is considered protective of all populations, including nursing infants and the unborn children of exposed workers.

3.4.1.2 Dermal absorption factor

A dermal absorption value of 10% was determined for fenamidone based on a rat in vivo study (PMRA No. 777301, 1396907).

3.4.2 Occupational exposure and risk assessment

There is potential for exposure to fenamidone in occupational scenarios from workers handling the fenamidone end-use product during mixing/loading and application activities, and from workers entering previously treated areas.

3.4.2.1 Mixer, loader, and applicator exposure and risk assessment

Foliar application:

For the commercial-class product, there are potential exposures for mixers, loaders, and applicators. The following occupational handler scenarios were assessed:

- Mixing/loading liquids
- Groundboom application
- Aerial application
- Mixing, loading, and applying by backpack sprayer
- Mixing, loading, and applying by manually-pressurised hand wand (MPHW)
- Mixing, loading, and applying by mechanically-pressurised hand gun (MPHG)
- Treating potato seed pieces with a liquid
- Cutting/sorting of potato seed pieces prior to treatment (inhalation exposure only)
- Driving/loading of planting equipment during planting of treated potato seed pieces
- Persons in the back of planter equipment during planting of treated potato seed pieces

Based on the number of applications and the timing of application, workers handling fenamidone would generally have a short- to intermediate-term (<6 months) duration of exposure.

The exposure estimates for mixer/loaders and applicators are based on single layer (that is, baseline) PPE: Long pants, long-sleeved shirt and chemical-resistant gloves.

No appropriate chemical-specific handler exposure data were available for fenamidone. Therefore, dermal and inhalation exposure for field applications were estimated using data from the Pesticide Handlers Exposure Database (PHED) and the Agricultural Handler Exposure Task Force (AHETF).

The PHED version 1.1 is a compilation of generic mixer/loader and applicator passive dosimetry data with associated software which facilitates the generation of scenario-specific exposure estimates based on formulation type, application equipment, mix/load systems and level of personal protective equipment. The AHETF was formed in 2001 with the objective of providing more up-to-date generic exposure data to replace the data currently being used in the PHED. The open cab groundboom, open mix/load liquid, and aerial liquid application scenarios from AHETF were used. Inhalation exposures were based on light inhalation rates (17 L/min) except for the backpack sprayer, which was assessed using a moderate inhalation rate (27 L/min). While there are limitations in the use of generic data, these exposure data represent the most reliable information currently available.

Fenamidone is registered for potato seed piece treatment. PHED and AHETF scenarios were not considered to be representative of exposure to workers treating or handling treated potato seed pieces. Surrogate treatment and planting exposure studies were used to estimate worker exposure. These are the best data available for the assessment of worker exposure during the treatment and handling of seeds and potato seed pieces.

For foliar applications, the results of the exposure and risk assessment are outlined Appendix VI, Table 1. Calculated MOEs for mixer/loaders and applicators of fenamidone exceeded target MOEs for all scenarios and risks were shown to be acceptable under the current conditions of use. No additional mitigation measures are proposed for these uses.

For potato seed piece treatment, the results of the treater and planter exposure and risk assessments are outlined in Appendix VI, Table 2. For all scenarios, except workers on the back of planting equipment, calculated MOEs were greater than the target MOE at single layer PPE and risks were shown to be acceptable. For planting, a closed cab is required to reflect the conditions of the exposure study. For the back of planter activity, MOEs were below the target MOE and risks were not shown to be acceptable at single layer PPE; however, potential risks are mitigated if coveralls over single layer PPE are worn

3.4.2.2 Postapplication worker exposure and risk assessment

The postapplication occupational risk assessment considered exposures to workers entering treated sites to conduct agronomic activities involving contact with treated foliage (for example, hand harvesting). For agricultural workers, there is potential for short- (1–30 days) to intermediate-term (30 days to 6 months) postapplication exposure when entering crops previously treated with a foliar spray.

Potential dermal exposure to postapplication workers was estimated using activity-specific transfer coefficients (TCs) and dislodgeable foliar residue (DFR) data. DFR refers to the amount of residue that can be dislodged or transferred from a surface, such as leaves of a plant. The TC is a measure of the relationship between exposure and DFRs for individuals engaged in a specific activity and is calculated from data generated in field exposure studies. The TCs are specific to a given crop and activity combination (for example, hand harvesting apples, scouting late season corn) and reflect standard agricultural work clothing worn by adult workers.

Activity-specific TCs from the Agricultural Re-Entry Task Force (ARTF) were used. For more information about estimating worker post application exposure, refer to Health Canada's Regulatory Proposal PRO2014-02, *Updated Agricultural Transfer Coefficients for Assessing Occupational Exposure to Pesticides*.

Three chemical-specific DFR studies were available for fenamidone. They were conducted on cantaloupe, brassica crops (broccoli, cauliflower and mustard greens) and grape. Foliage type has been observed to have an effect on peak DFR⁵. In general, hairy leaf crops tended to have higher peak DFR, smooth leaves with lower peak DFR, and even lower peak DFR for waxy leaf crops. The hairy leaves capture and retained droplets more effectively than waxy leaves, where the droplets tended to bead off. The most appropriate site(s) from the cantaloupe and brassica studies were selected to estimate DFR for registered Canadian agricultural crops based on a comparison of foliage types, application regime, study conditions, and climatic zones.

⁵ Analysis conducted for the development of the ARTF Transfer Coefficient database
<https://www.regulations.gov/document/EPA-HQ-OPP-2008-0673-0007>

Some study sites were not used due to major limitations, typically associated with rainfall. The grape study was not used, as trellis crops are not part of the registered use pattern and the dissipation rates were unreliable due to major rain events.

For field crops with hairy foliage, the peak DFR values of 32% of the application rate after 2 applications and 46% after 4 applications, with a dissipation rate of 6% per day were selected from the cantaloupe DFR study. For field crops with smooth foliage, the peak DFR of 41% of the application rate per application, with a dissipation rate of 16% per day was selected from the brassica DFR study, mustard green site. For field crops with waxy foliage, the peak value of 6% of the application rate per application was selected from the brassica DFR study, broccoli site with a standard dissipation rate of 10% per day as there was uncertainty with the study dissipation rates due to rain events. The standard dissipation rate is slower than that observed in the study and is not expected to underestimate foliar residues. For further information on this standard value, refer to Science Policy Note SPN2014-02, *Estimating Dislodgeable Foliar Residues and Turf Transferable Residues in Occupational and Residential Postapplication Exposure Assessments*.

Table 1 in Appendix VII summarizes the postapplication exposure and risk assessment including the REIs determined for each crop and activity combination. Risks are shown to be acceptable provided that the proposed REIs are followed. REIs range from 12 hours to 4 days and are considered to likely be agronomically feasible.

3.4.3 Non-occupational exposure and risk assessment

Non-occupational (residential) risk assessment involves estimating risks to the general population, including youth and children, during or after pesticide application.

Based on the registered use pattern, residential exposure is not expected. There is a potential for exposure to bystanders during outdoor agricultural applications. To minimize the potential for bystander exposure, the commercial-class product label currently includes a standard spray drift statement. An additional drift statement specifically for potato seed piece treatment is proposed to be added to the label. No additional mitigation measures are proposed.

3.5 Aggregate exposure and risk assessment

Aggregate exposure is the total exposure to a single pesticide that may occur from dietary (food and drinking water), residential and other non-occupational sources, and from all known or plausible exposure routes (oral, dermal, and inhalation). For fenamidone, the aggregate assessment consisted of combining food and water exposure only (see Sections 3.2.2 and 3.2.4), since residential exposure is not expected to occur. The most relevant toxicological endpoints and assessment factors for acute and chronic aggregate exposure are the same as those selected for the ARfD (see Section 3.2.1) and ADI (see Section 3.2.3), respectively. Aggregate exposure and risks for fenamidone from food and drinking water are shown to be acceptable (see Sections 3.2.2 and 3.2.4).

3.6 Cumulative assessment

The *Pest Control Products Act* requires that Health Canada consider cumulative exposure to pesticides with a common mechanism of toxicity. Accordingly, an assessment of potential common mechanisms of toxicity with other pest control products was undertaken for fenamidone.

Fenamidone belongs to the imidazolinone structural class of fungicides, for which it is the only member. The fungicidal mode of action consists of fenamidone binding to the Q_o site of complex III to inhibit mitochondrial electron transfer. Other pesticides with the same fungicidal mode of action include famoxadone and the strobilurin fungicides (for example, pyraclostrobin, azoxystrobin, kresoxim-methyl, trifloxystrobin, fluoxastrobin, and picoxystrobin). Common apical endpoints following exposure to strobilurins include non-specific changes to body weights and organ weights, including the liver.

Based on the above, Health Canada did not identify information indicating that fenamidone shares a common mechanism of mammalian toxicity with other pest control products and it does not appear to produce a toxic metabolite common with other pest control products.

3.7 Health incident reports

As of 11 February 2026, no human or domestic animal incidents involving fenamidone had been submitted to Health Canada.

4.0 Environmental assessment

4.1 Fate and behaviour in the environment

The fate and behaviour of fenamidone was previously assessed and presented in Regulatory Note REG2003-11 and Proposed Registration Decision PRD2007-07.

The fate and behaviour of fenamidone and its transformation products in the environment are summarized in Appendix VIII, Table 1. A summary of the transformation products of fenamidone detected in the environmental fate studies is provided in Appendix VIII, Table 2. A summary of the leaching assessment for fenamidone is provided in Appendix VIII, Table 3.

Fenamidone will be introduced to the environment when applied as a foliar spray on a large variety of crops, or as a seed piece treatment for potatoes. Fenamidone has limited localized systemic activity, and when applied as a seed piece treatment, is not expected to move upward through the plant or reach pollen and nectar. The primary routes of exposure are from spray drift and runoff.

The abiotic processes of hydrolysis of fenamidone and phototransformation in soil are not important routes of dissipation into the environment at neutral pH levels. However, the abiotic process of phototransformation in water is an important route of dissipation for fenamidone in the environment. Biotransformation in aerobic terrestrial and aquatic environments is also an important dissipation pathway for fenamidone. Fenamidone is non-persistent in soils but moderately persistent in aquatic systems. Depending on the soil or aquatic system, biotransformation of fenamidone may result in mineralization to CO₂ and residues that are strongly bound to soil or sediment. From the laboratory data, fenamidone has moderate mobility in soils with transformation products having a higher mobility than the parent in most examples.

The major transformation products of fenamidone identified in soil and aquatic systems are RPA 410193, RPA 413350, RPA 412636, RPA 412708, RPA 413255, RPA 411639, RPA 221607, RPA 418915 and RPA 221701.

Terrestrial field dissipation studies show that fenamidone dissipates relatively rapidly, demonstrating agreement between laboratory and field degradation rates and an unlikelihood for fenamidone to accumulate and carry over into the next growing season. Fenamidone was not detected below a soil depth of 30 cm, and major transformation products were not detected at concentrations above the limit of quantification below a soil depth of 30 cm, suggesting limited movement downward through the soil of both. Overall, taking into consideration results of laboratory studies, assessments using groundwater ubiquity scores (GUS) and the criteria of Cohen et al. (1984), and field studies, fenamidone and its residues are expected to have limited potential to leach to groundwater.

In addition, as part of the re-evaluation, one environmental aspect of concern identified in the 2018 EU decision under the Canadian context was potential for groundwater leaching by the metabolite RPA 412708. The leaching and “groundwater contamination” potential of RPA 412708 was determined to be low. Overall, despite some laboratory indicators suggesting potential high mobility, the field evidence does not show significant leaching of RPA 412708 to groundwater under the tested conditions. RPA 412708 was included in the residue definition for drinking water and its potential concentrations in groundwater were accounted for in water modelling for use in the drinking water component of the aggregate dietary risk assessment for human health.

Based on its low vapour pressure and Henry’s law constant, fenamidone is not expected to volatilize from water, moist soil, or vegetation to air. Long-range atmospheric transport is also unlikely.

Fenamidone and the major transformation products are not expected to bioaccumulate based on the log K_{ow} values.

4.2 Environmental risk characterization

An environmental risk assessment was conducted as described in the guidance document Health Canada’s Approach to Environmental Risk Assessment for Pest Control Products to estimate the potential for adverse effects on non-target species. Environmental exposure and ecotoxicology information were integrated by comparing estimated environmental concentrations (EECs) to effects-based values used to assess risk (effects metrics). EECs were estimated using standard models that consider application rate(s) and chemical and environmental fate properties, including pesticide dissipation between applications. The EECs used in this risk assessment are presented in Appendix VIII, Table 4.

Acute and chronic ecotoxicological data for non-target terrestrial, freshwater and estuarine/marine organisms are summarized in Appendix VIII, Table 5. In the risk assessment, toxicity endpoints were adjusted via an uncertainty factor (UF) to calculate the effects metrics. The effects metrics account for potential differences in species sensitivity as well as varying protection goals (in other words, protection at the community, population or individual level).

Initially, a screening level risk assessment was performed using simple methods, conservative exposure scenarios and sensitive effects metrics. A risk quotient (RQ) was calculated by dividing the EEC by the effects metric and was then compared to the applicable level of concern (LOC). When the screening level RQ was below the LOC, the risk was acceptable, and no further risk

characterization was necessary. When the screening level RQ was equal to or greater than the LOC, a refined risk assessment was performed to further characterize the risk.

The refined risk assessment considered additional effects metrics as well as more realistic exposure scenarios, including spray drift, runoff, and available water monitoring data. Refinements to the risk assessment continued until the risk was adequately characterized or the available data did not permit further refinements.

4.2.1 Risks to terrestrial organisms

Terrestrial organisms, such as earthworms, invertebrates, bees, birds, small wild mammals, and terrestrial vascular plants may be exposed to fenamidone through direct contact with spray or spray drift, contact with sprayed surfaces, or from ingestion of contaminated food. A risk assessment for fenamidone, its major transformation products (TPs) and its formulation, was conducted for terrestrial organisms based on available toxicity data. Screening level RQs were calculated based on the maximum application rate. The screening level risk assessment is presented in Appendix VIII, Table 6, for terrestrial organisms other than birds and small wild mammals, and Appendix VIII, Table 9, for birds and small wild mammals.

Earthworms and other soil invertebrates

Fenamidone was not toxic to earthworms and collembola on an acute or chronic basis at a concentration as high as 25 mg a.i./kg soil dw. The RQs for earthworms resulting from acute and chronic exposure to fenamidone or selected major TPs did not exceed the LOC at the screening level. When used according to label directions, the risk to earthworms from use of fenamidone is acceptable (Appendix VIII, Table 6).

Predators and parasitoids (beneficial arthropods)

Screening level risk assessment

Beneficial arthropods could be exposed to fenamidone when it is applied to crops, resulting in exposure to spray droplets during application or exposure to residues on plant or soil surfaces.

Fenamidone is not toxic to soil-dwelling beneficial arthropods at a concentration as high as 45.1 mg a.i./kg soil dw. The RQs for the predatory mite, *Hypoaspis aculeifer*, exposed to fenamidone or selected TPs did not exceed the LOC at the screening level. When used according to label directions, the risk to soil-dwelling beneficial arthropods from use of fenamidone is acceptable.

Foliage-dwelling beneficial arthropods could also be exposed to fenamidone spray droplets during application and to residues on plant surfaces. The RQs for both the standard foliar-dwelling species *Typhlodromus pyri* and *Aphidius rhopalosiphii* exceeded the on-field LOC at the screening level. The maximum application rate for ground boom application to various brassica crops was used as the screening level EEC. The risk to foliar-dwelling beneficial arthropods was further characterized using results from extended laboratory toxicity studies, and by adjusting the amount of exposure on-field and off-field by considering deposition fractions and vegetation distribution factors. The on-field EEC was calculated to be 662.2 g a.i./ha (using the highest rate of 300 g a.i./ha, 3 applications with a 5-day re-application interval and a default DT₅₀ of 10 days for leaf

surfaces) and the off-field EEC is calculated to be 6% of this value to account for the expected drift value equal to 39.73 g a.i./ha (Appendix VIII, Table 6).

Refined risk assessment

The refined risk assessment further characterized the risks to better reflect more realistic on-field and off-field exposure using the maximum rate for different application methods: ground boom application to various brassica crops and aerial application on potatoes. The on-field EEC for ground boom application was calculated by applying foliar interception factors to the screening level values. The on-field EEC for aerial application on potatoes was calculated to be 246 g a.i./ha (using the highest rate of 100 g a.i./ha, 6 applications with a 7-day re-application interval and a default DT₅₀ of 10 days for leaf surfaces) with different foliar interception factors applied and the off-field EEC is calculated to be 17% of this value to account for the expected drift value equal to 41.82 g a.i./ha.

The refined on-field risks to both species of foliage-dwelling beneficial arthropods exceeded the LOC for most of the crop-specific foliar interception scenarios (RQs <0.2 to <66). However, the off-field risk to *T. pyri* for both use scenarios (RQ <0.3) did not exceed the LOC. There were some off-field LOC exceedances for *A. rhopalosiphi* for the foliar application (RQ <4.0) and for the aerial application use (RQ <4.2) (Appendix VIII, Table 7).

The refined risk assessment used a study that tested spray residues on fully grown barley plants to characterize the risk to *A. rhopalosiphi*. This study did not allow for crop-specific foliar interception factors to be applied in the same manner as for other studies that examined spray residues on small leaf discs cut from plant material. Additionally, a default 10-day half-life value was used in the risk assessment to account for potential dissipation between applications of fenamidone. However, it is possible that the dissipation of residues could be faster or that rain could lower residues and exposure under actual field conditions. As a result of using this study and the default 10-day half-life, the EECs calculated overestimated exposure.

Since the off-field RQs for *T. pyri* (RQ <0.3) were all less than the LOC, and that only half of the available off-field RQs for *A. rhopalosiphi* exceeded the LOC (RQ <4.0 and <4.2) with an overestimation of exposure, it is expected that repopulation and/or recovery of foliage-dwelling beneficial arthropods would occur adjacent to treated fields.

Potential on-field effects were identified in the refined risk assessment for both species of foliage-dwelling beneficial arthropods where the RQ values exceeded the LOC (Appendix VIII, Table 7). Therefore, based on the available information, fenamidone is not considered compatible with certain beneficial arthropods in integrated pest management programs (IPM). In IPM, parasitic wasps such as *A. rhopalosiphi* are known to control a variety of pests, including aphids, caterpillars, whitefly, mealybugs and scales, stink bugs and leaf miners. The specific pests they target may vary depending on the species of parasitic wasp. Predatory mites such as *T. pyri* are used to control various pests, with spider mites, thrips, and whiteflies being among the most common prey. While some species specialize on specific pests, others are polyphagous, meaning they can feed on a wider range of insects and mites. Although there may be some overlap in the function between predators and parasitoids (in other words, if one group declines in numbers, there may be other less susceptible groups that may increase in population owing to increased food availability), there also appears to be some unique pests for parasitic wasp species that are

different than predatory mites, and result in impacting an IPM program depending on the target pest. To mitigate the potential on-field exposure of beneficial arthropods to fenamidone, all product labels must include precautionary statements indicating that fenamidone is toxic to certain beneficial arthropods and advise users that fenamidone may affect IPM programs that rely on the presence of beneficial arthropods.

Pollinators

Foraging bees may be exposed to fenamidone spray droplets during application (contact exposure) or through the ingestion of pollen and nectar contaminated with fenamidone (oral exposure). Additionally, immature and adult bees inside colonies may be exposed to fenamidone residues if foraging bees bring contaminated pollen and nectar back to the hive. This compound is only locally systemic and transport to nectar and pollen would be unlikely at significant concentrations. As such, there is little exposure expected from pre-bloom applications.

The pollinator risk assessment is conducted according to the *Guidance for Assessing Pesticide Risks to Bees* which uses a tiered approach in which the screening level risk assessment (Tier I) uses the most conservative assumptions. Tier II and Tier III use progressively more realistic assumptions. The screening level risk assessment considers the most relevant and conservative toxicity endpoints from laboratory studies. Individual flowers generally only bloom for a short period of time. Therefore, it is unlikely that the same forager bee would be exposed to a flower that was sprayed with fenamidone multiple times. Given this, the screening level risk assessment evaluates risk to bees using the maximum single spray application rate (300 g a.i./ha) to estimate the highest potential exposure. The most sensitive acute and chronic endpoints for adults and larvae were used in the risk assessment. It is noted that in the risk assessment, repeat exposure studies are preferred over acute exposure studies for larvae as they represent a more realistic exposure period and cover the developmental stages of the larvae.

Tier I screening level

Adult acute and chronic, and larval honey bee toxicity tests are available for fenamidone. Fenamidone is classified as practically non-toxic to adult bees on an acute basis; however, at the screening level risk assessment, the RQs for chronic adult and larval toxicity exceeded the LOC (Appendix VIII, Table 7), and higher-tier studies were considered to further characterize the risks.

Further risk characterization

Tier I refined risk assessment (laboratory studies compared to residues measured in the field)

A refinement of the Tier I risk assessment is to consider the mean and maximum levels of measured residues in pollen and nectar. This is done to better characterize the oral exposure route in pollinators. Field residues of fenamidone from several crops were available from data submitted for the human health risk assessment (PRD2007-07; Appendix VIII, Table 1; p. 26).

The RQs for adult chronic toxicity did not exceed the LOC when both the mean (RQ = 0.3) and maximum (RQ = 0.7) residue values were used in the calculation. The RQ for larval chronic toxicity did not exceed the LOC with the mean residue value (RQ = 0.8) but did exceed for the maximum residue value (RQ = 2.0). Residues measured in surrogate lettuce crop at 2 days after

last application (DALA) rather than at 0 DALA could underestimate residues, which is why maximum residues were also considered even though they are less relevant for chronic exposure. However, the overall residue levels are expected to be conservative given rates were much higher (1.2 kg a.i./ha) than Canadian application rates (0.2–0.3 kg a.i./ha). As well, lettuce would be expected to have greater exposure to spray (directly spraying leaves) than pollen/nectar (within a flower/protected), and the sample timing of 2 DALA falls within the period during which bees would be foraging after spray.

Tier II risk assessment

Two Tier II studies are available for fenamidone; a 28-day semi-field tunnel study and a brood feeding study (Appendix VIII, Table 8).

The 28-day semi-field tunnel study evaluated the effects of Fenamidone SC 500, applied to flowering *Phacelia tanacetifolia*, on foraging honey bees. Fenamidone SC 500 was applied at a rate of 150 g a.i./ha and the honey bees were exposed in the tunnel structure for 7 days, followed by a 21-day observation period. There were no adverse effects seen in honey bee adults or brood; however, there is uncertainty when comparing these results to the Canadian use pattern, as the study was conducted at a lower rate than the single highest registered Canadian rate (300 g a.i./ha) on a bee-attractive crop.

In the brood feeding study, the effects of Fenamidone SC 500 fed in sucrose to adult and larval bees was examined. Fenamidone SC 500 was applied at a feeding rate of 150 ppm (0.15 g a.i./L) to late winter bees to ensure the bees were feeding due to a lack of flowering crops or weeds. There were no adverse effects on adults, young or old larvae or on pupae termination. An increase in egg termination rate was observed. The oral exposure rate of 150 ppm in this study is an order of magnitude higher than the 29.4 mg a.i./kg diet (ppm) oral exposure estimate used for pollen and nectar in the screening level assessment. As such, negligible risk is expected.

Tier II refined (sucrose feeding study effects compared to residues measured in the field)

A refinement of the Tier II risk assessment is to compare the same mean and maximum levels of measured residues in pollen and nectar used in the Tier I refinement, against the Tier II risk assessment exposure values. By comparing the surrogate mean (6.81 ppm) and maximum (17.5 ppm) measured pollen and nectar values to the exposure level used in the sucrose feeding study (150 ppm), the results show that the measured values from the field trials where label rates were applied are orders of magnitude lower than the exposure level used in the Tier II brood feeding study. At the elevated exposure rate of 150 ppm, effects were seen on the egg termination rate; however, this comparison indicates that there is a low potential for field-level exposure to become high enough to result in similar negative effects to pollinators.

Overall conclusions for risk to pollinators

When all pollinator-related information is considered using a weight-of-evidence approach, use of fenamidone in accordance with label directions results in acceptable risk to pollinators. No mitigation measures are required on the label for pollinators.

Birds

The screening level RQs did not exceed the LOC for acute or chronic exposure to fenamidone or one of its transformation products for any feeding guilds of birds. The risks to birds are acceptable when fenamidone is used according to label directions (Appendix VIII, Table 9).

Mammals

Screening level risk assessment

For wild mammals, the acute RQs for fenamidone, and the TPs RPA 410193 and RPA 412636 did not exceed the LOC (Appendix VIII, Table 9). However, the LOC was exceeded for acute risk associated with the TP RPA 412708 and for chronic reproductive risk to all small-, medium-, and large-sized wild mammals. The screening level risk assessment considered maximum on-field nomogram residues. Therefore, the acute and chronic risks identified for small wild mammals from exposure to fenamidone were further characterized considering on- and off-field exposure, maximum and mean residues, and the amount of contaminated diet required to be consumed to reach the LOC for both foliar application to brassica crops and aerial application on potato.

Further risk characterization

Further characterizing the acute and chronic risks to small mammals associated with foliar application indicated that on-field chronic RQs for fenamidone exceeded the LOC for most feeding guilds (RQ range: 1.2–7.9), whereas no exceedances were identified for off-field exposures. For acute exposure to the TP RPA 412708, the on-field RQ exceeded the LOC for one feeding guild (insectivore) (RQ = 1.2 for mean residues and 1.7 for maximum residues, whereas off-field RQs did not exceed the LOC (Appendix VIII, Table 10).

Further characterizing the acute and chronic risks to small mammals associated with aerial application indicated that on-field chronic RQs for fenamidone exceeded the LOC for one feeding guild (insectivore) (RQ = 2.0 for mean residues and 2.9 for maximum residues), whereas no exceedances were identified for off-field exposures. For acute exposure to the TP 412708, the on-field RQ based on maximum residues exceeded the LOC for the insectivore feeding guild (RQ = 1.1), whereas off-field RQs did not exceed the LOC (Appendix VIII, Table 11).

Where the RQs for small wild mammals exceed the LOC following further risk characterization, additional factors related to the risk assessment methodology should be considered. Most on-field values are derived using conservative assumptions that are unlikely to represent realistic exposure conditions for wild mammals under natural foraging behaviour. The potential for risk when an RQ is above the LOC would assume that organisms are being exposed to residues on food items at levels equivalent to those present immediately after application and, in the case of the TP, without dissipation between applications. In addition, the assessment assumes that mammals within specific feeding guilds consume a single food item that is 100% contaminated (for example, small insects or grains/seeds) exclusively within the treated area. This scenario is unlikely, as wild mammals forage over wider areas and consume a mixed diet over the course of a feeding day. Given these conservative assumptions, it is unlikely that wild mammals would experience exposure levels sufficient to result in realistic risks of concern. Therefore, risks to wild mammals are considered acceptable, and no precautionary label statement is required.

Terrestrial vascular plants

In the seedling emergence and vegetative vigour studies with a fenamidone end-use product, little or no effect on the germination, emergence, and survival of ten plant species was observed up to the maximum application rate tested (1200 g a.i./ha). The calculated RQs did not exceed the LOC at the screening level. The risk to terrestrial vascular plants from use of fenamidone has been determined to be acceptable (Appendix VIII, Table 6).

4.2.2 Risks to aquatic organisms

Aquatic organisms, such as invertebrates, fish, amphibians and aquatic plants, could be exposed to fenamidone if spray drift or runoff enter aquatic habitats. A risk assessment for fenamidone, its formulation, and its TP was conducted for freshwater and estuarine/marine organisms based on available toxicity data. Screening level RQs were calculated based on the maximum application rate and assuming a direct overspray onto water surfaces. For groups where the risk quotient exceeds the LOC, a refined assessment is conducted to determine risk resulting from spray drift and runoff separately. The screening level and refined RQs are summarized in Appendix VIII, Tables 12–14.

The screening level RQs associated with the use of fenamidone did not exceed the LOC for freshwater vascular plants, some freshwater invertebrates and estuarine/marine fish. However, the screening level RQs did exceed the LOC for most of the freshwater invertebrates, freshwater fish, amphibians, and estuarine/marine invertebrates; therefore, further characterization of the risk was conducted.

The screening level RQ for green alga exposed to the TP RPA 413350 exceeded the LOC. However, this calculation is based on the highly conservative assumption that 100% of the TP would be directly applied to water with no degradation over time. The fate data indicates that this TP would not likely be present at high enough levels in water to be toxic to aquatic organisms under natural conditions. Therefore, the risk to algae from potential exposure to the TP RPA 413350 has been determined to be acceptable.

In addition, as part of the re-evaluation, the second environmental aspect of concern identified in the 2018 EU decision under the Canadian context was high risk to aquatic organisms from exposure to the metabolite acetophenone. Acetophenone is considered practically non-toxic to aquatic organisms, and, based on its chemical structure, it is expected to break down rapidly in the environment (see Appendix VIII, Table 5). No further review was required.

Further risk characterization

The risk to aquatic organisms from fenamidone was further characterized taking exposure from spray drift and runoff into consideration Appendix VIII, Tables 13 and 14.

Refined aquatic risk assessment from exposure to spray drift

Spray drift data were used to determine the maximum spray deposit into an aquatic habitat located 1 metre downwind from a treated field. The refined EECs were calculated for field sprayer (ground boom application on Brassica crops), and aerial applications (potato). The maximum

percent drift deposition for ground boom application using a medium droplet size is 6% and for aerial application for crops using a coarse droplet size is 17%.

For spray drift, the RQs for freshwater and estuarine/marine invertebrates and fish did not exceed the LOC. The RQ for chronic risks to amphibians exceeded the LOC (Appendix VIII, Table 13). To mitigate the potential exposure of amphibians to fenamidone spray drift, an aquatic spray buffer zone of 1 m and mitigative label statements informing users of the potential toxicity of fenamidone to aquatic organisms will be required. When used in accordance with label directions and prescribed risk mitigation measures, risks to aquatic organisms from spray drift of fenamidone are considered acceptable.

Refined aquatic risk assessment from exposure to runoff

Runoff can occur with compounds that are soluble in water (runoff with flow of water) or adsorbed to soil (soil-particle movement in runoff water). Both can enter aquatic systems in runoff and pose a risk to either free-swimming or sediment-dwelling organisms.

Modelled EEC values were used to assess risk of fenamidone due to runoff. The refined EECs were calculated for two different water depths, 80 cm (represents a permanent water body) and 15 cm (represents a seasonal water body used by aquatic-phase amphibians) and for two maximum application rate scenarios. The maximum foliar application scenario was based on 3 applications of 300 g a.i./ha on brassica crops in the PEI regional scenario. The maximum aerial application scenario was based on 152.75 g a.i./ha seed piece treatment plus 6 aerial applications of 100 g a.i./ha on potatoes in the PEI regional scenario.

For runoff, the RQs based on modelled EECs for some species of freshwater and estuarine/marine invertebrates, one species of freshwater fish, amphibians and estuarine/marine algae exceeded the LOC (Appendix VIII, Table 14). Where the aquatic organism RQs exceed the LOC after further risk characterization there are other factors with the risk assessment methods to consider. The EEC modelling approach incorporates several assumptions intended to provide protective (upper-bound) estimates of surface water exposure. Conservatism arises from four main sources: residue definition, fate inputs, model structure, and scenario selection.

Taken together, these assumptions are expected to result in EECs that are protective and unlikely to underestimate exposure from runoff. The magnitude of conservatism will vary depending on substance-specific properties and the representativeness of the selected scenarios and should be considered when evaluating the need for further refinement or risk mitigation. Given the highly conservative assumptions used for fenamidone, it is unlikely there will be a high enough exposure to cause realistic risks of concerns.

Canadian surface water monitoring data for fenamidone (including data from the Canadian Water Monitoring Program for Pesticides) were available from eight provinces of Canada (5845 samples between the years 2009 and 2023), with 85% of the samples from Ontario and Quebec. Monitoring data for a TP of fenamidone only identified as “fenamidone metabolite” in surface water were only available from Quebec (2843 samples). US data (2153 samples from the years 2014–2023) were available for fenamidone in surface water but were not available for any TPs of fenamidone. The maximum detected concentration of fenamidone and fenamidone metabolite in surface water samples relevant to the aquatic risk assessment from Canada and the US were 7.2

and 0.13 µg/L, respectively. Detection limits ranged from 0.005–0.12 µg/L for fenamidone and from 0.001 to 0.013 µg/L for fenamidone metabolite, over all monitoring programs. The overall detection frequency of fenamidone and fenamidone metabolite was 6.9% and 3.6%, respectively. Information confirming use of fenamidone occurred in the areas sampled was not available. Without this information, it is difficult to interpret results for non-detections, which represent approximately 94% of the samples available for fenamidone. Due to the absence of pesticide use information, the available water monitoring data were not used in the aquatic risk assessment for fenamidone and its transformation products.

To mitigate the identified risk to aquatic organisms from runoff, standard label statements informing users of best management practices to reduce runoff into adjacent aquatic habitats and a precautionary label statement informing users of the potential toxicity of fenamidone to aquatic organisms will be required. When used according to label directions and best management practices, the risks to aquatic organisms from runoff of fenamidone and its transformation products are acceptable.

4.2.3 Environmental incident reports

As of 8 May 2026, no environmental incident reports involving fenamidone have been submitted to Health Canada. As of 2015, one incident involving the use of fenamidone was reported in the USEPA's Ecological Incident Information System (EIIIS). The incident was listed as "possible" and involved plant damage to spinach following aerial application. Application of fenamidone (as REASON 500SC) to spinach is a registered use in Canada and the US, and application can occur throughout the growing season directly to the plant. Therefore, when REASON 500SC is applied according to label directions, damage to the spinach plant would seem unlikely unless there was a misuse. Health Canada concluded that the information from the incident report is not consistent with the lack of risk to terrestrial plants observed at the screening level risk assessment.

4.3 Toxic substances management policy considerations

The Toxic Substances Management Policy (TSMP) is a federal government policy developed to provide direction on the management of substances of concern that are released into the environment. The TSMP calls for the virtual elimination of Track 1 substances, in other words, those that meet all four criteria outlined in the policy: persistent (in air, soil, water and/or sediment), bio-accumulative, primarily a result of human activity, and toxic as defined by the *Canadian Environmental Protection Act*. The *Pest Control Products Act* requires that the TSMP be given effect in evaluating the risks of a pest control product.

During the review process, fenamidone and its transformation products were assessed in accordance with the PMRA Regulatory Directive DIR99-03⁶ and evaluated against the Track 1 criteria. Health Canada has reached the conclusion that fenamidone and its transformation products do not meet all of the TSMP Track 1 criteria.

Please refer to Appendix VIII, Table 15 for further information on the TSMP assessment.

⁶ DIR99-03, *The Pest Management Regulatory Agency's Strategy for Implementing the Toxic Substances Management Policy*

4.3.1 Formulants and contaminants of health or environmental concern

During the review process, contaminants in the active ingredient as well as formulants and contaminants in the end-use products are compared against Parts 1 and 3 of the *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern*.⁷ The list is used as described in the Science Policy Note SPN2020-018 and is based on existing policies and regulations, including the Toxic Substance Management Policy and *Formulants Policy*,⁹ and taking into consideration the Ozone-depleting Substances and Halocarbon Alternatives Regulations under the *Canadian Environmental Protection Act, 1999*, (substances designated under the *Montreal Protocol*).

Health Canada has reached the conclusion that fenamidone and its end-use product Reason 500SC do not contain any formulants or contaminants identified in the *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern*.

The use of formulants in registered pest control products is assessed on an ongoing basis through Health Canada formulant initiatives and Regulatory Directive DIR2006-02.

5.0 Value assessment

Fenamidone is a preventative, protectant fungicide registered to manage diseases on basil, carrot, brassica, bulb and cucurbit vegetables, ginseng, edible-podded and succulent shelled beans, potato, tomato, turnip greens, spinach, and tobacco. For some crops and diseases (*Phytophthora* blight on edible-podded and succulent shelled beans, and seed-borne late blight on potato) there are limited number of alternatives, therefore fenamidone is considered to be a tool for resistance management.

When used as a seed piece treatment on potato seeds infected with late blight, fenamidone increases levels of emergence and may prevent the spread of late blight spores when handling and planting seed pieces. The ability to tank mix fenamidone provides users with the ability to increase the spectrum of diseases controlled with a single seed treatment application.

With the exception of potatoes, tomatoes, and turnip greens, fenamidone was registered for use on all other labelled crops under the User Requested Minor Use Label Expansion program, and as such is important to the minor use community.

⁷ SI/2005-114, last amended on June 24, 2020. See Justice Laws website, Consolidated Regulations, *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern*.

⁸ PMRA's Science Policy Note SPN2020-01, *Policy on the List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern under paragraph 43(5)(b) of the Pest Control Products Act*

⁹ DIR2006-02, *Formulants Policy and Implementation Guidance Document*

List of abbreviations

%	percent
>	greater than
≥	equal to or greater than
↑	increased
↓	decreased
♀	female
♂	male
1/H	reciprocal of Henry's law constant
λ	wavelength
μg	microgram
μM	micromolar
°C	degrees centigrade
a.i.	active ingredient
abs	absolute
AC ₅₀	half-maximal activity concentration
AD	administered dose
ADI	acceptable daily intake
ADME	absorption, distribution, metabolism and elimination
AHETF	Agricultural Handler Exposure Task Force
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AOPWIN	Atmospheric Oxidation Program for Microsoft Windows
AR	applied radioactivity
ARfD	acute reference dose
ARTF	Agricultural Re-entry Exposure Task Force
AST	aspartate aminotransferase
atm	atmosphere
ATP	adenosine triphosphate
BAF	bioaccumulation factor
BCF	bioconcentration factor
BROD	7-benzyloxyresorufin O-dealkylase
bw	body weight
bwg	body weight gain
CAF	composite assessment factor
CAS	Chemical Abstracts Service
CEPA	Canadian Environmental Protection Act
cm	centimetres
cm ³	cubic centimetre(s)
d	day(s)
DACO	data code
DFR	dislodgeable foliar residue
DIR	directive
DMSO	dimethyl sulfoxide
DNA	deoxyribonucleic acid
DNT	developmental neurotoxicity

DT ₅₀	dissipation time 50% (the dose required to observe a 50% decline in concentration)
dw	dry weight
EDE	estimated daily exposure
EEC	estimated environmental concentration
EFSA	European Food Safety Authority
EPI	Estimation Programs Interface
ER ₂₅	effective rate for 25% of the population
ER ₅₀	effective rate for 50% of the population
ETC	electron transport chain
F ₁	first generation
F ₂	second generation
fc	food consumption
fe	food efficiency
FIR	food ingestion rate
FOB	functional observational battery
g	gram(s)
g/L	grams per litre
GD	gestation day
GLP	Good Laboratory Practice
GUS	groundwater ubiquity score
ha	hectare(s)
Hb	hemoglobin
Hct	hematocrit
HDL	high density lipoprotein
HDT	highest dose tested
hr(s)	hour(s)
IC ₅₀	inhibitory concentration at 50%
IgM	immunoglobulin M
IORE	indeterminate order rate equation
IPM	integrated pest management
IUPAC	International Union of Pure and Applied Chemistry
IVB	<i>in vitro</i> battery
JMPR	Joint FAO/WHO Meeting on Pesticide Residues
K _d	absorption coefficient
kg	kilogram(s)
K _{oc}	organic-carbon partition coefficient
K _{ow}	<i>n</i> -octanol-water partition coefficient
K _{owWIN}	K _{ow} for Windows
L	litre(s)
LC ₅₀	lethal concentration 50%
LD	lactation day
LD ₅₀	lethal dose 50%
LDH	lactate dehydrogenase
LDL	low density lipoprotein
LOAEL	lowest observed adverse effect level
LOC	level of concern
Log K _{ow}	Octanol-water partition coefficient

LOO	limits of quantification
LR ₅₀	lethal rate 50%
M	molar
m ³	cubic metre(s)
MAS	maximum average score
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
mg	milligram(s)
MIS	maximum irritation score
mL	millilitre
M/L/A	mixer/loader/applicator
MOA	mode of action
MOE	margin of exposure
mol	mole
MPHG	mechanically-pressurized hand gun
MPHW	manually-pressurized hand wand
MRID	US Master Record Identification Number
MRL	maximum residue limit
N/A	not applicable
NCE	normochromatic erythrocyte
NIS	sodium/iodide symporter
NOAEL	no observed adverse effect level
NOAEC	no observed adverse effect concentration
NOEC	no observed effect concentration
OC	organic carbon content
OECD	Organisation for Economic Co-operation and Development
OH	hydroxyl radical
P	parental generation
PCE	polychromatic erythrocyte
PCNA	proliferating cell nuclear antigen
PCPA	<i>Pest Control Products Act</i>
PHED	Pesticide Handles Exposure Database
PHI	preharvest interval
pKa	dissociation constant
PMRA	Pest Management Regulatory Agency
PND	postnatal day
PPE	personal protective equipment
ppm	parts per million
PRD	Proposed registration decision
PROD	7-pentoxoresorufin O-dealkylase
PRVD	Proposed Re-evaluation Decision
PTU	propylthiouracil
Q _o	quinone outside inhibitor
RBC	red blood cells
REI	restricted-entry interval
rel	relative
RQ	risk quotient
SFO	single first order

SPN	science policy note
SRBC	sheep red blood cells
$t_{1/2}$	half-life
T3	tri-iodothyronine
T4	thyroxine
TC	transfer coefficient
TG	test guideline
TID	thermoionic detection
$T_{\max}$	time to maximum concentration
TP	transformation product
TPO	thyroid peroxidase
tR	representative half-life
TSH	thyroid stimulating hormone
TSMP	Toxic Substances Management Policy
UDP-GT	uridine glucuronosyl transferase
UF	uncertainty factor
USEPA	United States Environmental Protection Agency
UV	ultraviolet
WBC	white blood cells
wt	weight

Appendix I Registered products containing fenamidone in Canada¹**Table 1 Products containing fenamidone subject to proposed label amendments**

Registration number	Marketing class	Registrant	Product name	Formulation type	Active ingredient (% , g/L)
27461	Technical	Gowan Company, L.L.C.	Fenamidone Technical Fungicide	Solid	99%
27462	Commercial	Gowan Company, L.L.C.	Reason 500SC Fungicide	Suspension	500 g/L

¹ As of 22 June 2026, excluding discontinued products or products with a submission for discontinuation .

Appendix II Registered uses of Fenamidone in Canada¹

Table 1 Registered commercial uses of fenamidone in Canada

Site	Pest(s)	Formulations	Application method and equipment	Maximum single application rate (g a.i./ha)	Maximum cumulative application rate per year	Maximum number of applications per year (g a.i./ha)	Minimum interval between applications (days)
Use-site category 10 – Seed and plant propagation materials food and feed							
Potato	Seed-borne late blight (<i>Phytophthora infestans</i>)	Suspension	Seed treatment Not stated	96–153	153	1	N/A
Use-site category 14 – Terrestrial food crops							
Basil	Downy Mildew (<i>Peronospora belbarhii</i>)	Suspension	Foliar Ground: (boom sprayer)	200	800	4	7
Broccoli; Brussels sprouts; Cabbage; Cabbage, Chinese, Napa; Cauliflower and Kohlrabi	Downy mildew (<i>Peronospora parasitica</i>) (suppression)	Suspension	Foliar Ground: (boom sprayer)	200–300	900	3	5
Leafy Greens: Arugula; Broccoli raab; Broccoli, Chinese; Cabbage, Abyssinian; Cabbage, seakale; Chinese cabbage, bok choy; Collards; Cress, garden; Cress, upland, Hanover salad, Kale; Maca, Mizuna; Mustard greens; Radish, leaves; Rape greens; Rocket,	Downy mildew (<i>Peronospora parasitica</i>) (suppression)	Suspension	Foliar Ground: (boom sprayer)	200–300	900	3	5

Site	Pest(s)	Formulations	Application method and equipment	Maximum single application rate (g a.i./ha)	Maximum cumulative application rate per year	Maximum number of applications per year (g a.i./ha)	Minimum interval between applications (days)
wild; Shepherd's purse; Watercress							
Bulb Vegetables (Crop Group 3): Garlic, great-headed garlic, leek, onion (dry bulb and green), Welch onion, shallot, chive (fresh leaves), chive (Chinese, fresh leaves), daylily (bulb), Hosta, elegans, Fritillaria (bulb and leaves), garlic (serpent), kurrat, lady's leek, Lily (bulb), wild leek, onion (Beltsville bunching), onion (Chinese bulb), onion (fresh), onion (macrostem), onion (pearl), onion (potato bulb), onion (tree tops)	Downy mildew (<i>Peronospora destructor</i>) (suppression)	Suspension	Foliar Ground: (boom sprayer)	200	800	4	5
Carrot	Damping off (<i>Pythium spp.</i>) Cavity spot (<i>Pythium spp.</i>)	Suspension	Foliar Ground: (boom sprayer)	300	600	2	7
Cucurbit crops including: Chinese cucumbers, cucumbers, gourds, pumpkin, summer squash, winter squash, citron melon,	Downy Mildew (<i>Pseudoperonospora cubensis</i>)	Suspension	Foliar Ground: (boom sprayer)	200	800	4	5

Site	Pest(s)	Formulations	Application method and equipment	Maximum single application rate (g a.i./ha)	Maximum cumulative application rate per year	Maximum number of applications per year (g a.i./ha)	Minimum interval between applications (days)
muskmelon, watermelon, cantaloupes							
Edible-podded beans: Bean (<i>Phaseolus</i> spp.) (includes runner bean, snap bean, and wax bean), Bean (<i>Vigna</i> spp.) (includes asparagus bean, Chinese longbean, moth bean, yardlong bean), Jackbean (<i>Canavalia ensiformis</i>), Sword bean (<i>Canavalia gladiata</i>)	Cottony leak (<i>Pythium aphanidermatum</i>) Phytophthora blight (<i>Phytophthora capsici</i>) (suppression)	Suspension	Foliar Ground: (boom sprayer)	300	900	3	7
Ginseng	Phytophthora blight and root rot (<i>Phytophthora cactorum</i>)	Suspension	Foliar Ground: (boom sprayer)	300	900	3	8
Kohlrabi	Downy mildew (<i>Peronospora parasitica</i>) (suppression)	Suspension	Foliar Ground: (boom sprayer)	200–300	900	3	5
Potato	Early Blight (<i>Alternaria solani</i>) Late blight (<i>Phytophthora infestans</i>)	Suspension	Foliar Ground: (boom sprayer) Aerial: fixed-wing or rotary aircraft equipment	100	600	6	7

Site	Pest(s)	Formulations	Application method and equipment	Maximum single application rate (g a.i./ha)	Maximum cumulative application rate per year	Maximum number of applications per year (g a.i./ha)	Minimum interval between applications (days)
Spinach, baby spinach	Downy mildew (<i>Peronospora farinosa</i> f. sp. <i>spinaciae</i>) (suppression)	Suspension	Foliar Ground: (boom sprayer)	200	800	4	7
Succulent shelled beans: Bean (<i>Phaseolus</i> spp.) (includes lima bean), Bean (<i>Vigna</i> spp.) (includes blackeyed pea, southern pea), Broad bean (fava bean) (<i>Vicia faba</i>)	Cottony leak (<i>Pythium aphanidermatum</i>) Phytophthora blight (<i>Phytophthora capsici</i>) (suppression)	Suspension	Foliar Ground: (boom sprayer)	300	900	3	7
Tobacco	Blue mold (<i>Peronospora tabacina</i>)	Suspension	Foliar Ground: (boom sprayer)	200–300	800	(2 at max rate and 4 at min rate)	5
Tomato	Early Blight (<i>Alternaria solani</i>) Late blight (<i>Phytophthora infestans</i>)	Suspension	Foliar Ground: (boom sprayer)	100	600	6	7
Turnip greens	Downy mildew (<i>Peronospora parasitica</i>)	Suspension	Foliar Ground: (boom sprayer)	200–300	600	2	5

¹ As of 4 March 2026, excluding discontinued products or products with a submission for discontinuation.

² All information is derived from registered product labels, except for data calculated by Health Canada which is indicated by ().

Appendix III Toxicology Information for Health Risk Assessment

Table 1 Identification of select metabolites of fenamidone

Code name (Other names)	Chemical name (IUPAC)
RPA 407213 (Fenamidone)	(5S)-5-methyl-2-methylthio-5-phenyl-3-(phenylamino)-3,5-dihydro-4H-imidazol-4-one
	Rat metabolites
(S)-RPA 412636 (Racemate = RPA 717879)	(S)-5-methyl-5-phenylimidazolidine-2,4-dione
(S)-RPA 412708 (Racemate = RPA 408056)	(S)-5-methyl-2-methylthio-5-phenyl-3,5-dihydroimidazol-4-one
Racemic RPA 409445	5-methyl-3-[(4-aminophenyl)amino]-5-phenyl-2,4-imidazolidinedione
Racemic RPA 409352	5-methyl-2-(methylthio)-3-[(4-aminophenyl)amino]-5-phenyl-3,5-dihydro-4H-imidazole-4-one
Racemic RPA 409361	5-methyl-2-(methylthio)-3-[(4-hydroxyphenyl)amino]-5-phenyl-3,5-dihydro-4H-imidazol-4-one
	Environmental metabolites
(S)-RPA 411639 (Racemate = RPA 406012)	(5S)-5-methyl-2-(methylthio)-3-(4-nitrophenyl)amino)-5-phenyl-3,5-dihydro-4H-imidazol-4-one
(S)-RPA 413255 (Racemate = RPA 410914)	(5S)-5-methyl-2-(methylthio)-3-(2-nitrophenyl)amino)-5-phenyl-3,5-dihydro-4H-imidazol-4-one
(S)-RPA 221607 (Racemate = RPA 409446)	(5S)-5-methyl-3-[(4-nitrophenyl)amino]-5-phenyl-2,4-imidazolidinedione
(S)-RPA 221701 (Racemate = RPA 410995)	(5S)-5-methyl-3-[(2-nitrophenyl)amino]-5-phenyl-2,4-imidazolidinedione
(S)-RPA 410193 (Racemate = RPA 405862)	(S)-5-Methyl-5-phenyl-3-(phenylamino)-2,4-imidazolidinedione

Table 2 Toxicology reference values for use in human health risk assessment for fenamidone

Exposure scenario	Study	Point of departure and endpoint	CAF ¹ or target MOE
Acute Dietary (all populations)	Developmental neurotoxicity study in rats	Developmental NOAEL = 93 mg/kg bw Increased size of frontal cortex (PND 21 and 75) and cerebellum (PND 75) in male offspring	1000 PCPA factor = 10-fold
	ARfD = 0.09 mg/kg bw		
Repeated Dietary (all populations)	2-generation reproductive toxicity study in rats	Offspring NOAEL = 5.2 mg/kg bw/day Decreased body weight (F1/F2) and body weight gain (F2) in offspring, and decreased brain weight in F2 female offspring	300 PCPA factor = threefold
	ADI = 0.02 mg/kg bw/day		
Short-, intermediate-and long-term dermal	2-generation reproductive toxicity study in rats	Offspring NOAEL = 5.2 mg/kg bw/day Decreased body weight (F1/F2) and body weight gain (F2) in offspring, and decreased brain weight in F2 female offspring	300 PCPA factor = threefold

Exposure scenario	Study	Point of departure and endpoint	CAF ¹ or target MOE
Short-, intermediate-and long-term inhalation	2-generation reproductive toxicity study in rats	Offspring NOAEL = 5.2 mg/kg bw/day Decreased body weight (F1/F2) and body weight gain (F2) in offspring, and decreased brain weight in F2 female offspring	300 PCPA factor = threefold
Cancer	A cancer risk assessment was not required		

¹ CAF (composite assessment factor) refers to a total of uncertainty and PCPA factors for dietary assessments; MOE refers to a target MOE for occupational and residential assessments.

² Since an oral NOAEL was selected, a dermal absorption factor of 10% was used in a route-to-route extrapolation.

³ Since an oral NOAEL was selected, an inhalation absorption factor of 100% (default value) was used in route-to-route extrapolation.

Table 3 Toxicity profile of technical fenamidone

Effects observed in both sexes are presented first followed by sex-specific effects in males, then females, each separated by semi-colons. Organ weight effects reflect both absolute organ weights and relative organ to body weights unless otherwise noted.

Note: Unless otherwise specified, studies listed in this table are considered Acceptable according to [Information Note, Determining Study Acceptability for use in Pesticide Risk Assessments](#).

Study type/Animal/ PMRA No.	Study results
Toxicokinetic studies – Fenamidone	
Absorption, Distribution, Metabolism and Excretion (ADME) Sprague-Dawley rats PMRA No. 777144, 1065335	Single low-dose (3 mg/kg bw) or high-dose (300 mg/kg bw) (suspended in methylcellulose) via oral route of ¹⁴C-fenamidone, or repeated oral low-dose of unlabelled fenamidone for 14 days, followed by a labelled dose on day 15. Radiolabelled fenamidone was rapidly and highly absorbed, distributed and excreted following oral administration in rats. Total 96 hr recoveries of the radioactivity were high for all groups (~96%–107% of the administered dose (AD)). After dosing with N-phenyl-[U-¹⁴C]-fenamidone, elimination via the feces was greater than via the urine for males. Urinary excretion was similar to, or greater than, fecal elimination for females. Fecal elimination accounted for 64.3% (single low dose) and 52.0% (repeat low dose) of the 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-¹⁴C]-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%

Study type/Animal/ PMRA No.	Study results
	(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. In bile-cannulated rats, mass balance data showed that recovery of radioactivity was greater than 92%. The majority of radioactivity was found in the bile (71–80%), followed by the urine (6–18%), with little radioactivity was present in the feces (1–4%). Biliary excretion and mass balance data indicated that systemic absorption was approximately 90–95% following a single oral low dose of either C-phenyl-[U-¹⁴C]-fenamidone or N-phenyl-[U-¹⁴C]-fenamidone, and a part of the radioactivity excreted via the bile could be reabsorbed (enterohepatic circulation) and subsequently re-excreted via the urine. Blood kinetic experiments revealed that at 3 mg/kg bw, peak concentrations of radioactivity in the blood occurred at 4 hrs post-dosing, both sexes, and at 300 mg/kg bw, peak concentrations of radioactivity in the blood occurred at 8 hrs and 24 hrs, 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 $t_{1/2}$ of elimination was estimated to be ~103 hrs in the high dose group and ~61–73 hrs for the low dose group. Tissue distribution and bioaccumulation of fenamidone were minimal; <0.66% of the AD 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. The thyroid, in particular, displayed a high tissue to plasma ratio, indicating equilibrium in favour of the thyroid with respect to plasma. Clearance from the thyroid was slower than from other organs. Metabolism of fenamidone was extensive with the numerous metabolites characterized and isolated in the feces, bile and urine (22 metabolites isolated from urine and bile, and 24 metabolites from feces). In addition to fenamidone, Phase I metabolites (hydroxylation, oxidation and reduction products) and Phase II metabolites (conjugation) were isolated. The major (>10% of AD) metabolites of fenamidone identified included racemic RPA 409352, RPA 409361, RPA 408056 (S-enantiomer RPA 412708) and RPA 717879 (S-enantiomer RPA 412636). 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. Higher amount of parent fenamidone 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 toxicity studies - Fenamidone	
Acute Oral Toxicity (Gavage)	LD₅₀ > 5000 mg/kg bw (♂) LD₅₀ = 2028 mg/kg bw (♀)

Study type/Animal/ PMRA No.	Study results
Sprague-Dawley rats PMRA No. 777088	≥ 1000 mg/kg bw: ↓ motor activity (♀) ≥ 2000 mg/kg bw: ↑ mortality, ↑ clinical signs of toxicity (white/soft/mucoid feces, ↓ motor activity hunched posture, staggering gait, bradypnea, prostration, piloerection, tremors, dyspnea, palpebral ptosis, and absent righting reflex. Recovery was complete by day 3) (♀) 5000 mg/kg bw: ↑ clinical signs of toxicity (white/soft/mucoid feces, hunched posture, tremors, bradypnea, soiled fur), all resolved within two days (♂) Low acute toxicity
Acute Dermal Toxicity (Limit test) Sprague-Dawley rats PMRA No. 777089	LD₅₀ > 5000 mg/kg bw (♂/♀) No clinical signs of toxicity were observed. Low acute toxicity
Acute Inhalation Toxicity (Nose-only) Sprague-Dawley rats PMRA No. 777090	LC₅₀ > 2.1 mg/L (♂/♀) Exaggerated respiratory movements during dosing and lethargy, uncoordinated movement of the limbs, noisy respiration, hunched posture, gasping, ↓ fc and water consumption post-dosing. All animals recovered by day 2. Low acute toxicity
Primary Dermal Irritation New Zealand White rabbits PMRA No. 777092	MAS = 0/8; MIS = 0/8 Non-irritating to the skin
Primary Eye Irritation New Zealand White rabbits PMRA No. 777091	MAS = 0.22/110 (24–72 hrs), MIS = 3.33/110 (at 1 hr) Minimally irritating to the eye
Dermal Sensitization (Maximization Test) Dunkin-Hartley guinea pigs PMRA No. 777093	Negative No dermal reactions observed at 24 or 48 hrs post-challenge.
Acute toxicity studies - Metabolites	

Study type/Animal/ PMRA No.	Study results
Acute Oral Toxicity (Gavage) RPA 410193 (Metabolite) Sprague-Dawley rats PMRA No. 777161	LD ₅₀ > 2000 mg/kg bw (♂/♀) No clinical signs of toxicity were observed Low acute toxicity
Acute Oral Toxicity (Gavage) RPA 412636 (Metabolite) Sprague-Dawley rats PMRA No. 777155	LD ₅₀ = 1520 mg/kg bw (♂/♀) ≥ 500 mg/kg bw: ↑ incidence of clinical findings (sedation, piloerection and lateral recumbency) ≥ 1000 mg/kg bw: ↑ mortality, incidence of dyspnea and coma 2000 mg/kg bw: ↑ mortality Slight acute toxicity
Acute Oral Toxicity (Gavage) RPA 412708 (Metabolite) Sprague-Dawley rats PMRA No. 777167	LD ₅₀ = 176 mg/kg bw (♂/♀) Mortality was observed in the 150 and 200 mg/kg bw groups. ≥ 100 mg/kg bw: Clinical signs of toxicity noted for all animals, including sedation, hypoactivity, lateral recumbency, piloerection and dyspnea. Complete recovery was observed by day 4. High acute toxicity
Short-term toxicity studies – Fenamidone	
Dose range-finding 14-Day Oral Toxicity (Gavage) CD-1 mice PMRA No. 3197509	Acceptable with limitations ≥ 300 mg/kg bw/day: ↑ abs liver wt, ↑ liver centrilobular hypertrophy, ↓ AST (♂); ↑ bilirubin, ↑ pale yellowish discolouration of liver (♀) 1000 mg/kg bw/day: ↑ pale yellowish discolouration of liver, ↑ rel liver wt (♂); ↑ liver wt, ↑ liver centrilobular hypertrophy, mild liver enlargement (♀) Limitations: Limited number of animals and parameters assessed.
90-Day Oral Toxicity (Diet) C57 mice PMRA No. 777098	NOAEL = 45/54 mg/kg bw/day (♂/♀) LOAEL = 220/274 mg/kg bw/day (♂/♀) ≥ 45/54 mg/kg bw/day: ↑ pale liver (not adverse) (♂/♀) ≥ 220/274 mg/kg bw/day: ↑ total bilirubin (♂/♀); ↑ hepatocellular microvacuolation, ↑ diffuse corneal opacity (♂); ↓ cholesterol (♀) 1064/1375 mg/kg bw/day: ↑ liver wt (♂); ↑ rel liver wt (♀)

Study type/Animal/ PMRA No.	Study results
Dose range-finding 90-Day Oral Toxicity (Diet) CD-1 mice PMRA No. 3197514	Acceptable with limitations $\geq 11/15$ mg/kg bw/day: $\uparrow$ total bilirubin, $\uparrow$ liver centrilobular hypertrophy (σ) $\geq 110/146$ mg/kg bw/day: $\uparrow$ total bilirubin, $\uparrow$ liver centrilobular hypertrophy (φ) 1102/1468 mg/kg bw/day: $\uparrow$ liver wt (σ/φ); $\uparrow$ mortality, $\uparrow$ clinical signs of toxicity (pallor, $\downarrow$ motor activity, staggering gait, prostration, and dyspnea) (σ) Limitations: Limited number of animals and parameters assessed.
Exploratory 14-day Oral Toxicity (Gavage) -non-guideline Sprague-Dawley rats PMRA No. 3197515	Acceptable with limitations ≥ 100 mg/kg bw/day: enlarged liver, $\uparrow$ BROD activity, $\uparrow$ CYP450 IIB protein (σ) $\geq 300/100$ mg/kg bw/day: $\uparrow$ PROD activity (σ/φ); $\downarrow$ ALP, $\uparrow$ thyroid wt (σ); thyroid follicular cell hyperplasia, $\uparrow$ BROD activity, $\uparrow$ CYP450 IIB protein (φ) 1000/300 mg/kg bw/day: $\uparrow$ neutrophil %, $\downarrow$ lymphocyte count, $\uparrow$ PCNA positive cells (σ/φ); $\downarrow$ bw, $\uparrow$ total bilirubin, $\uparrow$ total protein, $\uparrow$ total cholesterol, $\uparrow$ liver weight, darkened liver, centrilobular hypertrophy, liver necrosis (σ) 1000/300 mg/kg bw/day (interim sacrifice): $\uparrow$ liver wt, $\uparrow$ PCNA positive cells (σ/φ); centrilobular hypertrophy (σ) Limitations: Limited number of animals and parameters assessed.
Exploratory 28-day Oral Toxicity (diet) -non-guideline Sprague-Dawley rats PMRA No. 3197513	Acceptable with limitations > 83 mg/kg bw/day: $\uparrow$ liver hypertrophy (σ) 419/450 mg/kg bw/day: $\uparrow$ liver wt, enlarged livers, $\downarrow$ bw, $\uparrow$ rel thyroid wt (σ/φ); $\downarrow$ bwg, $\uparrow$ thyroid follicular cell hypertrophy (σ); $\uparrow$ liver hypertrophy (φ) Thyroid hormone assessment: No clear treatment-related effect on T3, T4, or TSH levels. Limitations: Limited number of animals and parameters assessed.
Dose range-finding 28-Day Oral Toxicity (Diet) Sprague-Dawley rats PMRA No. 777105	Acceptable with limitations ≥ 39 mg/kg bw/day: $\downarrow$ bwg, $\downarrow$ bw, $\downarrow$ fc, $\uparrow$ pituitary chromophobe cells (equivocal) (σ) $\geq 389/405$ mg/kg bw/day: $\downarrow$ glucose, $\downarrow$ ALT, $\uparrow$ liver wt, $\uparrow$ dark colour of spleen, $\uparrow$ hyperplasia of splenic germinative follicle of the white pulp, $\uparrow$ mild to moderate diffuse liver hypertrophy (σ/φ); $\uparrow$ total cholesterol, $\uparrow$ rel thyroid wt (σ); $\downarrow$ fc (φ) 1203/1194 mg/kg bw/day: $\uparrow$ spleen wt (σ/φ); $\downarrow$ AST, $\uparrow$ total bilirubin (σ); $\downarrow$ bwg, $\uparrow$ enlarged spleen (φ)

Study type/Animal/ PMRA No.	Study results
	Limitations: Limited number of animals and parameters assessed.
90-Day Oral Toxicity (Diet) Sprague-Dawley rats PMRA No. 777094	NOAEL = 30/35 mg/kg bw/day (♂/♀) LOAEL = 306/337 mg/kg bw/day (♂/♀) 306/337 mg/kg bw/day: ↓ bw, ↓ bwg, ↓ fc, ↓ RBC, ↓ Hb (slight), ↑ rel liver wt, ↑ thyroid wt (♂/♀); ↓ AST, ↓ ALT, ↓ thymus wt, ↑ hepatocyte macro-/microvacuolation, ↑ bile duct hyperplasia, ↑ prominent splenic germinal centres, ↑ renal extramedullary hematopoiesis (♂)
90-Day Oral Toxicity (Diet) Sprague-Dawley rats PMRA No. 777096	NOAEL = 68/12 mg/kg bw/day (♂/♀) LOAEL = 344/381 mg/kg bw/day (♂/♀) ≥ 68/83 mg/kg bw/day: ↑ ground glass cytoplasm in hepatocytes (not adverse) (♂); ↓ bw, ↓ bwg (♀) 344/381 mg/kg bw/day: ↓ fc, ↑ cholesterol, ↑ dark liver colour (♂/♀); ↓ bw, ↓ bwg, ↑ thyroid wt, ↓ thymus wt, ↑ rel liver wt (♂); ↑ liver wt, ↑ ground glass cytoplasm in hepatocytes (♀)
Dose range-finding 28-Day Oral Toxicity (Capsule) Beagle dogs PMRA No. 777107	Acceptable with limitations 100 mg/kg bw/day: slight bw loss during the last two weeks of the study (not adverse) (♀) Limitations: Limited number of animals and parameters assessed.
Dose range-finding 28-Day Oral Toxicity (Diet) Beagle dogs PMRA No. 3197508	Acceptable with limitations ≥ 9.1/9.7 mg/kg bw/day: bile duct hyperplasia (♂/♀); cortical atrophy of thymus, centrilobular sinusoidal dilation (♀) 595/429 mg/kg bw/day: emaciation, diarrhea, vomiting, ↓ bw, ↓ fc, ↓ RBC, ↓ Hb, ↓ Hct, ↓ thymus wt, ↓ neutrophil counts, ↑ prothrombin time, ↓ calcium, ↓ total protein, ↓ albumin, ↓ total cholesterol, ↑ total bilirubin, ↑ rel liver wt (♂/♀); ocular discharge, ↓ activated partial thromboplastin time, cortical atrophy of thymus, centrilobular sinusoidal dilation (♂); ↑ activated partial thromboplastin time, ↑ ALT, ↓ phosphate, ↓ uterus wt (♀) Limitations: Limited number of animals and parameters assessed.
90-Day Oral Toxicity (Capsule) Beagle dogs PMRA No. 777100	NOAEL = 500 mg/kg bw/day LOAEL = not established 500 mg/kg bw/day: Red discolouration of the tongue, hypersalivation (♂/♀) (not adverse); ↑ cholesterol, ↑ spleen wt (not adverse) (♀)
12-Month Oral Toxicity (Capsule) Beagle dogs PMRA No. 777102	NOAEL = 100 mg/kg bw/day (♂/♀) LOAEL = 1000 mg/kg bw/day (♂/♀) ≥ 100 mg/kg bw/day: ↑ liver wt (not adverse) (♀)

Study type/Animal/ PMRA No.	Study results
28-Day Dermal Toxicity (Limit test) Sprague-Dawley rats PMRA No. 777108, 3197477	1000 mg/kg bw/day: ↑ vomiting, hypersalivation, ↑ ALP, ↑ biliary proliferation (♂/♀); ↑ abs liver wt (♂) NOAEL = not established /1000 mg/kg bw/day (♂/♀) LOAEL = 1000 mg/kg bw/day/ not established (♂/♀) 1000 mg/kg bw/day: ↓ bw, ↓ bwg, ↓ fc (♂)
Short-term toxicity studies – RPA 410193 Metabolite	
Exploratory 14-day Oral Toxicity (gavage) -non-guideline RPA 410193 (Metabolite) Sprague-Dawley rats PMRA No. 3197519	Acceptable with limitations ≥ 30/37 mg/kg bw/day: ↑ total CYP450 protein content, ↑ BROD activity, ↑ thyroid follicular epithelial hypertrophy (♂); ↑ total cholesterol (♀) ≥ 299/374 mg/kg bw/day: ↑ PROD activity, ↑ liver wt, ↑ enlarged livers, ↑ centrilobular hepatocellular hypertrophy (♂/♀); ↑ total cholesterol, ↑ lobulation of liver, ↑ rel kidney wt (♂); thyroid follicular hypertrophy, ↑ BROD activity (♀) 1098/1133 mg/kg bw/day: ↓ RBC, ↑ total bilirubin (♂); ↑ total CYP450 protein content, ↓ bwg (week 1 only), ↓ Hb, ↓ Hct, ↓ spleen wt, ↑ prominent lobulation of liver, ↑ diffuse microvacuolation and lipid content of hepatocytes (♀) 1098/1133 mg/kg bw/day (interim sacrifice): ↑ liver wt, ↑ centrilobular hypertrophy, ↑ PCNA positive cells (♂/♀); ↑ centrilobular mitotic figures (♂); ↑ diffuse microvacuolation of hepatocytes (♀) Limitations: Limited number of animals and parameters assessed.
90-Day Oral Toxicity (Diet) RPA 410193 (Metabolite) Sprague-Dawley rats PMRA No. 777165	NOAEL = 9.4/12 mg/kg bw/day (♂/♀) LOAEL = 93/115 mg/kg bw/day (♂/♀) ≥ 93/115 mg/kg bw/day: ↑ albumin, ↑ liver hypertrophy (♂/♀); ↑ cholesterol, ↑ liver wt, ↑ enlarged liver (♂); ↑ thymus involution (♀) 978/1090 mg/kg bw/day: marginal ↓ blood parameters (RBC, Hct, MCHC), ↑ triglycerides, ↑ total protein (♂/♀); ↓ T4, ↑ TSH (week 2 only), ↑ kidney wt, ↑ thymus involution (♂); ↑ cholesterol, ↑ liver wt, ↑ heart wt, ↑ prominent liver lobulation (♀)
Short-term toxicity studies – RPA 412636 Metabolite	
Exploratory 14-day Oral Toxicity (Gavage) -non-guideline RPA 412636 (Metabolite)	Acceptable with limitations ≥ 23/25 mg/kg bw/day: ↑ BROD activity, ↑ PROD activity (♂/♀); ↓ total bilirubin, enlarged liver, prominent liver lobulation, hepatocytic hypertrophy, hepatocellular necrosis, ↑ eosinophilic droplets, ↑ total CYP450 protein content (♂)

Study type/Animal/ PMRA No.	Study results
Sprague-Dawley rats PMRA No. 3197522	≥ 90/97 mg/kg bw/day: ↓ WBC, ↓ lymphocytes, ↑ neutrophil %, ↑ liver wt, pale pinpoints in kidney, cortical tubular hyaline degeneration (♂); enlarged liver, ↓ spleen wt, hepatocytic hypertrophy (♀) 215/233 mg/kg bw/day: ↓ bwg, ↓ fc, dark colour in liver (♂/♀); positive a2uG granular staining in numerous cortical kidney cells (♂); ↓ bw, ↑ urea, ↑ total cholesterol, hepatocellular necrosis, ↑ total CYP450 protein content (♀) 215/233 mg/kg bw/day (interim sacrifice): ↑ liver wt, enlarged liver, hepatocytic mitosis, ↑ PCNA positive cells (♂/♀); ↓ bw, ↑ liver nodules, ↑ centrilobular hypertrophy, periportal infiltrates, lobar necrosis of liver (♂) Limitations: Limited number of animals and parameters assessed.
90-Day Oral Toxicity (Diet) RPA 412636 (Metabolite) Sprague-Dawley rats PMRA No. 777156	NOAEL = 6.4/7.7 mg/kg bw/day (♂/♀) LOAEL = 33/39 mg/kg bw/day (♂/♀) ≥ 33/39 mg/kg bw/day: ↑ incidence of crystals in urine, ↑ hepatocyte hypertrophy (♂/♀); ↑ liver wt, enlarged livers, prominent lobulation in the liver, hepatocyte vacuolation, ↑ severity of eosinophilic droplets in renal proximal tubules, ↑ thyroid follicular hypertrophy (♂) 162/196 mg/kg bw/day: ↓ fc (slight), ↑ cholesterol, ↓ thymus wt (♂/♀); ↑ ALT, ↑ creatinine, ↑ adrenal wt, adrenal gland hypertrophy, ↑ thyroid colloid depletion and agglomeration, ↑ severity of thymus involution (♂); ↓ overall bwg, ↑ triglycerides, ↑ liver wt, enlarged liver, prominent lobulation in liver (♀)
Chronic toxicity/Oncogenicity studies – Fenamidone	
80-Week Oral Toxicity (Diet) C57BL10 mice PMRA No. 777110, 1064827	NOAEL = 48/64 mg/kg bw/day (♂/♀) LOAEL = 526/691 mg/kg bw/day (♂/♀) ≥ 48/64 mg/kg bw/day: ↑ liver wt (not adverse) (♂/♀) ≥ 526/691 mg/kg bw/day: ↓ bw, ↓ bwg, ↑ liver wt, ↑ fc, ↓ fe, ↑ incidence of pleomorphism with or without increased cytoplasmic eosinophilia and occasional giant cells and eosinophilic globules within the cytoplasm of hepatocytes, ↓ glycogen deposition (♂/♀); ↑ platelet count, ↑ clear cell liver foci (♀) 1100/1392 mg/kg bw/day: ↓ Hb, ↓ RBC, ↓ Hct (not adverse) (♀) No evidence of tumourigenicity
2-Year Oral Toxicity (Diet) Sprague-Dawley rats PMRA No. 777112, 777113, 777114	NOAEL = 2.8/3.6 mg/kg bw/day (♂/♀) LOAEL = 7.1/9.2 mg/kg bw/day (♂/♀) ≥ 2.8/3.6 mg/kg bw/day: ↑ granular appearance in the kidney (equivocal) (♂) ≥ 7.1/9.2 mg/kg bw/day: ↑ kidney wt at terminal sacrifice, ↑ thyroid follicular cell hyperplasia and/or hypertrophy at interim sacrifice, ↑ severity of thyroid C-cell hyperplasia at terminal sacrifice (♂/♀)

Study type/Animal/ PMRA No.	Study results
PMRA No. 777124 Complementary study to the 2-year oral toxicity study in rats (PMRA No. 777112), using a revised high-dose starting approximately a month after	48/61 mg/kg bw/day: ↑ thyroid wt at interim sacrifice, ↑ kidney wt at interim sacrifice, ↑ enlarged thyroid, ↑ basophilia colloid in the thyroid, ↓ ALT, AST (♂/♀); ↑ liver wt (interim and terminal sacrifices), enlarged liver, ↑ thyroid wt at terminal sacrifice, ↑ incidence of thyroid follicular cell hyperplasia at terminal sacrifice (♂); ↓ bw (♀) 260/335 mg/kg bw/day: ↑ kidney wt (interim sacrifice), ↑ thyroid follicular cell hypertrophy/hyperplasia, ↑ thyroid colloid basophilia, ↑ follicular diameter, ↑ hepatocyte vacuolation (♂/♀); ↓ bw, ↑ liver wt, ↑ thyroid wt, enlarged thyroids, diffuse thyroid C-cell hyperplasia, foamy hepatocyte cytoplasm and eosinophilic inclusions (♂); ↓ bw, ↓ bwg, ↓ fc, hepatocyte hypertrophy (♀) After a 3-month recovery period: partial recovery of body weight, ↑ thyroid wt (slight); foamy hepatocyte cytoplasm (♂) No evidence of tumourigenicity
Reproduction/Developmental toxicity studies – Fenamidone	
Dose range-finding 1-Generation Reproductive Toxicity (Diet) Sprague-Dawley rats PMRA 1065312, 1065313	Acceptable with limitations Parental Toxicity ≥ 5.5/5.7 mg/kg bw/day: ↓ fc (premating) (♀) ≥ 101/165 mg/kg bw/day: ↓ bwg (premating), ↓ bw and bwg (gestation) (♀) 665/776 mg/kg bw/day: ↓ slight bwg and fc (premating) (♂) Reproductive Toxicity 776 mg/kg bw/day: ↓ pup birth bw Offspring Toxicity ≥ 5.7 mg/kg bw/day: ↓ pup bw PND 4 onwards 776 mg/kg bw/day: ↓ viability index, ↓ weaning index, ↓ probability of survival to PND 21 Limitations: limited number of animals and parameters assessed.
2-Generation Reproductive Toxicity (Diet) Sprague-Dawley rats PMRA No. 777132, 1065313	Acceptable with limitations Parental Toxicity NOAEL = 3.9/5.2 mg/kg bw/day (♂/♀) LOAEL = 64/84 mg/kg bw/day (♂/♀) ≥ 64/84 mg/kg bw/day: ↓ bwg (P and F1 premating) (♂); ↓ bwg and fc (F1 gestation and lactation), ↓ abs brain wt (F1) (♀)

Study type/Animal/ PMRA No.	Study results
	328/460 mg/kg bw/day: ↓ bw (P and F1 pre-mating), ↓ terminal bw, ↓ fc (F1 pre-mating), ↑ liver wt (P and F1), ↑ spleen wt (P and F1) (♂/♀); ↓ bw (P gestation and lactation), ↓ bw (F1 gestation) ↑ bwg (F1 lactation) (♀) Reproductive Toxicity NOAEL = 328/460 mg/kg bw/day (♂/♀) LOAEL = Not established No treatment-related reproductive effects were observed Offspring Toxicity NOAEL = 5.2 mg/kg bw/day (♂/♀) LOAEL = 64/84 mg/kg bw/day (♂/♀) ≥ 84 mg/kg bw/day: ↓ bw (F1 and F2), ↓ bwg (F2) (♂/♀); ↓ brain wt (F2) (♀) 460 mg/kg bw/day: ↓ bw and bwg (F1), ↑ rel brain (F1) (♂/♀); ↓ abs brain wt (F2), ↑ rel brain wt (F2) (♂) No evidence of sensitivity of the young Limitations: ovarian follicle counts and thyroid weights were not assessed.
Developmental Toxicity (Gavage) Sprague-Dawley rats PMRA No. 777136	Acceptable with limitations Maternal Toxicity NOAEL =150 mg/kg bw/day LOAEL =1000 mg/kg bw/day 1000 mg/kg bw/day: ↓ bw (GD 6-9), ↓ bwg, ↓ fc Developmental Toxicity NOAEL = 150 mg/kg bw/day LOAEL = 1000 mg/kg bw/day 1000 mg/kg bw/day: ↓ fetal bw, ↑ slight incidence of incomplete ossification of the parietal bone and hyoid body, ↑ slight incidence of unossified 5th sternbrae No evidence of treatment-related malformations No evidence of sensitivity of the young Limitations: the maternal dosing period (GD 6-15) was shorter than that required by current OECD test guideline standards (GD 6-20), anogenital distance was not measured, and a thyroid hormone assessment was not conducted.
Dose range-finding Developmental Toxicity (Gavage) New Zealand White rabbits	Acceptable with limitations Maternal Toxicity ≥ 200 mg/kg bw/day: ↑ incidence of little to no feces, abdominal hair loss, ↓ bw, ↓ fc, ↑ liver wt, ↑ white areas, abnormal color and friable liver, accentuated

Study type/Animal/ PMRA No.	Study results
PMRA 1065314	lobular pattern in liver, ↑ abortion, ↑ post-implantation loss (2/8 with 100% loss) 500 mg/kg bw/day: ↑ mortality, ↑ abortions, ↑ stomach perforations, ↓ implantations/dam, ↓ live fetuses/dam Developmental Toxicity ≥ 200 mg/kg bw/day: ↑ post-implantation loss, ↑ abortion, ↓ fetal bw 500 mg/kg bw/day: ↓ live fetuses/dam (Note: only 1 litter was available for assessment) Limitations: limited number of animals and parameters assessed.
Developmental Toxicity (Gavage) New Zealand White rabbits PMRA No. 777137, 1065315	Acceptable with limitations Maternal Toxicity NOAEL = 30 mg/kg bw/day 30 mg/kg bw/day: ↑ liver wt (non-adverse) 100 mg/kg bw/day: ↓ bwg (GD 6-10), ↓ fc (GD 6-10) (non-adverse); ↑ liver wt (+37%) Developmental Toxicity NOAEL = 100 mg/kg bw/day No treatment-related developmental effects were observed up to 100 mg/kg bw/day. Dose range-finding study reported toxicity at higher dose levels. No evidence of treatment-related malformations No evidence of sensitivity of the young Limitation: a thyroid hormone assessment was not conducted.
Genotoxicity studies – Fenamidone	
Bacterial Reverse Mutation Assay S. typhimurium (TA98, TA100, TA102, TA1535, TA1537) PMRA No. 777138	Negative ± metabolic activation Tested up to a precipitating concentration
Mammalian forward gene mutation assay (in vitro)	Positive (+ metabolic activation) Negative (- metabolic activation) A marked increase in the number of small colonies were observed, which may indicate clastogenicity.

Study type/Animal/ PMRA No.	Study results
L5178Y mouse lymphoma cells PMRA No. 777139	
Chromosome aberration assay (in vitro) Human lymphocytes PMRA No. 777140	Positive ± metabolic activation Effect was more pronounced in presence of metabolic activation There was no clear positive response in the absence of metabolic activation due to excessive cytotoxicity and few analyzable concentrations.
Unscheduled DNA synthesis assay (in vitro) Primary rat hepatocytes PMRA No. 777142	Negative Tested up to a limit concentration
Unscheduled DNA synthesis assay (in vivo) Wistar rats PMRA No. 777143	Negative
Micronucleus assay (in vivo) CD-1 mice PMRA No. 777141	Negative
Genotoxicity studies – RPA 410193 Metabolite	
Bacterial Reverse Mutation Assay RPA 410193 (Metabolite) S. typhimurium (TA98, TA100, TA1535, TA1537); E. coli (WP2 uvrA) PMRA No. 777162	Negative ± metabolic activation Tested up to a precipitating concentration
Mammalian forward gene mutation assay (in vitro)	Negative ± metabolic activation Tested up to a precipitating concentration

Study type/Animal/ PMRA No.	Study results
RPA 410193 (Metabolite) L5178Y mouse lymphoma cells PMRA No. 777163	
Micronucleus assay (in vivo) RPA 410193 (Metabolite) CD-1 mouse bone marrow cells PMRA No. 777164	Negative
Genotoxicity studies – RPA 412636 Metabolite	
Bacterial Reverse Mutation Assay RPA 412636 (Metabolite) S. typhimurium (TA98, TA100, TA1535, TA1537); E. coli (WP2 uvrA) PMRA No. 777158	Negative ± metabolic activation
Mammalian forward gene mutation assay (in vitro) RPA 412636 (Metabolite) L5178Y mouse lymphoma cells PMRA No. 777159, 3211772	Negative ± metabolic activation
Micronucleus assay (in vivo) RPA 412636 (Metabolite)	Negative 300 mg/kg bw/day: lethargy, unsteady gait, prostration, and irregular breathing

Study type/Animal/ PMRA No.	Study results
CD-1 mouse bone marrow cells PMRA No. 777160	
Genotoxicity studies – RPA 412708 Metabolite	
Bacterial Reverse Mutation Assay RPA 412708 (Metabolite) S. typhimurium (TA98, TA100, TA1535, TA1537), E. coli (WP2 uvrA) PMRA No. 777168	Negative ± metabolic activation
In vivo mammalian cytogenetic (Micronucleus assay) RPA 412708 (Metabolite) CD-1 mouse bone marrow cells PMRA No. 777169	Negative
Neurotoxicity studies – Fenamidone	
Acute Neurotoxicity (Gavage) Sprague-Dawley rats PMRA No. 777147	NOAEL = 500/125 mg/kg bw (♂/♀) LOAEL = 2000/500 mg/kg bw/day (♂/♀) ≥ 500 mg/kg bw: Mucus in the feces on day 1 (not adverse) (♂/♀); ↑ soiling/staining of anogenital area and unsteady gait on day 1 (♀) 2000 mg/kg bw: ↓ locomotor activity for the first 10 minutes (♂/♀); ↑ soiling/staining of the fur on day 1 (♂); ↑ urination, ↑ sitting/walking in a hunched posture and ↓ rectal temperature on day 1 (♀) No evidence of selective neurotoxicity
90-day Neurotoxicity (Diet) Sprague-Dawley rats PMRA No. 777153	NOAEL = 74/83 mg/kg bw/day (♂/♀) LOAEL = 392/414 mg/kg bw/day (♂/♀) 392/414 mg/kg bw/day: ↓ bw, ↓ bwg, ↓ fc (♂/♀); ↓ abs brain wt (♂) Evidence of neurotoxicity
Developmental Neurotoxicity (Diet)	Acceptable with limitations

Study type/Animal/ PMRA No.	Study results
Wistar rats PMRA No. 3197478	Maternal Toxicity NOAEL = 429 mg/kg bw/day LOAEL = not established 429 mg/kg bw/day: ↓ bwg, ↓ bw (marginal, non-adverse) Developmental Toxicity NOAEL = 92 mg/kg bw/day LOAEL = 429 mg/kg bw/day 429 mg/kg bw/day: ↓ preweaning bw, ↓ preweaning bwg, ↓ early postweaning bw (♂/♀), ↑ caudate putamen size (PND 21) (equivocally related to treatment), ↑ frontal cortex size (PND 21 and 75), ↑ cerebellum size (PND 75) (♂) No treatment-related effects on functional or behavioural assessment parameters observed. Limitation: brain measurements were limited to control and high dose groups only. Evidence of developmental neurotoxicity Evidence of sensitivity of the young
Immunotoxicity Studies - Fenamidone	
28-day Immunotoxicity (Diet) Sprague-Dawley rats PMRA No. 3197496	NOAEL = 118 mg/kg bw/day LOAEL = 39 mg/kg bw/day ≥ 39 mg/kg bw/day: ↓ anti-SRBC IgM (equivocal at low and mid-dose) 388 mg/kg bw/day: ↓ bw, ↓ bwg, ↓ fc, ↓ thymus wt, ↑ thymus atrophy/small thymus, ↑ spleen wt, ↓ anti-SRBC IgM Evidence of immune system dysregulation
Mechanistic studies – Fenamidone	
Mechanistic 7- and 90-day dietary toxicity study – Liver proliferation and thyroid hormone metabolism (Diet) - Non-guideline Sprague-Dawley rats PMRA No. 3486357	Acceptable with limitations 7-day interim sacrifice: ≥ 118/139 mg/kg bw/day: ↓ AST, ↑ liver wt (♂); ↑ rel kidney wt (♀) 438/479 mg/kg bw/day: ↓ bwg, ↑ total cholesterol, ↑ HDL, ↑ LDL, ↑ reticulocytes, ↓ creatine kinase, ↓ LDH, ↑ thyroid colloid (♂/♀); ↑ triglycerides, ↓ fe, ↓ thymus wt, ↑ liver hypertrophy (♂); ↓ ALT, ↓ AST, ↓ triglycerides, ↑ albumin, ↑ total protein, ↑ liver wt (♀) 90-day main sacrifice: ≥ 30/36 mg/kg bw/day: ↑ thyroid follicular cell hypertrophy (♂/♀); ↓ thymus wt (♂); ↑ kidney wt, ↓ uterus/cervix wt (♀)

Study type/Animal/ PMRA No.	Study results
	≥ 92/109 mg/kg bw/day: ↓ ALT, ↑ liver wt, ↑ liver hypertrophy (♂/♀); ↓ RBC, ↑ MCV, ↑ reticulocytes, ↓ thyroid wt, ↑ rel kidney wt, ↑ thyroid follicular cell hypertrophy (♂); ↓ AST, ↑ rel pituitary wt (♀) 306/378 mg/kg bw/day: ↓ fe, ↓ neutrophils, ↑ monocytes (♂/♀); ↓ bw, ↓ AST, ↑ rel spleen wt (♂); ↓ bw, ↓ bwg, ↓ RBC, ↑ reticulocytes, ↓ LDH, ↑ total cholesterol, ↑ HDL, ↑ LDL, ↑ thyroid wt, ↓ thymus wt, ↑ thyroid follicular cell hypertrophy (♀) Thyroid hormone analysis: Overall there were no clear changes in thyroid hormone levels. Limitations: not all parts of the study were conducted according to GLP. Limited number of animals and parameters assessed.
Thyroid peroxidase (TPO) inhibition assay (in vitro) - Non-guideline Rat thyroid microsomes PMRA No. 3486352	Acceptable with limitations Negative Fenamidone was not an inhibitor of rat TPO when tested up to a non-precipitating concentration of 40 µM. In solubility tests, fenamidone was soluble up to 50 µM in 0.25% DMSO Positive control propylthiouracil (PTU) was a potent inhibitor of rat TPO activity. The IC₅₀ for PTU was 0.248 µM Limitations: study not conducted according to GLP.
Sodium-iodide symporter (NIS) inhibition assay (in vitro) - Non-guideline FRTL-5 Fischer rat thyroid follicular cell line PMRA No. 3486350	Acceptable with limitations A concentration-dependent decrease in ATP content was observed in FRTL-5 cells following exposure to fenamidone. Overall, the data suggests that fenamidone can inhibit the NIS at concentrations associated with decreased ATP content, in the absence of corroborating cytotoxicity (lack of microscopic findings and negative in the Resazurin assay). Positive controls (ITB5, sodium perchlorate) and negative controls (PTU, sodium fluoride) showed appropriate responses that were within provided historical control ranges. Limitations: study not conducted according to GLP.
Published studies - Fenamidone	
In vitro transcriptional changes - Non-guideline Published study	Acceptable with limitations Fenamidone was not cytotoxic at 10 µM for 24 hours. Fenamidone clustered together with other chemicals that showed concordance with the aging human brain and various neurological disorders involving dopamine pathways.

Study type/Animal/ PMRA No.	Study results
Cortical neuron-enriched cultures in mice PMRA No. 3849895	Fenamidone showed the ability to destabilize microtubules, but did not interact with microtubules directly. There was a concentration-dependent increase in superoxide formation. Pre-treatment with antioxidants or a microtubule stabilizer prevented the formation of superoxide. These results agree with the proposed fungal mode of action, which is inhibition of the ETC. Limitations: the individual data was not provided, and the test substance was not characterized; however, it was a commercially purchased analytical standard. The study does not provide valid endpoints for use in a quantitative risk assessment.
In vitro effects on the electron transport chain and mitochondrial dynamics - Non-guideline Published study HepG2 human hepatocytes PMRA No. 3849919	Acceptable with limitations Complex I and Complex III inhibitors (including fenamidone) perturbed mitochondrial membrane potential and mitochondrial cellular ATP levels and cell viability in a concentration- and time-dependent fashion. These results agree with the proposed fungal mode of action, which is inhibition of the ETC. Limitations: the individual data was not provided, and the test substance was not characterized; however, it was a commercially purchased analytical standard. The study does not provide valid endpoints for use in a quantitative risk assessment.
In vitro effects on mitochondrial respiratory inhibition - Non-guideline Published study HepG2 human hepatocytes and RPTEC/TERT1 human epithelial cells PMRA No. 3849912	Acceptable with limitations Fenamidone was shown to be cytotoxic (~60% viability at 10E-5 M) to RPTEC/TERT1 cells with increasing concentrations; no cytotoxicity was observed in HepG2 cells. Basal and maximal oxygen consumption rate was reduced in both cell lines in a concentration-dependent manner. Mitochondrial membrane potential was also decreased in a concentration-dependent manner. There were increased levels of supernatant lactate, suggesting increased glycolysis. Fenamidone was not tested in experiments replacing glucose with galactose (to show dependency on glycolysis). These results agree with the proposed fungal mode of action, which is inhibition of the ETC. Limitations: the individual data was not provided, and the test substance was not characterized; however, it was a commercially purchased analytical standard. The study does not provide valid endpoints for use in a quantitative risk assessment.
In vitro effects on mitochondrial	Acceptable with limitations Fenamidone was not a dopaminergic neurotoxicant when tested up to 10E-4 M.

Study type/Animal/ PMRA No.	Study results
respiration and dopaminergic neurons - Non-guideline Published study U2OS human osteosarcoma cell SH- SY5Y human neuroblastoma cells, LUHMES human neuronal-like precursor cells PMRA No. 3849892	Limitations: the individual data was not provided, and the test substance was not characterized; however, it was a commercially purchased analytical standard. The study does not provide valid endpoints for use in a risk assessment.

Appendix IV Dietary Exposure and Risk Assessments

Table 1.1 Acute dietary exposure and risk estimates for fenamidone and metabolites

Population Subgroup	Water only ¹		Food only		Food plus water	
	Exposure (mg/kg/day)	%ARfD ²	Exposure (mg/kg/day)	%ARfD	Exposure (mg/kg/day)	%ARfD
General U.S. Population	0.003937	4	0.026546	30	0.028493	32
All Infants (<1 year old)	0.013509	15	0.017978	20	0.022559	25
Children 1–2 years old³	0.005687	6	0.035300	39	0.037358	42
Children 3–5 years old	0.004477	5	0.034694	39	0.036492	41
Children 6–12 years old	0.003513	4	0.023407	26	0.025055	28
Youth 13–19 years old	0.003285	4	0.020713	23	0.021855	24
Adults 20–49 years old	0.003854	4	0.026100	29	0.028135	31
Adults 50+ years old	0.003353	4	0.027706	31	0.029758	33
Females 13–49 years old	0.003890	4	0.027276	30	0.029394	33

¹ Acute (highest 1 day average) Estimated Environmental Concentrations of fenamidone in water = 74 µg a.i./L

² ARfD = 0.09 mg/kg bw

³ **Bolded** population subgroup represents the most exposed population.

Table 1.2 Chronic Dietary Exposure and Risk Estimates for Fenamidone and Metabolites

Population Subgroup	Water only ¹		Food only		Food plus water	
	Exposure (mg/kg/day)	% ADI ²	Exposure (mg/kg/day)	% ADI	Exposure (mg/kg/day)	% ADI
General U.S. Population	0.000242	1	0.003140	16	0.003382	17
All Infants (<1 year old)	0.000906	5	0.001786	9	0.002692	14
Children 1–2 years old³	0.000333	2	0.005170	26	0.005503	28
Children 3–5 years old	0.000271	1	0.004252	21	0.004524	23
Children 6–12 years old	0.000202	1	0.002988	15	0.003190	16
Youth 13–19 years old	0.000171	1	0.002181	11	0.002351	12
Adults 20–49 years old	0.000241	1	0.003010	15	0.003251	16
Adults 50+ years old	0.000234	1	0.003407	17	0.003641	18
Females 13–49 years old	0.000237	1	0.003100	16	0.003337	17

¹ Chronic (yearly average) Estimated Environmental Concentrations of fenamidone in water = 12 µg a.i./L

² ADI = 0.02 mg/kg bw/day

³ **Bolded** population subgroup represents the most exposed population.

Appendix V Food Residue Chemistry Summary

Fenamidone is a imidazolinone fungicide registered for control of early and late blight in potato and tomato. It is also used to control and/or suppress various diseases in carrot, ginseng, spinach (including baby spinach), edible-podded and succulent shelled beans (except cowpea), cucurbit vegetables, bulb vegetables, basil, Brassica leafy greens, Brassica head and stem vegetables, kohlrabi, potato, turnip greens, and tobacco. It is foliar-applied by ground application (field sprayer) for all crops and is also registered for aerial application and as a seed piece treatment on potato. The seasonal foliar application rates on crops are between 600–900 g a.i./ha season in 2–4 applications/season. The seasonal rates for tobacco treatment are up to 800 g a.i./ha season in 2 or 4 applications/season. The potato seed piece treatment is done by one application of 5 g a.i./100 kg seed (the equivalent of 152.75 g a.i./ha). Due to updates in the crop nomenclatures, the registered crop use of “Brassica leafy greens” is proposed to be replaced on the label with “leafy vegetables”

The residue chemistry database is adequate to assess the acceptability of the registered food uses through this evaluation. The nature of the residue in livestock and plant commodities is adequately understood for the registered uses of fenamidone, based on acceptable metabolism studies in ruminants, poultry, lettuce, potatoes, tomatoes, grapes and carrots. No change is proposed to the residue definition (RD) for enforcement. However, based on the plant and animal metabolism reviews and on updated toxicological profile of fenamidone metabolites, the residue definition for risk assessment was updated from parent fenamidone to the sum of the parent fenamidone and the metabolites RPA 412636, RPA 412708 and RPA 410193 for plant commodities and the sum of the parent fenamidone and the metabolites RPA 412636 and RPA 412708 for animal commodities.

Analytical methods were previously reviewed and found to be acceptable for data collection and enforcement for the parent metabolite as well for the metabolites RPA 412636, RPA 412708 and RPA 410193. The reviewed methods use gas chromatography with nitrogen phosphorus (GC-NP) detection, thermoionic detection (TID), gas chromatography with mass spectrometry (GC-MS) or liquid chromatography with mass spectrometry (LC-MS/MS). Typical limits of quantification (LOQs) achieved for plant and animal commodities fall in the range of 0.01–0.02 mg/kg. Fenamidone is adequately analysed by multiresidue analytical methods (MRM) available.

The field trials and experimental processing studies were reviewed to determine the magnitude of residues in crops that included the parent fenamidone and the metabolites RPA 412636, RPA 412708 and RPA 410193. Animal feeding studies were also reviewed to determine the magnitude of residues in eggs, milk and animal tissues that included the parent fenamidone and the metabolites RPA 412636 and RPA 412708. Sufficient field trial residue data and animal feeding trial data are available to adequately assess the dietary exposure and risk from fenamidone and metabolites. A level 1 estimation of potential contamination of drinking water sources, in other words, modelling of environmental concentrations (EECs) was conducted and was used in the dietary exposure assessment.

Adequate freezer storage stability studies in crops are available. No freezer studies are available for animal commodities as they were analyzed within 30 day from sampling. Experimental processing studies were available for potatoes, cotton, grapes, wheat, field corn, soybeans and tomatoes. Confined or field rotational crop studies are available and the residues identified in feed commodities were used to estimate potential conservative anticipated residues in animal commodities.

The dietary (acute and chronic) risk assessment for fenamidone and metabolites is a slightly refined assessment using the most conservative residue data available (MRLs, tolerances, highest experimental or default processing factors and considered all registered crops to be completely treated). Since the risk estimates are well below Health Canada's level of concern, no refinements to the residue data are necessary at this time.

Appendix VI Mixer/Loader and applicator exposure and risk assessment

Table 1 Short- to intermediate-term mixer/loader/applicator exposure and risk assessment for fenamidone (Foliar Applications)

Application method	Crop ¹	Application rate ²	ATPD ³	Exposure (ug/kg bw/day) ⁴		MOE (Target = 300)			
				Dermal	Inhal	Dermal ⁵	Inhal ⁵	Combined ⁶	
Single Layer, CR Gloves (M/L/A)									
Aerial (mixer/loader)	Potato	100 g a.i./ha	400 ha	2.93	0.32	1778	16 508	1605	
Aerial (applicator)				0.13	0.005	39 000	1 070 000	37 600	
Groundboom (farmer) - large field crops				107 ha	3.37	0.93	1540	5610	1210
Groundboom(custom) - large field crops				360 ha	11.3	3.12	459	1670	360
Groundboom (farmer) - vegetable, fruit, tobacco	All field crops - Max rate	300 g a.i./ha	26 ha	0.82	0.23	6360	23 100	4980	
Backpack	All field crops - Max rate	2 g a.i./L ⁷	150 L	2.04	0.23	2550	22 300	2290	
MPHW			150 L	0.35	0.17	14 700	30 700	9940	
MPHG		300 g a.i./ha	2 ha ⁸	4.19	1.13	1240	4590	977	

ATPD = Area Treated Per Day/volume handled per day; Inhal = inhalation; MOE = Margin of Exposure; M/L = Mixer/Loader; A = Applicator; CR = chemical-resistant; Single layer = long-sleeved shirt, long pants; MPHW = manually-pressurized hand wand; MPHG = mechanically-pressurized hand gun; NOAEL = no observed adverse effect level

¹ Where possible, the highest rate for outdoor crops was used in the risk assessment for each application equipment.

² Application rate on the label is expressed in g a.i./ha. For handheld application equipment, the maximum application rate of 300 g a.i./ha and the minimum spray volume on the label of 150 L/ha was used to calculate the maximum application rate in g a.i./L across all field crops.

³ Standard ATPD values were used.

⁴ Exposure (ug/kg bw/day) was calculated: unit exposure (ug/kg a.i. handled) × application rate (g a.i./L or ha) × ATPD (L or ha) × dermal absorption of 10% (for dermal exposure route)/body weight (80 kg).

⁵ MOE = NOAEL/exposure. Calculated using a based on the short-, intermediate-term NOAEL of 5.2 mg/kg bw/day from an oral rat 2-generation reproductive toxicity study, target MOE of 300.

⁶ Combined MOE = 1/[(1/dermal MOE) + (1/inhalation MOE)].

⁷ The minimum spray volume across all crops of 150 L/ha was used. It is uncertain if handheld equipment would be used in all registered crops for spot treatment.

⁸ The refined ATPD of 2 ha was assumed as it is representative of spot treatment using handheld equipment.

Table 2 Short- to intermediate-term mixer/loader/applicator exposure and risk assessment for fenamidone (Potato seed piece)

Activity ¹	Form	Application rate (g a.i./kg seed)	Throughput ² (kg seed /day)	MOE (Target = 300)		
				Dermal ³	Inhalation ³	Combined ⁴
Mackie, 2006: Open mix/load, wearing single layer, CR gloves						
Treater	Liquid	0.05	290 400	985	2491	706
Cutter/sorter				N/A ⁵	1592	N/A
Treater/sorter/cutter ⁵				985	1592	608
Lange, 2015: Open loading, closed cab planting, wearing single layer, gloves (no specific type)						
Planter driver/loaders	Liquid	0.05	178 000	1270	2520	846
Back of planter				164	748	134
Lange, 2015: Open loading, closed cab planting, wearing coveralls over single layer, gloves (no specific type)						
Back of planter	Liquid	0.05	178 000	481	748	300

Bolded cells indicate where MOEs were below the target MOE and risks are not shown to be acceptable.

Form = formulation; CR = chemical-resistant; Single layer = long-sleeved shirt, long pants; MOE = margin of exposure; Treater = worker who mixes, loads, and treats the potato seed pieces; NOAEL = no observed adverse effect level; N/A = not applicable

¹ Activities are determined by the tasks performed by workers in each exposure study.

² Throughput is dependent on seeding rate and area planted. High-end commercial throughput data were used for all crops.

³ MOE = NOAEL/exposure. Calculated based on the short-, intermediate-term NOAEL of 5.2 mg/kg bw/day from an oral rat 2-generation reproductive toxicity study, target MOE of 300. Exposure (µg/kg bw/day) = [(application rate (g a.i./kg seed) × kg/1000 g × throughput (kg seed/day) × unit exposure (µg/ kg a.i. handled) × dermal absorption (10%; dermal route only)]/80 kg body weight].

⁴ Combined MOE = 1/[(1/dermal MOE)+(1/inhalation MOE)].

⁵ Treaters and cutters/sorters were combined to estimate exposure for treaters who also help cut and sort. However, as the potato seed pieces are treated after they are cut and sorted, the dermal PPE will not be required for cutters/sorters.

Appendix VII Occupational postapplication exposure and risk assessment

Table 1 Postapplication occupational exposure and risk assessment for fenamidone (Foliar applications)

Registered Crop/Crop Group ¹	Surrogate/ Representative Crops ²	Max. Rate (g a.i./ha)	Max. Apps.	Min. RTI (days)	Activity	TC ³ (cm ² /hr)	Day 0 DFR ⁴	Day 0 MOE ⁵ (Target = 300)	REI ⁶ (days)
Field Crops (Use-site category 14)									
Basil, spinach, baby spinach	Parsley, spinach	200	4	7	Irrigation (hand set)	1750	1.15 (s)	257	1
					Hand harvesting	1100		409	0.5
					Transplanting	230		1960	
					Scouting	210		2140	
					Hand weeding, hand thinning plants	70		6430	
Kohlrabi	Cabbage	300	3	5	Hand weeding	4400	0.35 (w)	339	0.5
					Irrigation (hand set)	1750		851	
					Hand harvesting, MA harvesting, scouting, hand thinning plants	1300		1150	
					Transplanting	230		6480	
Brassica head and stem vegetable	Crop group 5-13 (Broccoli, Brussels sprouts, cabbage, cauliflower)	300	3	5	Hand harvesting ⁷	5150	0.35 (w)	290	0.5
					Hand weeding	4400		339	
					Scouting (full), tying/training, topping	4000		372	
					Irrigation (hand set)	1750		851	
					Scouting (min), hand thinning plants	1300		1150	
					Transplanting	230		6480	
Brassica leafy greens (proposed to be changed to leafy vegetables)	Crop group 4-13 (Cabbage, Napa Chinese cabbage, Bok Chi Chinese cabbage)	300	3	5	Hand weeding	4400	0.35 (w)	339	0.5
					Irrigation (hand set)	1750		851	
					Hand harvesting, MA harvesting, scouting, hand thinning plants	1300		1150	
					Transplanting	230		6480	
	Crop group 4-13 (Collards, kale, leafy	300	3	5	Irrigation (hand set)	1750	1.96 (s)	152	4
					Hand harvesting	1100		241	1

Registered Crop/Crop Group ¹	Surrogate/ Representative Crops ²	Max. Rate (g a.i./ ha)	Max. Apps.	Min. RTI (days)	Activity	TC ³ (cm ² /hr)	Day 0 DFR ⁴	Day 0 MOE ⁵ (Target = 300)	REI ⁶ (days)
	greens, mustard greens, watercress)				Transplanting	230		1150	0.5
					Scouting	210		1260	
					Hand weeding, hand thinning plants	70		3790	
Turnip greens	Turnip	300	2	5	Irrigation (hand set)	1750	1.74 (s)	170	3
					Hand harvesting	1100		271	1
					Scouting	210		1420	0.5
					Hand thinning plants, hand weeding	70		4260	
Bulb vegetables	Crop group 3-07 (Bulb onion, green onion)	200	4	5	Hand weeding	4400	0.26 (w)	459	0.5
					Irrigation (hand set)	1750		1150	
					Hand harvesting, scouting, hand thinning plants	1300		1550	
Carrot	Carrot	300	2	7	Irrigation (hand set)	1750	1.59 (s)	187	3
					Hand harvesting	1100		297	0.5
					Scouting	210		1550	
					Hand weeding	70		4660	
Edible podded bean, Succulent shelled bean	Crop group 6-21 (Snap bean, dry bean)	300	3	7	Irrigation (hand set)	1750	1.70 (s)	175	3
					Hand harvesting, scouting (full foliage)	1100		278	1
					Scouting (min foliage)	210		1460	0.5
					Hand weeding	70		4370	
Cucurbit crops	Crop group 9 (Cucumber, cantaloupe, gourd, pumpkin, watermelon, summer/winter squash)	200	4	5	Irrigation (hand set)	1750	0.92 (h)	323	0.5
					Hand harvesting, MA harvesting, training, turning	550		1030	
					Transplanting	230		2460	
					Scouting, hand thinning fruit, hand weeding, hand pruning	90		6280	
Ginseng	Sweet potato	300	3	8	Irrigation (hand set)	1750	1.61 (s)	185	3
					Transplanting	230		1540	0.5
					Scouting	210		4610	
					Hand weeding	70		1400	

Registered Crop/Crop Group ¹	Surrogate/ Representative Crops ²	Max. Rate (g a.i./ ha)	Max. Apps.	Min. RTI (days)	Activity	TC ³ (cm ² /hr)	Day 0 DFR ⁴	Day 0 MOE ⁵ (Target = 300)	REI ⁶ (days)
	Strawberry ⁸				Hand harvesting	1100		294	
Potato	Potato	100	6	7	Irrigation (hand set)	1750	0.58 (s)	511	0.5
					Roguing	1100		813	
					Scouting	210		4260	
					Hand weeding	70		12800	
Tobacco ⁹	Tobacco	300	2	5	Irrigation (hand set)	1750	0.96 (h)	310	0.5
					Hand harvesting, MA harvesting, canopy management	800		677	
					Transplanting	230		2360	
					Scouting, hand weeding	90		6020	
Tomato	Tomato	100	6	7	Irrigation (hand set)	1750	0.58 (s)	511	0.5
					Hand harvesting, tying/training	1100		813	
					Transplanting	230		3890	
					Scouting	210		4260	
					Hand pruning, hand weeding	70		12800	

Bolded cells indicate those calculated MOEs where risks were not shown to be acceptable on day 0 (the day of the last application).

Apps = applications; RTI = Re-treatment Interval; DFR = Dislodgeable Foliar Residue; REI = Restricted-Entry Interval; MOE = margin of exposure; MA = mechanically-assisted harvesting; full = full foliage; min = minimum foliage; s = smooth foliage; h = hairy foliage; w = waxy foliage.

¹ In some cases crop groups are listed in the label.

² Surrogate or representative crops were chosen to reflect the appropriate postapplication activities and associated transfer coefficients for several crops. Crop groups were assessed together using the representative crops for the crop group.

³ Transfer coefficients (TC). Activities that have minimal postapplication exposure to treated foliage and have a transfer coefficient of zero are not included in this table.

⁴ Day 0 DFR = Dislodgeable Foliar Residues on Day 0 after all applications. Dislodgeable foliar residue values were calculated using chemical-specific data depending on the foliage type of the surrogate/representative crop. For smooth foliage crops, the peak DFR of 41% of the application rate after a single application and 16% dissipation per day were used to calculate DFR. For waxy foliage crops, the peak DFR of 6% of the application rate after a single application and 10% dissipation per day were used. For hairy foliage crops, the peak DFR of 46% of the application rate after 4 applications and 32% of the application rate after 2 applications were used along with a dissipation rate of 6% per day.

⁵ Dermal MOE on Day 0 = NOAEL / (DFR_{Day 0} × Dermal absorption (10%) × Transfer Coefficient × 8 hr / 80 kg). MOE on day 0 after application; based on the short-, intermediate-term NOAEL of 5.2 mg/kg bw/day from an oral rat 2-generation reproductive toxicity study, target MOE of 300.

⁶ Day at which the dermal exposure results in an MOE where risks are shown to be acceptable.

⁷ Hand harvesting of cabbage has a lower TC (1300 cm²/hr) and is addressed by the hand harvesting TC for other crops in this crop group.

⁸ The hand harvesting TC from strawberry was also included to address hand harvesting of ginseng berries, as this activity is not addressed by sweet potato TCs.

⁹ The 2 applications at maximum application rate scenario addresses the 4 applications at the minimum application rate scenario.

Appendix VIII Environmental assessment

Table 1 Fate and behaviour in the environment

Property	Test substance	Value	Transformation products	Comments	PMRA No.
Parent, fenamidone					
Abiotic transformation					
Hydrolysis	25°C, pH 4, 5, 7, 9 C-phenyl label of the pure S-enantiomer of fenamidone	pH 4: $t_R / DT_{50} = 41.5$ d (SFO) pH 5: $t_R / DT_{50} = 221.7$ d (SFO) pH 7: $t_R / DT_{50} = 410.7$ d (SFO) pH 9: $t_R / DT_{50} = 28.6$ d (SFO)	pH 4: Major TP = RPA 410193; Minor TP = RPA 412708, RPA 413350 pH 5: Minor TP = RPA 410193, RPA 413350, RPA 412708 pH 7: Minor TP = RPA 410193, RPA 413350, RPA 412708 pH 9: Major TP: RPA 413350, RPA 412708; Minor: RPA 410193	Hydrolysis of fenamidone primarily occurs only under alkaline and acidic conditions	777188, 3772726
Phototransformation in soil	20°C, sandy loam; 2.1% OM C-phenyl labelled fenamidone	t_R / DT_{50} irradiated = 12.9 d (SFO) t_R / DT_{50} non-irradiated = 6.0 d (SFO)	Major: RPA 412636, RPA 412708 Minor: RPA 409445, RPA 410193, RPA 411639, RPA 413255	Phototransformation in soil is not a significant route of dissipation for fenamidone in the environment	777189 3772726
	20°C, sandy loam; 2.1% OM N-phenyl-U-[¹⁴ C]-labelled fenamidone	t_R / DT_{50} irradiated = 15.6 d (SFO) t_R / DT_{50} non-irradiated = 9.2 d (SFO)	Major: None Minor: RPA 410193, RPA 411639, RPA 413255		777190 3772726
Phototransformation in water	DIRECT C-phenyl-labelled fenamidone	$t_R / DT_{50} = 1.4$ d (SFO); equivalent to 6.7 d under natural sunlight	Major: RPA 412708, RPA 410193, RPA 418915	Phototransformation in water is an important route of dissipation of fenamidone in the environment	777191 3772726
	DIRECT N-phenyl-labelled fenamidone	$t_R / DT_{50} = 1.7$ d (SFO); equivalent to 7.8 d under natural sunlight	Major: None ¹ Minor: RPA 410193, RPA 418915		777192 3772726
	INDIRECT C-phenyl-labelled fenamidone	$t_R / DT_{50} = 7.4$ d (SFO); equivalent to 5.8 d under natural sunlight	Major: RPA 412708, acetephone		3197468 3772726
Biotransformation					
Parent, fenamidone					

Property	Test substance	Value	Transformation products	Comments	PMRA No.
Biotransformation in aerobic soil ²	C-phenyl- and N-phenyl- labelled fenamidone Soil types tested: loam (96/52) silt loam (97/10) sandy loam (97/12) loam 1 (97/13) loam 2 (96/52) US sandy loam (98/32) US loam (98/33)	Parent: DT ₅₀ = 0.49–10.37 d (IORE and SFO) t _R = 1.5–23.97 d adjusted to 20°C TPs: RPA 412708 DT ₅₀ = 18.7–423 d RPA 412636 DT ₅₀ = 84.4–1000 d RPA 413255 DT ₅₀ = 73.8–201 d RPA 221607 DT ₅₀ = 12.9–239.6 d RPA 221701 DT ₅₀ = 14.1–301.4 d RPA 410193 DT ₅₀ = 0.15–0.36 d RPA 411639 DT ₅₀ = 56.6–149 d	Major: RPA 412708, RPA 412636, RPA 413255, RPA 221607, RPA 221701, RPA 411639 Minor: RPA 413255, RPA 410193, RPA 411639, RPA 409445, RPA 221607	Fenamidone is not persistent. Bio-transformation in aerobic soil is an important route of dissipation for fenamidone in the environment	3197471 3197472 3772714 3772726
TP, RPA 412636					
Biotransformation in aerobic soil	Clay loam, 20°C C- and N-phenyl label	DT ₅₀ >1000 d (SFO)	Major: none identified Minor: none identified	Biotransformation in aerobic soils is not an important route of dissipation for RPA 412636.	777195 3772726
	Silty clay loam, 20°C C-phenyl label	DT ₅₀ = 195 d (SFO)			
	Sandy loam, 20°C C-phenyl label	DT ₅₀ >1000 d (SFO)			
	Clay loam, 20°C C-phenyl label	DT ₅₀ >1000 d (SFO)			3772726
	Sandy loam, 20°C C- and N-phenyl label	DT ₅₀ >1000 d (SFO)			
	Loam, 20°C C-phenyl label	DT ₅₀ >1000 d (SFO)			
	Sand, 20°C C-phenyl label	DT ₅₀ = 410 d (SFO)			
	Clay loam, 20°C C-phenyl label	DT ₅₀ 112 days (SFO)			
	Silt loam, 20°C C-phenyl label	DT ₅₀ 457 days (SFO)			
TP, RPA 221607					
Biotransformation in aerobic soil	Sandy loam, 20°C C- and N-phenyl label	DT ₅₀ 386 days (SFO)	Major: none identified Minor: none identified	Biotransformation in aerobic soils is not an important route of dissipation for RPA 221607.	3772726
	Silt loam, 20°C	DT ₅₀ 18.5 days (SFO)			
	Clay loam, 20°C	DT ₅₀ 18.4 days (SFO)			
	Silt loam, 20°C	DT ₅₀ 12.9 days (SFO)			

Property	Test substance	Value	Transformation products	Comments	PMRA No.
	Silt loam, 20°C	DT ₅₀ 19.2 days (SFO)			
TP, RPA 221701					
Biotransformation in aerobic soil	Sandy loam, 20°C C- and N-phenyl label	DT ₅₀ 486 days (SFO)	Major: none identified Minor: none identified	Biotransformation in aerobic soils is not an important route of dissipation for RPA 221701.	3772726
	Silt loam, 20°C	DT ₅₀ 25.9 days (SFO)			
	Clay loam, 20°C	DT ₅₀ 14.1 days (SFO)			
	Silt loam, 20°C	DT ₅₀ 19.1 days (SFO)			
	Silt loam, 20°C	DT ₅₀ 44.3 days (SFO)			
TP, RPA 410193					
Biotransformation in aerobic soil	Silt loam, 20°C	DT ₅₀ 5.5 days (SFO)	Major: none identified Minor: none identified	Biotransformation in aerobic soils is not an important route of dissipation for RPA 410193.	3772726
	Clay loam, 20°C	DT ₅₀ 8.7 days (SFO)			
	Silt loam, 20°C	DT ₅₀ 5.9 days (SFO)			
	Silt loam, 20°C	DT ₅₀ 3.6 days (SFO)			
TP, BCS-CV62706					
Biotransformation in aerobic soil	Loamy sand, 20°C	DT ₅₀ 66.2 days (SFO)	Major: none identified Minor: none identified	Biotransformation in aerobic soils is not an important route of dissipation for BCS CV62706.	3772726
	Silt loam, 20°C	DT ₅₀ 334 days (SFO)			
	Loam, 20°C	DT ₅₀ 60.6 days (SFO)			
	Silt loam, 20°C	DT ₅₀ 59.7 days (SFO)			
Parent, fenamidone					
Biotransformation in anaerobic soil	Loam (96/50), 20°C	Due to the limited degradation it was not possible to calculate the DT ₅₀ of fenamidone in either the soil or the total system.	Major: none identified Minor: none identified	Fenamidone is stable in soil under anaerobic conditions. Biotransformation in anaerobic soils is not an important route of dissipation for fenamidone.	3197470 3772726
Biotransformation in aerobic aquatic systems	UK Ongar sandy clay loam (97/07), 20°C	Whole system: t _R / DT ₅₀ = 106.6 d (SFO)	Major: RPA 412708	Fenamidone is moderately	777196 3774669

Property	Test substance	Value	Transformation products	Comments	PMRA No.
	C-phenyl-labelled fenamidone		Minor: RPA 412636, RPA 410193	persistent in aerobic aquatic environments. Biotransformation in water is a route of dissipation for fenamidone.	
	UK Manningtree sandy loam (97/08), 20°C C-phenyl-labelled fenamidone	Whole system: $t_R / DT_{50} = 66.81 \text{ d}$ (SFO)			
	UK Manningtree II loam (98/08), 20°C N-phenyl-labelled fenamidone	Whole system: $t_R / DT_{50} = 128.87 \text{ d}$ (SFO)		777197 3774669	
Biotransformation in anaerobic aquatic systems	UK Ongar clay sediment(97/17), 20°C C-phenyl-labelled fenamidone	Whole system: $t_R / DT_{50} = 1105 \text{ d}$ (SFO)	Major: none identified Minor: RPA 410193, RPA 412708, RPA 412636, RPA 413350	Fenamidone is persistent under anaerobic water/sediment systems. Biotransformation in water is a route of dissipation for fenamidone.	777198 3774669
Bioconcentration					
Bioconcentration in fish	The experimentally-derived log K _{OW} of fenamidone is 2.8. The experimentally-derived log K _{OW} of RPA 412636 is 1.02. The modelled estimated range of log K _{OW} is 0.94–3.84 for the following TPs: RPA412636, RPA 412708, RPA 411639, RPA 413255, RPA 221607, RPA 221701, RPA 410193, RPA 418915, RPA 413350. Fenamidone and its TPs are not expected to bioaccumulate in the tissues of fish.				
Mobility					
Parent, fenamidone					
Adsorption / desorption in soil	4 soils and 1 sediment (2 US soils; 2 UK soils; 1 UK sediment)	K _{oc} = 241.5–437.6	N/A	Fenamidone is classified as having moderate mobility in soil.	777200 3772726
TP, RPA 412636					
Adsorption / desorption in soil	4 soils and 1 sediment (2 US soils; 2 UK soils; 1 UK sediment)	K _{oc} = 13.8–28.2	N/A	RPA 412636 is classified as having very high mobility in soil.	777201 3772726
	4 soils (1 Italy soil; 1 UK soil; 1 France soil; 1 Germany soil)	K _{oc} = 21.77–29.76			3197469 3772726

Property	Test substance	Value	Transformation products	Comments	PMRA No.
TP, RPA 412708					
Adsorption / desorption in soil	4 soils and 1 sediment (2 US soils; 2 UK soils and 1 UK sediment)	K _{oc} = 13.99–49.25	N/A	RPA 412708 is classified as having very high mobility in soil.	777202 3772726
TP, RPA 411639					
Adsorption / desorption in soil	4 soils and 1 sediment (2 US soils; 2 UK soils and 1 UK sediment)	K _{oc} = 354–864.6	N/A	RPA 411639 is classified as having low to moderate mobility in soil.	777203 3772726
TP, RPA 413255					
Adsorption / desorption in soil	4 soils and 1 sediment (2 US soils; 2 UK soils and 1 UK sediment)	K _{oc} = 273.3–674.3	N/A	RPA 413255 is classified as having low to moderate mobility in soil.	777204 3772726
TP, RPA 221607					
Adsorption / desorption in soil	4 soils and 1 sediment (2 US soils; 2 UK soils and 1 UK sediment)	K _{oc} = 87.64–401.4	N/A	RPA 221607 is classified as having moderate to high mobility in soil.	3197474 3772726
TP, RPA 221701					
Adsorption / desorption in soil	4 soils and 1 sediment (2 US soils; 2 UK soils and 1 UK sediment)	K _{oc} = 84.2–243.8	N/A	RPA 221701 is classified as having moderate to high mobility in soil.	3197475 3772726
TP, RPA 410193					
Adsorption / desorption in soil	4 soils and 1 sediment	K _{oc} = 77.21–81.31	N/A	RPA 410193 is classified as having high mobility in soil.	3772726 3772726
Soil leaching	No soil leaching study with fenamidone was submitted and none is required.				
Volatilization	Fenamidone is not expected to be volatile under field conditions from water surfaces or moist soils based on its vapour pressure (3.4 × 10 ⁻⁴ mPa at 25°C) and it's Henry's law Constant (0.7523 Pa and 1/H = 1.825 × 10 ⁸).				
Field studies					

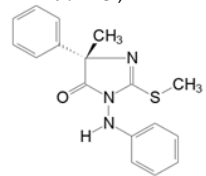
Property	Test substance	Value	Transformation products	Comments	PMRA No.
Terrestrial field dissipation	Canada: PEI ecoregion 5.3; sandy loam; 3.4% organic matter ON ecoregion 8.1; loamy sand; 2.4% organic matter MB ecoregion 9.2; clay loam; 5.5% organic matter End-use product EXP10623A(500 g a.i./L)	PEI DT ₅₀ = 14 d ON DT ₅₀ = 21 d MB DT ₅₀ = 14 d	Major: RPA 412708, RPA 412636 Minor: RPA 406012, RPA 410914	Fenamidone is unlikely to accumulate in soil and carry over to the next growing season. At the sites tested, fenamidone did not appear to be susceptible to leaching.	777360
	US: North Dakota ecoregion 9.2 Washington ecoregion 10.1 End-use product (200 g a.i./ha)	North Dakota DT ₅₀ = 24 d Washington DT ₅₀ = 8.4 d	Major: RPA 412708, RPA 412636		777362
	EU: Italy soil France soil Germany soil UK soil	Italy DT ₅₀ = 14.3 d France DT ₅₀ = 3.7 d Germany DT ₅₀ = 7.7 d UK DT ₅₀ = 8.5 d	Major: RPA 412708 Minor: RPA 412636, RPA 411639, RPA 413255		3197516 3775406
	EU: Italy soil UK soil Germany soil France soil German soil	Italy DT ₅₀ = 4.5 d UK DT ₅₀ = not calculated Germany DT ₅₀ = 4.8 d France DT ₅₀ = not calculated Germany DT ₅₀ = not calculated	Major and minor (depending on soil): RPA 412708, 412636		3775406
	EU: Germany soil with sand cover	Germany DT ₅₀ = 9.2 d	Major: None ³ Minor: RPA 412636, RPA 412708		3197530 3197531 3775406
Field leaching	No field leaching study with fenamidone was submitted and none was required.				

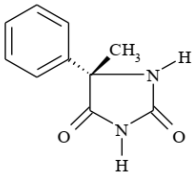
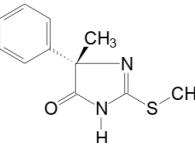
¹ The highest amount of TP recovered was 9.2% of RPA 418915. All other TPs tested for were < 10%.

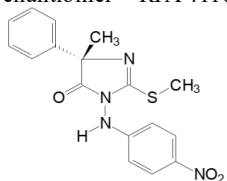
² The biotransformation in soil studies for the parent are presented together in one row to better reflect the information that was used in the risk assessment from foreign reviews and submitted studies.

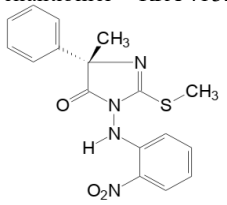
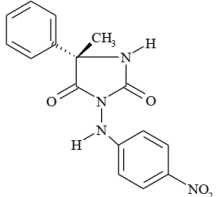
³ The highest amount of TP recovered was < 10%. This study only tested for the TPs RPA 412636 and RPA 412708.

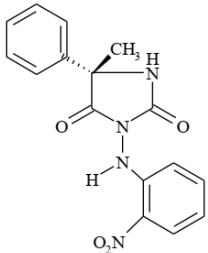
Table 2 Transformation products of fenamidone in the environment

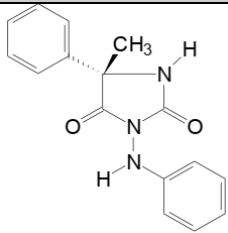
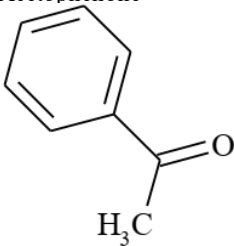
Code name, chemical name and structure	Study type (PMRA No.)	System conditions	Max % AR (d)	% AR at study end (study length, (d)
Parent				
Parent Fenamidone (RPA 407213)  IUPAC name: (S)-5-Methyl-2-methylthio-5-phenyl-3-phenylamino-3,5-dihydroimidazol-4-one CAS name: 4H-Imidazol-4-one, 3,5-dihydro-5-methyl-2-(methylthio)-5-phenyl-3-(phenylamino)-, (S)- 311.4 g/mol	Hydrolysis (777188)	pH 4	100 (0)	59.81 (31)
		pH 5	100 (0)	91.25 (31)
		pH 7	100 (0)	95.7 (31)
		pH 9	100 (0)	47.57 (231)
	Soil phototransformation (777189)	Irradiated	101.26 (0)	27.54 (30)
		Non-irradiated	101.26 (0)	12.68 (30)
	Soil phototransformation (777190)	Irradiated	100.09 (0)	31.08 (30)
		Non-irradiated	100.09 (0)	20.31 (30)
	Aqueous phototransformation (777191)	Irradiated	101 (0)	28.7 (2)
		Non-irradiated	100.5 (0)	100.5 (2)
	Aqueous phototransformation (777192)	Irradiated	99.8 (0)	37.19 (2)
		Non-irradiated	99.47 (2)	99.47 (2)
	Aqueous phototransformation, indirect with natural sterilised water (3197468)	Irradiated	100.15 (0)	1.72 (16)
		Non-irradiated	100.15 (0)	94.14 (16)
	Aerobic soil biotransformation (3197472)	UK loam	99.09 (0)	2.16 (365)
	Aerobic soil biotransformation (3197471)	UK silt loam	94.36 (0)	3.66 (193)
		US sandy loam	93.33 (0)	2.38 (181)
		UK loam 1	71.48 (0)	1.34 (181)
		UK loam 2	95.72 (0)	2.56 (365)
	Aerobic soil biotransformation (777193)	US sandy loam	100.31 (0)	4.26 (365)
		US loam	95.75 (0)	4.01 (365)
	Anaerobic soil biotransformation (777196)	UK loam	106.58 (3)	95.52 (121)
	Aerobic aquatic biotransformation (777196)	UK sandy clay loam sediment	100.37 (0.02)	53.31 (152)
		UK sandy loam sediment	98.49 (0.02)	27.69 (152)
	Aerobic aquatic biotransformation (777197)	UK loam	94.89 (0.02)	27.69 (152)
	Anaerobic aquatic biotransformation (777198)	UK clay sediment	101.71 (0)	79.01 (364)

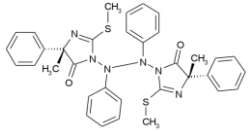
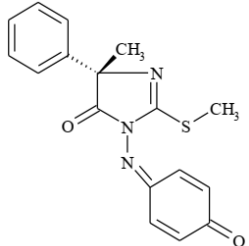
Code name, chemical name and structure	Study type (PMRA No.)	System conditions	Max % AR (d)	% AR at study end (study length, (d)
Major ($\geq 10\%$) transformation products				
S-enantiomer = RPA 412636  (racemate = RPA 717879) IUPAC name: 5-Methyl-5-phenylimidazolidine-2,4-dione CAS name: 2,4-Imidazolidinedione, 5-methyl-5-phenyl- 190.2 g/mol	Hydrolysis	N/A	N/A	N/A
	Soil phototransformation (777189)	Irradiated	12.44 (3)	12.44 (30)
		Non-irradiated	11.21 (21)	9.68 (30)
	Aqueous phototransformation	N/A	N/A	N/A
	Aerobic soil biotransformation (3197472)	UK loam	23.85 (365)	23.85 (365)
	Aerobic soil biotransformation (3197471)	UK silt loam	11.86 (193)	11.86 (193)
		US sandy loam	32.21 (181)	32.21 (181)
		UK loam 1	32.13 (90)	27.1 (181)
		UK loam 2	18.78 (365)	18.78 (365)
	Aerobic soil biotransformation (777193)	US sandy loam	35.47 (365)	35.47 (365)
		US loam	24.45 (272)	22.26 (365)
	Anaerobic soil biotransformation	N/A	N/A	N/A
	Aerobic aquatic biotransformation (777196)	UK sandy clay loam sediment	4.66 (78)	2.56 (152)
		UK sandy loam sediment	9.67 (152)	9.67 (152)
	Anaerobic aquatic biotransformation (777198)	UK clay sediment	1.31 (364)	1.31 (364)
S-enantiomer = RPA 412708  (racemate = RPA 408056) IUPAC name: 5-Methyl-2-methylthio-5-phenyl-3,5-dihydroimidazol-4-one CAS name:	Hydrolysis (777188)	pH 4	1.28 (31)	1.28 (31)
		pH 5	0.99 (31)	0.99 (31)
		pH 7	1.21 (31)	1.21 (31)
		pH 9	10.19 (31)	10.19 (31)
	Soil phototransformation (777189)	Irradiated	18.02 (9)	17.78 (30)
		Non-irradiated	20.41 (9)	12.97 (30)
	Aqueous phototransformation (777191)	Irradiated	37.1 (2)	37.1 (2)
		Non-irradiated	1 (2)	1 (2)
	Aqueous phototransformation, indirect (3197468)	Irradiated	41.05 (7)	27.25 (16)
		Non-irradiated	Not formed	Not formed

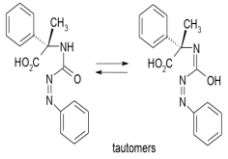
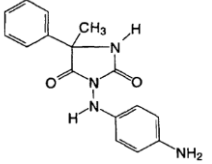
Code name, chemical name and structure	Study type (PMRA No.)	System conditions	Max % AR (d)	% AR at study end (study length, (d)
4<i>H</i>-Imidazol-4-one, 3,5-dihydro-5-methyl-2-(methylthio)-5-phenyl- 220.29 g/mol	Aerobic soil biotransformation (3197472)	UK loam	15.8 (14)	7.59 (193)
	Aerobic soil biotransformation (3197471)	UK silt loam	15.08 (29)	7.59 (193)
		US sandy loam	16.98 (14)	2.01 (181)
		UK loam 1	12.43 (4)	0 (181)
		UK loam 2	17.81 (92)	6.39 (365)
	Aerobic soil biotransformation (777193)	US sandy loam	17.39 (14)	1.09 (365)
		US loam	17.9 (14)	12.29 (365)
	Anaerobic soil biotransformation	N/A	N/A	N/A
	Aerobic aquatic biotransformation (777196)	UK sandy clay loam sediment	21.73 (152)	21.73 (152)
		UK sandy loam sediment	25.41 (120)	4.73 (152)
	Anaerobic aquatic biotransformation (777198)	UK clay sediment	2.76 (273)	1.32 (364)
S-enantiomer = RPA 411639  (racemate = RPA 406012) IUPAC name: 5-Methyl-2-methylthio-3-(4-nitrophenylamino)-5-phenyl-3,5-dihydroimidazol-4-one CAS name: 4 <i>H</i> -Imidazol-4-one, 3,5-dihydro-5-methyl-2-(methylthio)-3-[(4-nitrophenyl)amino]-5-phenyl- 356.4 g/mol	Hydrolysis	N/A	N/A	N/A
	Soil phototransformation (777189)	Irradiated	1.04 (9)	0.56 (30)
		Non-irradiated	0.79 (9)	0.7 (30)
	Soil phototransformation (777190)	Irradiated	4.31 (15)	2.46 (30)
		Non-irradiated	3.03 (15)	2.51 (30)
	Aqueous phototransformation	N/A	N/A	N/A
	Aerobic soil biotransformation (3197472)	UK loam	7.69 (64)	2.15 (365)
	Aerobic soil biotransformation (3197471)	UK silt loam	8.13 (14)	1.25 (193)
		US sandy loam	2.61 (56)	0.25 (181)
		UK loam 1	2.14 (14)	0.43 (181)
		UK loam 2	4.03 (56)	2.25 (365)
	Aerobic soil biotransformation (777193)	US sandy loam	13.98 (56)	1.45 (365)
		US loam	9.94 (56)	0.41 (365)
	Anaerobic soil biotransformation	Not applicable	N/A	N/A

Code name, chemical name and structure	Study type (PMRA No.)	System conditions	Max % AR (d)	% AR at study end (study length, (d)
S-enantiomer = RPA 413255  (racemate = RPA 410914) IUPAC name: 5-Methyl-2-methylthio-3-(2-nitrophenylamino)- 5-phenyl-3,5-dihydroimidazol-4-one CAS name: 4<i>H</i>-Imidazol-4-one, 3,5-dihydro-5-methyl-2-(methylthio)-3-(2-nitrophenylamino)-5-phenyl- 356.4 g/mol	Aerobic aquatic biotransformation	N/A	N/A	N/A
	Anaerobic aquatic biotransformation	N/A	N/A	N/A
	Hydrolysis	N/A	N/A	N/A
	Soil phototransformation (777189)	Irradiated	Not formed	Not formed
		Non-irradiated	0.56 (30)	0.56 (30)
	Soil phototransformation (777190)	Irradiated	6.96 (15)	5.04 (30)
		Non-irradiated	8.96 (30)	8.96 (30)
	Aqueous phototransformation	N/A	N/A	N/A
	Aerobic soil biotransformation (3197472)	UK loam	10.07 (64)	4.17 (365)
	Aerobic soil biotransformation (3197471)	UK silt loam	13.48 (14)	6.57 (193)
		US sandy loam	4.41 (56)	3.56 (181)
		UK loam 1	3.76 (28)	3.15 (181)
		UK loam 2	4.39 (56)	3.08 (365)
	Aerobic soil biotransformation (777193)	US sandy loam	12.95 (56)	3.91 (365)
		US loam	7.93 (56)	2.3 (365)
	Anaerobic soil biotransformation	N/A	N/A	N/A
	Aerobic aquatic biotransformation	N/A	N/A	N/A
	Anaerobic aquatic biotransformation	N/A	N/A	N/A
S-enantiomer = RPA 221607  (racemate = RPA 409446)	Hydrolysis	N/A	N/A	N/A
	Soil phototransformation	N/A	N/A	N/A
	Aqueous phototransformation	N/A	N/A	N/A
	Aerobic soil biotransformation (777193)	US sandy loam	16.01 (181)	10.26 (365)
		US loam	0.21 (121)	Not detected (365)
	Anaerobic soil biotransformation	N/A	N/A	N/A
	Aerobic aquatic biotransformation	N/A	N/A	N/A

Code name, chemical name and structure	Study type (PMRA No.)	System conditions	Max % AR (d)	% AR at study end (study length, (d))
IUPAC name: 5-Methyl-3-(4-nitrophenylamino)-5-phenylimidazolidine-2,4-dione CAS name: 2,4-Imidazolidinedione, 5-methyl-3-(4-nitrophenylamino)-5-phenyl- 326.31 g/mol	Anaerobic aquatic biotransformation	N/A	N/A	N/A
S-enantiomer = RPA 221701  (racemate = RPA 410995) IUPAC name: 5-Methyl-3-(2-nitrophenylamino)-5-phenylimidazolidine-2,4-dione CAS name: 2,4-Imidazolidinedione, 5-methyl-3-[(2-nitrophenyl)amino]-5-phenyl- 326.31 g/mol	Hydrolysis	N/A	N/A	N/A
	Soil phototransformation	N/A	N/A	N/A
	Aqueous phototransformation	N/A	N/A	N/A
	Aerobic soil biotransformation (777193)	US sandy loam	14.98 (181)	11.04 (365)
		US loam	Not formed	Not formed
	Anaerobic soil biotransformation	N/A	N/A	N/A
	Aerobic aquatic biotransformation	N/A	N/A	N/A
	Anaerobic aquatic biotransformation	N/A	N/A	N/A
S-enantiomer = RPA 410193 (AE 0540049)	Hydrolysis (777188)	pH 4	38.82 (31)	38.82 (31)
		pH 5	6.89 (31)	6.89 (31)
		pH 7	0.98 (31)	0.98 (31)

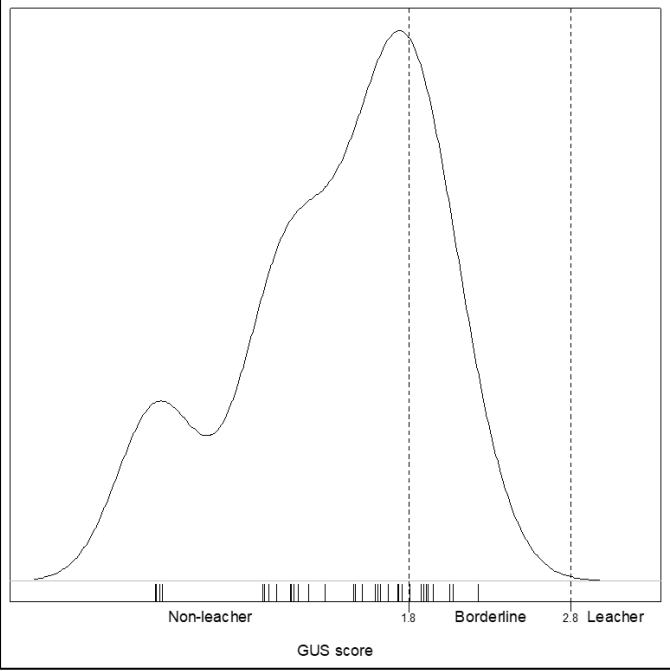
Code name, chemical name and structure	Study type (PMRA No.)	System conditions	Max % AR (d)	% AR at study end (study length, (d)
 (racemate = RPA 405862) IUPAC name: 5-Methyl-5-phenyl-3-phenylaminoimidazolidine-2,4-dione CAS name: 2,4-Imidazolidinedione, 5-methyl-5-phenyl-3-(phenylamino)- 281.31 g/mol		pH 9	3.89 (0)	3.89 (31)
	Soil phototransformation (777189)	Irradiated	2.34 (30)	2.34 (30)
		Non-irradiated	2.55 (21)	1.66 (30)
	Soil phototransformation (777190)	Irradiated	7.6 (21)	7.42 (30)
		Non-irradiated	4.22 (9)	1.69 (30)
	Aqueous phototransformation (777191)	Irradiated	13.6 (2)	13.6 (2)
		Non-irradiated	0.5 (2)	0.5 (2)
	Aqueous phototransformation (777192)	Irradiated	2.73 (2)	2.73 (2)
		Non-irradiated	0.71 (2)	0.71 (2)
	Aqueous phototransformation, indirect (3197468)	Irradiated	5.05 (9)	0 (16)
		Non-irradiated	Not formed	Not formed
	Aerobic soil biotransformation (777193)	US sandy loam	3.8 (3)	2.24 (365)
		US loam	0.52 (7)	Not detected (365)
	Anaerobic soil biotransformation	N/A	N/A	N/A
 Acetophenone	Hydrolysis	Not formed		
		Not formed		
	Aqueous phototransformation	N/A	N/A	N/A
	Aqueous phototransformation, indirect (3197468)	Irradiated	16.31 (9)	12.73 (13)
		Non-irradiated	Not formed	Not formed
	Aerobic soil biotransformation	N/A	N/A	N/A
	Anaerobic soil biotransformation	N/A	N/A	N/A

Code name, chemical name and structure	Study type (PMRA No.)	System conditions	Max % AR (d)	% AR at study end (study length, (d))
IUPAC name: 1-Phenylethanone CAS name: Ethanone, 1-phenyl- 120.2 g/mol	Aerobic aquatic biotransformation	N/A	N/A	N/A
	Anaerobic aquatic biotransformation	N/A	N/A	N/A
BCS-CV62706  IUPAC name: (5S,5'S)-3,3'-(1,2-diphenylhydrazine-1,2-diyl) bis[5-methyl-2-(methylthio)-5-phenyl-3,5-dihydro-4H-imidazol-4-one] 620.8 g/mol	Hydrolysis	No data		
	Soil phototransformation	No data		
	Aqueous phototransformation	No data		
	Aerobic soil biotransformation (3197471)	UK silt loam	6.82 (14)	5.72 (193)
	Anaerobic soil biotransformation	N/A	N/A	N/A
	Aerobic aquatic biotransformation	N/A	N/A	N/A
	Anaerobic aquatic biotransformation	N/A	N/A	N/A
	Field studies	No data		
RPA 418915  Not racemic IUPAC name: (S)-(S)-5-methyl-2-methylthio-3-[(4-oxo-2,5-cyclohexadien-1-ylidene) amino]-5-phenyl-3,5-dihydroimidazol-4-one 325.4 g/mol	Hydrolysis	N/A	N/A	N/A
	Soil phototransformation	N/A	N/A	N/A
	Aqueous phototransformation (777191)	Irradiated	5.7 (2)	5.7 (2)
		Non-irradiated	Not formed	Not formed
	Aqueous phototransformation (777192)	Irradiated	10.41 (1.6)	10.01 (2)
		Non-irradiated	0 (2)	0 (2)
	Aerobic soil biotransformation	N/A	N/A	N/A
	Anaerobic soil biotransformation	N/A	N/A	N/A
	Aerobic aquatic biotransformation	N/A	N/A	N/A
	Anaerobic aquatic biotransformation	N/A	N/A	N/A

Code name, chemical name and structure	Study type (PMRA No.)	System conditions	Max % AR (d)	% AR at study end (study length, (d)
S-enantiomer = RPA 413350  (racemate = RPA 409344) IUPAC name: 2-Phenyl-2-(phenyldiazenylcarboxamido)-propanoic acid CAS name: Propanoic acid, 2-phenyl-2-[[[(phenylazo)carbonyl]amino]- 297.32 g/mol	Hydrolysis (777188)	pH 4	0.75 (19)	0.38 (31)
		pH 5	1.16 (31)	1.16 (31)
		pH 7	2.92 (31)	2.92 (31)
		pH 9	32.33 (31)	32.33 (31)
	Soil phototransformation	N/A	N/A	N/A
	Aqueous phototransformation	N/A	N/A	N/A
	Aqueous phototransformation, indirect (3197468)	Irradiated	Not formed	Not formed
		Non-irradiated	10.91 (6)	7.47 (16)
	Aerobic soil biotransformation	N/A	N/A	N/A
	Anaerobic soil biotransformation	N/A	N/A	N/A
RPA 409445  IUPAC name: 3-(4-Aminophenylamino)-5-methyl-5-phenylimidazolidine-2,4-dione CAS name: 2,4-Imidazolidinedione, 3-(4-aminophenylamino)-5-methyl-5-phenyl- 296.33 g/mol	Hydrolysis	N/A	N/A	N/A
	Soil phototransformation (777189)	Irradiated	3.17 (30)	3.17 (30)
		Non-irradiated	2.58 (9)	1.65 (30)
	Aqueous phototransformation	N/A	N/A	N/A
	Aerobic soil biotransformation	N/A	N/A	N/A
	Anaerobic soil biotransformation	N/A	N/A	N/A
	Aerobic aquatic biotransformation	N/A	N/A	N/A
	Anaerobic aquatic biotransformation	N/A	N/A	N/A
	Minor (≤10%) transformation products			

Note: **Bolded** values indicate when transformation products were measured at ≥10% applied radioactivity.

Table 3 Leaching assessment of fenamidone

Leaching criteria of Cohen et al. (1984)¹		
Criteria	Value (Parent, fenamidone)	Meets leaching criterion?
Solubility in water at 20°C	7.8 mg/L (20–25°C)	No
K _d (mL/g): <5 and usually <1 or 2	2.13–8.94 mL/g	No
K _{oc} : <300	242–438	No
Henry's law constant (atm m ³ /mol): <10 ⁻²	1.34 × 10 ⁻¹⁰	Yes
pK _a : Negatively charged (either fully or partially) at ambient pH	N/A	No
Hydrolysis half-life: >20 weeks (>140 days)	411 days at pH 7	Yes
Soil phototransformation half-life: >1 week (>7 days)	Not a route of transformation	Yes
Half-life in soil: >2–3 weeks (>14–21 days)	16 days	Yes
Groundwater ubiquity score (GUS)² assessment		
Leachability classification based on calculated GUS indices: >2.8: leacher; >1.8 and <2.8: borderline leacher; <1.8: non-leacher.		
		
The GUS distribution indicate that fenamidone is considered a borderline leacher (<1.8 to <2.8).		

¹ Cohen et al. 1984. Potential pesticide contamination of groundwater from agricultural uses. In: R.F. Kruger and J.D., Seibor, eds. Treatment and disposal of pesticide wastes. American Chemistry Society Symposium Series No. 259, American Chemical Society: Washington, DC.

² Gustafson, D.I. 1989. Groundwater ubiquity score: A simple method for assessing pesticide leachability. Environmental Toxicology and Chemistry 8:339-357.

Table 4 Estimated environmental concentrations (EECs) for fenamidone and its transformation products in the environment (Excluding birds and small wild mammals)

Substance	EEC	Method of calculation	Notes
Soil: Screening level risk assessment			
Fenamidone	0.328 mg a.i./kg soil	The maximum cumulative application rate to soil based on 3×300 g a.i./ha at 5-day intervals to brassica crops and considering a representative half-life (t_R) of 16.25 days (90% upper confidence bound on the mean of 7 available values) in aerobic soil. The EEC in soil was calculated based on the maximum cumulative application rate to soil, assuming a soil bulk density of 1.5 g/cm^3 and a soil depth of 15 cm.	EECs in mg/kg dw soil were used to evaluate risks to earthworms, other soil invertebrates, and soil-dwelling beneficial arthropods. EECs in g a.i./ha were used to evaluate risks to non-target terrestrial plants (seedling emergence).
BCS-CV62706	0.797 mg TP/kg dw soil	EECs for the major TPs in soil were calculated based on the maximum application rate, assuming that 100% of the parent transformed into each TP on a molar basis and that no dissipation occurred between applications. The molar conversion factor was calculated as the molecular weight of the TP divided by the molecular weight of the parent. See Appendix I, Table 2 for the molecular weight of each compound.	EECs in mg TP/kg dw soil were used to evaluate risks to earthworms, other soil invertebrates, and soil-dwelling beneficial arthropods.
Water: Screening level risk assessment			
Fenamidone	15-cm depth	80-cm depth	EECs in surface water at 15-cm depth were used to determine risk to amphibians, and the 80-cm depth EECs were used to evaluate risks to all other aquatic organisms.
	0.583 mg a.i./L	0.109 mg a.i./L	
RPA 412636	0.366 mg TP/L	0.069 mg TP/L	
RPA 410193	0.54 mg TP/L	0.102 mg TP/L	
RPA 221701	0.63 mg TP/L	0.118 mg TP/L	
RPA 411639	0.687 mg TP/L	0.129 mg TP/L	
		The maximum cumulative application rate to water was calculated based on 3×300 g a.i./ha at 5-day intervals to brassica crops and considering a representative half-life (t_R) of 119.98 days (maximum of two available values in aerobic total aquatic systems). EECs in surface water were calculated considering a direct overspray of the maximum cumulative application rate to a 1-ha wetland with depths of 15 and 80 cm. EECs for the major TPs in soil were calculated based on the maximum application rate, assuming that 100% of the parent transformed into each TP on a molar basis and that no dissipation occurred between applications. The molar conversion factor was calculated as the molecular weight of the TP divided by the molecular weight of the parent. See Appendix I, Table 2 for the molecular weight of each compound.	

Substance	EEC		Method of calculation		Notes
RPA 412708	0.424 mg TP/L	0.08 mg TP/L			
RPA 413255	0.687 mg TP/L	0.129 mg TP/L			
RPA 413350	0.573 mg TP/L	0.107 mg TP/L			
RPA 418915	0.63 mg TP/L	0.118 mg TP/L			
BCS-CV62706	1.2 mg TP/L	0.224 mg TP/L			
RPA 221607	0.63 mg TP/L	0.118 mg TP/L			
Acetophenone	0.23 mg TP/L	0.043 mg TP/L			
Water: Refined risk assessment - Spray drift to freshwater environments					
Fenamidone	15-cm depth	80-cm depth	The refined spray drift EECs represent the percent drift at 1 m downwind from the point of direct pesticide application and are calculated by multiplying the screening level EEC by a drift factor based on application method and spray quality. Foliar ground boom application: 6% (medium spray drift droplet size) of 3×300 g a.i./ha applied to brassica crops at 5-day intervals with a representative half-life (t_R) of 119.98 days. Aerial application: 17% (coarse spray drift droplet size) of 6×100 g a.i./ha applied to potato at 7-day intervals with a representative half-life (t_R) of 119.98 days.		Freshwater drift EECs were calculated using the maximum cumulative rate.
	Ground: 0.035 mg a.i./L Aerial: 0.062 mg a.i./L	Ground: 0.00656 mg a.i./L Aerial: 0.0116 mg a.i./L			
Water: Refined risk assessment - Spray drift to estuarine/marine environments					
Fenamidone	15-cm depth	80-cm depth	The refined spray drift EECs represent the percent drift at 1 m downwind from the point of direct pesticide application and are calculated by multiplying the screening level EEC by a drift factor based on application method and spray quality.		Estuarine/marine drift EECs were based on the maximum rate from a single application.
	N/A	Ground: 0.00225 mg a.i./L Aerial: 0.00213 mg a.i./L			
Water: Refined risk assessment - Runoff					
Fenamidone	15-cm depth	80-cm depth	Pore water	Ecological modelling was conducted on fenamidone alone, as transformation products were generally much	All EECs were based on the PEI regional scenario because it was the

Substance	EEC		Method of calculation				Notes							
	Foliar ground boom applications			less toxic than the parent and would not likely be found in the environment at high enough levels to cause risks of concern. The runoffEECs in water are calculated by modelling a 10-ha field adjacent to 1-ha water bodies at two different depths, 80 cm and 15 cm, using the Pesticide in Water Calculator (PWC; version 2.0). The PWC model calculates the amount of pesticide entering the water body and the subsequent transformation of the pesticide in the water and sediment. In ecological modelling, pesticide enters the water by runoff only, and deposition of pesticide on the water body due to spray drift is not included. The model is run for 50 years.			highest concentrations out of all regional scenarios modelled.							
	96-hr: 0.1532 mg a.i./L	24-hr: 0.0495 mg a.i./L	Peak: 0.0359 mg a.i./L				EECs in surface water at 15-cm depth were used to determinerisk to amphibians,							
	21-d: 0.1013 mg a.i./L	96-hr: 0.0486 mg a.i./L					EECs in surface water at 80-cm depth were used to evaluate risks to all other aquatic organisms.							
	Seed piece treatment + aerial applications			For each year of the simulation, PWC calculates peak (or daily maximum) and time-averaged concentrations. The time-averaged concentrations are calculated by averaging the peak concentrations over different time periods (24 hours, 96 hours, 21 days, 60 days, and 90 days). The highest value of these averages for each calendar year is then calculated. The 90 th percentiles of these yearly maxima are reported as the EECs for that period. In addition, the peak and 21-day average EECs in sediment pore water are generated by the model. Ecological water model input parameters are presented below:	<table><tr><th>Parameter</th><th>Drinking Water</th><th>Ecological Water</th><th>Details</th></tr><tr><td>K_{oc} (L/kg)</td><td>16.6</td><td>309.1</td><td>Drinking water: The 20th percentile of 5 values for the transformation product RPA 412708 (the lowest K_{oc} among all compounds in</td></tr></table>		Parameter	Drinking Water	Ecological Water	Details	K _{oc} (L/kg)	16.6	309.1	Drinking water: The 20 th percentile of 5 values for the transformation product RPA 412708 (the lowest K _{oc} among all compounds in
	Parameter	Drinking Water	Ecological Water				Details							
	K _{oc} (L/kg)	16.6	309.1				Drinking water: The 20 th percentile of 5 values for the transformation product RPA 412708 (the lowest K _{oc} among all compounds in							
96-hr: 0.0638 mg a.i./L	24-hr: 0.0239 mg a.i./L	Peak: 0.0180 mg a.i./L	EECs in pore water were used to determine risk to sediment dwelling organisms.											
21-d: 0.0466 mg a.i./L	96-hr: 0.0235 mg a.i./L													
		21-d: 0.0225 mg a.i./L												

Substance	EEC		Method of calculation				Notes
						the residue definition). Ecological: The 20 th percentile of 5 values for parent.	
			Water column metabolism half-life ¹ (day) at 20 °C	630.5	119.98	80 th percentile of 3 values (2 studies).	
			Benthic metabolism half-life ² (day) at 20 °C	2257	1105	Single study	
			Aqueous photolysis half-life (day) at 40 °N	24.6	7.4	3 studies (80 th percentile of 3 values from the studies)	
			Hydrolysis half-life (day) at 25 °C (pH 7)	Stable	410.7	Single study	
			Soil half-life ³ (day) at 20 °C	2.23 × 1011	16	90% upper confidence bound on the mean of 7 values (3 studies).	
¹ Aerobic aquatic whole system ² Anaerobic aquatic whole system ³ Biodegradation in aerobic soil							
Plant surfaces: Screening level							

Substance	EEC	Method of calculation	Notes	
Fenamidone	On-field: 662.2 g a.i./ha	The on-field EEC is calculated with the highest rate of 300 g a.i./ha, 3 applications with a 5-day re-application interval and a default DT ₅₀ of 10 days for leaf surfaces and the off-field EEC is calculated to be 6% of this value to account for the expected spray drift using a medium droplet size from field sprayer application equipment.	EECs used to evaluate on-field and off-field risks to beneficial arthropods and non-target terrestrial plants (vegetative vigour).	
	Off-field: 39.73 g a.i./ha			
Plant surfaces: Refined risk assessment				
Predators and Parasitoids - Ground boom application on brassica crops (3 × 300 g a.i./ha)				
Fenamidone (EXP10623A; 517 g a.i./L)	<i>T. pyri</i> On-field, using 0.9 foliar interception factor: 596 g a.i./ha	The on-field EECs are calculated differently depending on the study methodology for the different beneficial arthropods.	EECs used to evaluate on-field and off-field refined risks to beneficial arthropods.	
	<i>T. pyri</i> On-field, using 0.25 foliar interception factor: 165.5 g a.i./ha	The on-field EECs for <i>T. pyri</i> were further refined by multiplying a foliar interception factor by the screening level EEC value. No refinement was needed for the off-field EEC.		
	<i>T. pyri</i> Off-field: Refinement not required, did not exceed LOC at screening level.	The on-field EECs for <i>A. rhopalosiphii</i> did not require further foliar interception factors applied to the screening level EEC because the study provided applied fenamidone to potted plants which would have already accounted for a more realistic foliar application interception factor. No refinement was needed to better characterize the on- or off-field risk.		
	<i>A. rhopalosiphii</i> On-field: 662.2 g a.i./ha ¹			
	<i>A. rhopalosiphii</i> Off-field: 39.73 g a.i./ha ¹			
Predators and Parasitoids - Aerial application on potatoes (6 × 100 g a.i./ha)				
Fenamidone (EXP10623A; 517 g a.i./L)	<i>T. pyri</i> On-field: 246 g a.i./ha	The on-field EECs are calculated differently depending on the study methodology for the different beneficial arthropods.	EECs used to evaluate on-field and off-field refined risks to beneficial arthropods.	
	<i>T. pyri</i> On-field, using 0.8 foliar interception factor: 196.8 g a.i./ha			
	<i>T. pyri</i> On-field, using 0.50 foliar interception factor: 123 g a.i./ha			
	<i>T. pyri</i> On-field, using 0.15 foliar interception factor: 36.9 g a.i./ha	For both species, the on-field EEC is calculated with the highest aerial application rate of 100 g a.i./ha, 6 applications with a 7-day re-application interval and a default DT ₅₀ of 10 days for leaf surfaces. For <i>T. pyri</i> , various foliar interception factors were applied to refine the on-field risk. For the off-field risk a 17% drift factor was applied.		
	<i>T. pyri</i> Off-field (17% drift): 41.82 g a.i./ha			
	<i>A. rhopalosiphii</i> On-field: 246 g a.i./ha			For <i>A. rhopalosiphii</i> , the off-field risk was refined by applying a 17% drift factor and then also a vegetation distribution factor.
	<i>A. rhopalosiphii</i> Off-field (17% drift):			

Substance	EEC	Method of calculation	Notes
	41.82 g a.i./ha <i>A. rhopalosiphi</i> Off-field (17% drift), using 0.1 vegetation distribution factor: 4.2 g a.i./ha		
Bee matrices			
Fenamidone (98% purity)	8.58 µg a.i./bee/d (adult, acute oral) 29.4 mg a.i./kg diet (larval chronic)	Oral exposure estimates for bees (where the toxicity endpoints are in µg a.i./bee): - For foliar applications: maximum single application rate (kg a.i./ha) × 98 µg a.i./g (default tall grass residues) × consumption rate* - For soil applications: maximum single application rate (kg a.i./ha) × Briggs EEC × consumption rate* - For seed treatments: default residue level of 1 µg a.i./g × consumption rate* * The consumption rate is 0.292 g/bee/day for adult bees and 0.124 g/bee/day for larvae. [Note that consumption rates are for honey bee, which are used as a surrogate for all bees. If bee toxicity for non-honey bees is being used in the risk assessment, consumption rates for relevant bee should be used.] Notes: - Where the toxicity endpoint is a concentration (mg a.i./kg diet), the level of exposure should also be estimated as the concentration in the same units. For chronic adult and larva studies, the concentration-based endpoint (mg a.i./kg diet) should be used in the risk assessment as it is considered more reliable than the daily-dose-based endpoint (µg a.i./bee/day). This is because it represents the exposure irrespective of bee growth and variations in daily food consumption throughout the study, which can be highly variable. - Empirical residue data can be used to refine the risk assessment, ideally as residues measured from plant pollen and nectar.	Used to evaluate risks to pollinators (bees).
Fenamidone SC 500 G (43% purity)	29.4 mg a.i./kg diet (adult chronic)		
Fenamidone (98% purity)	0.72 µg a.i./bee/d (adult acute contact)		
		Estimated contact exposure (µg a.i./bee) = 2.4 µg a.i./bee per kg a.i./ha × maximum single application rate (300 kg a.i./ha)	

Table 5 Toxicity to Non-Target Species

Organism	Exposure	Test substance	Endpoint	Degree of toxicity ¹ and/or comments	PMRA No.
Terrestrial Invertebrates					
Earthworm (<i>Eisenia fetida</i>)	14-d Acute	Fenamidone	LC ₅₀ = 25 mg a.i./kg soil dw	N/A	777013
	56-d Chronic	Fenamidone	NOEC = 0.63 mg a.i./kg soil dw No significant effects up to the highest tested concentration.	N/A	3197487, 3775400
		BCS-CV62706	NOEC = 10 mg TP/kg soil dw No significant effects up to the highest tested concentration.	N/A	3775400
Collembola (<i>Folsomia candida</i>)	28-d Chronic	Fenamidone	NOEC = 4.51 mg a.i./kg soil dw No significant effects up to the highest tested concentration.	N/A	3775400
		BCS-CV62706	NOEC = 50 mg TP/kg soil dw No significant effects up to the highest tested concentration.	N/A	3775400
Predatory arthropod (<i>Typhlodromus pyri</i>)	14-d Contact (extended laboratory test)	EXP10623A (517 g a.i./L)	LR ₅₀ > 159.6 g a.i./ha	N/A	777019
Parasitic arthropod (<i>Aphidius rhopalosiphi</i>)	48-h Contact (extended laboratory test)	EXP10623A (517 g a.i./L)	LR ₅₀ > 9.98 g a.i./ha and < 133 g a.i./ha ²	N/A	777020
Predatory arthropod (<i>Hypoaspis aculeifer</i>)	14-d Reproductive	Fenamidone SC 500G (45.1% purity)	NOEC = 45.1 mg a.i./kg soil dw (number of juveniles) LOEC = 80.3 mg a.i./kg soil dw	N/A	3775400
	14-d Reproductive	BCS-CV62706	NOEC = 50 mg TP/kg soil dw No significant effects up to the highest tested concentration.	N/A	3775400

Organism	Exposure	Test substance	Endpoint	Degree of toxicity ¹ and/or comments	PMRA No.
Pollinators (<i>Apis mellifera</i>)	Adult acute oral (96-hr)	Fenamidone (98% a.i.)	LD ₅₀ > 159.8 µg a.i./bee/d	Practically nontoxic	777017, 3775400
	Adult acute contact (96-hr)	Fenamidone (98% a.i.)	LD ₅₀ = 25.7 µg a.i./bee/d	Practically nontoxic	3775400
	22-d Larval repeated exposure (4-d exposure)	Fenamidone (98% purity)	NOAEC = 8.64 mg a.i./kg diet (emergence)	N/A	3197502
	10-d Adult chronic	Fenamidone SC 500G (43% purity)	NOAEC = 25 mg a.i./kg diet (mortality)	N/A	2558360, 3775400
Birds					
Bobwhite quail (<i>Colinus virginianus</i>)	Acute oral	Fenamidone	LD ₅₀ > 2000 mg a.i./kg bw	Practically nontoxic	777050, 3775400
	5-d Dietary	RPA 412708	LD ₅₀ = 723 mg TP/kg bw/day	Slightly toxic	3197523, 3775400
Mallard duck (<i>Anas platyrhynchos</i>)	140-d Reproduction	Fenamidone	NOAEL = 120 mg a.i./kg bw/day No significant effects up to the highest tested concentration.	N/A	3197483
Small wild mammals					
Rat	Acute oral	Fenamidone	LD ₅₀ = 2028 mg a.i./kg bw	Practically nontoxic	777088
		RPA 410193	LD ₅₀ > 2000 mg TP/kg bw	Practically nontoxic	777161
		RPA 412636	LD ₅₀ = 1520 mg TP/kg bw	Slightly toxic	777155
		RPA 412708	LD ₅₀ = 176 mg TP/kg bw	Moderately toxic	777167
	2-Generation reproduction	Fenamidone	NOAEL = 3.9 / 5.2 mg a.i./kg bw/day (males/females) LOAEL ≥ 63.8 / 84.4 mg/kg bw/day, males/females (decreased body weight gain)	N/A	777132, 1065313
Terrestrial vascular plants					
Vascular plant	21-d Seedling emergence (<i>Lactuca sativa</i>)	EXP10623A (517 g Fenamidone/L)	ER ₂₅ / ER ₅₀ > 1200 g a.i./ha	N/A	777036, 3775400
	21-d Vegetative vigour (Various species)	EXP10623A (517 g Fenamidone/L)	ER ₂₅ > 1200 g a.i./ha	N/A	3197490, 3775400
Freshwater species					

Organism	Exposure	Test substance	Endpoint	Degree of toxicity ¹ and/or comments	PMRA No.
Water flea (<i>Daphnia magna</i>)	48-h Acute	Fenamidone	EC ₅₀ = 0.055 mg a.i./L	Very highly toxic	3197504, 3775400
		RPA 412636	EC ₅₀ > 97.4 mg TP/L	No effects observed at the highest concentration	777022, 3775400
		RPA 410193	EC ₅₀ > 21.1 mg TP/L	No effects observed at the highest concentration	777023, 3775400
		RPA 221701	EC ₅₀ > 10 mg TP/L	No effects observed at the highest concentration	3775400
		RPA 411639	EC ₅₀ = 2.5 mg TP/L	Moderately toxic	3197481, 3775400
		RPA 412708	EC ₅₀ > 100.8 mg TP/L	Practically nontoxic	777024, 3775400
		RPA 413255	EC ₅₀ = 9.7 mg TP/L	Moderately toxic	777025, 3775400
		RPA 413350	EC ₅₀ = 3.78 mg TP/L	Moderately toxic	3775400
		RPA 418915	EC ₅₀ = 1.21 mg TP/L	Moderately toxic	3775400
		BCS-CV62706	EC ₅₀ = 0.8 mg TP/L	Highly toxic	3775400
		RPA 221607	EC ₅₀ > 10 mg TP/L	No effects observed at the highest concentration	3775400
		Acetophenone	LC ₅₀ = 162 mg TP/L	Practically nontoxic	3775411
	21-d Chronic	Fenamidone	NOEC = 0.0125 mg a.i./L (live juveniles/adult/d, length of survivors)	N/A	777026
		RPA 412708	NOEC = 16 mg TP/L (parental length and body weight)	N/A	3775400
Midge (<i>Chironomus tentans</i>)	10-d Chronic (water-sediment system; spiked sediment)	Fenamidone	Pore water: NOEC = 0.285 mg a.i./L (growth) Overlying water: NOEC = 0.0415 mg a.i./L (growth)	N/A	3197503, 3775400
	48-h Acute	BCS-CV62706	LC ₅₀ = 0.78 mg TP/L	Highly toxic	3775400

Organism	Exposure	Test substance	Endpoint	Degree of toxicity ¹ and/or comments	PMRA No.
Harlequin fly (<i>Chironomus riparius</i>)	24-d Chronic (water-sediment system; spiked water)	Fenamidone	NOEC = 0.05 mg a.i./L (mean development and emergence rates)	N/A	1108385, 3775400
Rainbow trout (<i>Oncorhynchus mykiss</i>)	96-hr Acute	Fenamidone	LC ₅₀ = 0.74 mg a.i./L	Highly toxic	777042, 3775400
		RPA 412636	LC ₅₀ > 34.4 mg TP/L	No effects observed at the highest concentration	777043, 3775400
		RPA 412708	LC ₅₀ > 98 mg TP/L	No effects observed at the highest concentration	777044, 3775400
		RPA 413255	LC ₅₀ = 3.61 mg TP/L	Moderately toxic	777045, 3775400
		RPA 413350	LC ₅₀ = 3.2 mg TP/L	Moderately toxic	3197527, 3775400
Fathead minnow (<i>Pimephales promelas</i>)	Acute	Acetophenone	LC ₅₀ = 155 mg TP/L	Practically nontoxic	3775411
	32-d Chronic (early life stage)	Fenamidone	NOEC = 0.041 mg a.i./L No significant effects up to the highest tested concentration.	N/A	777048, 3775400
Amphibians (fish endpoints used as surrogate data)	96-hr Acute	Fenamidone	LC ₅₀ = 0.74 mg a.i./L	Highly toxic	777042, 3775400
	32-d Chronic (early life stage)	Fenamidone	NOEC = 0.041 mg a.i./L No significant effects up to the highest tested concentration.	N/A	777048, 3775400
Green alga (<i>Pseudokirchneriella subcapitata</i>)	72-hr Acute	RPA 412636	EC ₅₀ > 35 mg TP/L	No effects observed at the highest concentration	3772714
		RPA 413350	EC ₅₀ = 0.099 mg TP/L	Very highly toxic	3772714
Diatom (<i>Navicula pelliculosa</i>)	5-d Acute	Fenamidone	EC ₅₀ > 0.9 mg a.i./L	No effects observed at the highest concentration	777034, 3775400
Duckweed (<i>Lemna gibba</i>)	14-d Acute	Fenamidone	EC ₅₀ > 0.88 mg a.i./L	No effects observed at the highest concentration	777037, 3775400
Estuarine/Marine species					

Organism	Exposure	Test substance	Endpoint	Degree of toxicity ¹ and/or comments	PMRA No.
Mysid shrimp (<i>Americamysis bahia</i>)	96-hr Acute	Fenamidone	LC ₅₀ = 0.069 mg a.i./L	Very highly toxic	777028, 3775400
	21-d Chronic full life cycle	Fenamidone	NOEC = 0.0095 mg a.i./L (offspring/female/repro day)	N/A	777041, 3775400
Atlantic oyster (<i>Crassostrea virginica</i>)	96-hr Acute	Fenamidone	EC ₅₀ = 0.12 mg a.i./L	Highly toxic	777040, 3775400
Sheepshead minnow (<i>Cyprinodon variegatus</i>)	96-hr Acute	Fenamidone	LC ₅₀ = 2.5 mg a.i./L	Moderately toxic	777047, 3775400
Diatom (<i>Skeletonema costatum</i>)	72-hr Acute	Fenamidone	EC ₅₀ = 0.08 mg a.i./L	Very highly toxic	777035, 3775400

¹ USEPA classification, where applicable.

² In study PMRA No. 777020, a non-definitive endpoint was determined (>9.89 g a.i./ha) however, a rate at which mortality was greater than 50% was also provided (133 g a.i./ha). At the 9.98 g a.i./ha rate, mortality was 47.5% and it was 100% at the 133 g a.i./ha rate. As such, the true LR₅₀ is between the rate range of 9.98 and 133 g a.i./ha.

Table 6 Screening level risk assessment for non-target terrestrial organisms (Excluding birds and small wild mammals)

Organism	Test substance	Exposure type	EEC	Endpoint value	UF	Effects metric	RQ	LOC	LOC exceeded?
Invertebrates									
Earthworm (<i>Eisenia fetida</i>)	Fenamidone	14-d Acute	0.328 mg a.i./kg soil	25 mg a.i./kg soil dw	2	12.5 mg a.i./kg soil dw	0.03	1	No
	Fenamidone	56-d Chronic	0.328 mg a.i./kg soil	0.63 mg a.i./kg soil dw	1	0.63 mg a.i./kg soil dw	0.5	1	No
	BCS-CV62706	56-d Chronic	0.797 mg TP/kg soil	10 mg TP/kg soil dw	1	10 mg TP/kg soil dw	0.08	1	No
Collembola (<i>Folsomia candida</i>)	Fenamidone	28-d Chronic	0.328 mg a.i./kg soil	4.51 mg a.i./kg soil dw	1	4.51 mg a.i./kg soil dw	0.07	1	No
	BCS-CV62706	28-d Chronic	0.797 mg TP/kg soil	50 mg TP/kg soil dw	1	50 mg TP/kg soil dw	0.02	1	No
Predatory arthropod (<i>Typhlodromus pyri</i>)	EXP10623A (517 g a.i./L)	14-d Contact	On-field: 662.2 g a.i./ha	> 159.6 g a.i./ha	1	> 159.6 g a.i./ha	< 4.2	1	Yes
			Off-field: 39.73 g a.i./ha	> 159.6 g a.i./ha	1	> 159.6 g a.i./ha	< 0.3	1	No

Organism	Test substance	Exposure type	EEC	Endpoint value	UF	Effects metric	RQ	LOC	LOC exceeded?
Parasitic arthropod (<i>Aphidius rhopalosiphi</i>)	EXP10623A (517 g a.i./L)	14-d Contact	On-field: 662.2 g a.i./ha	> 9.98 g a.i./ha	1	> 9.98 g a.i./ha	< 66	1	Yes
				< 133 g a.i./ha	1	< 133 g a.i./ha	> 5.0	1	Yes
			Off-field: 39.73 g a.i./ha	> 9.98 g a.i./ha	1	> 9.98 g a.i./ha	< 4.0	1	Yes
				< 133 g a.i./ha	1	< 133 g a.i./ha	> 0.3	1	No
Predatory arthropod (<i>Hypoaspis aculeifer</i>)	Fenamidone SC 500 G (45.1% purity)	14-d Reproductive	0.328 mg a.i./kg soil	45.1 mg a.i./kg soil dw	1	45.1 mg a.i./kg soil dw	0.07	1	No
	BCS-CV62706	14-d Reproductive	0.797 mg TP/kg soil	50 mg TP/kg soil dw	1	50 mg TP/kg soil dw	0.02	1	No
Pollinator (<i>Apis mellifera</i>)	Fenamidone (98% a.i.)	Adult acute oral (96-hr)	8.58 µg a.i./bee/d	> 159.8 µg a.i./bee/d	1	> 159.8 µg a.i./bee/d	< 0.05	0.4	No
	Fenamidone (98% a.i.)	Adult acute contact (96-hr)	0.72 µg a.i./bee/d	25.7 µg a.i./bee/d	1	25.7 µg a.i./bee/d	0.03	0.4	No
	Fenamidone (98% purity)	22-d Larval repeated exposure (4-d exposure)	29.4 mg a.i./kg diet	8.64 mg a.i./kg diet	1	8.64 mg a.i./kg diet	3.4	1	Yes
	Fenamidone SC 500 G (43% purity)	10-d Adult chronic	29.4 mg a.i./kg diet	25 mg a.i./kg diet	1	25 mg a.i./kg diet	1.2	1	Yes
Vascular plants									
Vascular plants	EXP106	21-d Seedling emergence	738 g a.i./ha	> 1200 g a.i./ha	1	> 1200 g a.i./ha	< 0.6	1	No
		21-d Vegetative vigour	662 g a.i./ha	> 1200 g a.i./ha	1	> 1200 g a.i./ha	< 0.6	1	No

Table 7 Refined risk assessment for non-target terrestrial organisms (Excluding birds and small wild mammals)

Organism	Test substance	Exposure type	EEC	Endpoint value	UF	Effects metric	RQ	LOC	LOC exceeded?
Invertebrates									
Predators and parasitoids - Ground boom application on brassica crops (3 × 300 g a.i./ha)									
Predatory arthropod (<i>Typhlodromus pyri</i>)	EXP10623A (517 g a.i./L)	14-d Contact (extended laboratory test)	On-field, using 0.9 foliar interception factor: 596 g a.i./ha	> 159.6 g a.i./ha	1	> 159.6 g a.i./ha	< 3.7	1	Yes
			On-field, using 0.25 foliar interception factor: 165.5 g a.i./ha	> 159.6 g a.i./ha	1	> 159.6 g a.i./ha	< 1.0	1	Yes
			Off-field: Refinement not required, did not exceed LOC at screening level.	> 159.6 g a.i./ha	1	> 159.6 g a.i./ha	Refinement not required. < LOC in screening level	1	No
Parasitic arthropod (<i>Aphidius rhopalosiphi</i>) ¹	EXP10623A (517 g a.i./L)	14-d Contact (extended laboratory test)	On-field: 662.2 g a.i./ha	> 9.98 g a.i./ha	1	> 9.98 g a.i./ha	< 66	1	Yes
				< 133 g a.i./ha	1	< 133 g a.i./ha	> 5.0	1	Yes
			Off-field: 39.73 g a.i./ha	> 9.98 g a.i./ha	1	> 9.98 g a.i./ha	< 4.0	1	Yes
				< 133 g a.i./ha	1	< 133 g a.i./ha	> 0.3	1	No
Predators and parasitoids - Aerial application on potatoes (6 × 100 g a.i./ha)									
Predatory arthropod (<i>Typhlodromus pyri</i>)	EXP10623A (517 g a.i./L)	14-d Contact (extended laboratory test)	On-field: 246 g a.i./ha	> 159.6 g a.i./ha	1	> 159.6 g a.i./ha	< 1.5	1	Yes
			On-field, using 0.8 foliar interception factor: 196.8 g a.i./ha	> 159.6 g a.i./ha	1	> 159.6 g a.i./ha	< 1.2	1	Yes
			On-field, using 0.50 foliar interception factor: 123 g a.i./ha	> 159.6 g a.i./ha	1	> 159.6 g a.i./ha	< 0.8	1	No
			On-field, using 0.15 foliar interception factor: 36.9 g a.i./ha	> 159.6 g a.i./ha	1	> 159.6 g a.i./ha	< 0.2	1	No
			Off-field (17% drift): 41.82 g a.i./ha	> 159.6 g a.i./ha	1	> 159.6 g a.i./ha	< 0.3	1	No

Organism	Test substance	Exposure type	EEC	Endpoint value	UF	Effects metric	RQ	LOC	LOC exceeded?
Parasitic arthropod (<i>Aphidius rhopalosiphi</i>)	EXP10623A (517 g a.i./L)	14-d Contact (extended laboratory test)	On-field: 246 g a.i./ha	>9.98 g a.i./ha	1	> 9.98 g a.i./ha	< 25	1	Yes
				< 133 g a.i./ha	1	< 133 g a.i./ha	> 1.8	1	Yes
			Off-field (17% drift): 41.82 g a.i./ha	> 9.98 g a.i./ha	1	> 9.98 g a.i./ha	< 4.2	1	Yes
				< 133 g a.i./ha	1	< 133 g a.i./ha	> 0.3	1	No
			Off-field (17% drift), using 0.1 vegetation distribution factor: 4.2 g a.i./ha	> 9.98 g a.i./ha	1	> 9.98 g a.i./ha	< 0.4	1	No
				< 133 g a.i./ha	1	< 133 g a.i./ha	>0.03	1	No
Pollinators – Tier I refined risk assessment (laboratory studies compared to residues measured in the field ²)									
Pollinator (<i>Apis mellifera</i>)	Fenamidone (98% purity)	22-d Larval repeated exposure (4-d exposure)	Mean leaf lettuce residue: 6.81 mg a.i./kg diet	8.64 mg a.i./kg diet	1	8.64 mg a.i./kg diet	0.8	1	No
			Maximum leaf lettuce residue: 17.5 mg a.i./kg diet	8.64 mg a.i./kg diet	1	8.64 mg a.i./kg diet	2.0	1	Yes
	Fenamidone SC 500 G (43% purity)	10-d Adult chronic	Mean leaf lettuce residue: 6.81 mg a.i./kg diet	25 mg a.i./kg diet	1	25 mg a.i./kg diet	0.3	1	No
			Maximum leaf lettuce residue: 17.5 mg a.i./kg diet	25 mg a.i./kg diet	1	25 mg a.i./kg diet	0.7	1	No

¹ The screening level risk assessment for parasitic arthropods (*Aphidius rhopalosiphi*) is used for the refined risk assessment as well because the study provided applied fenamidone to potted plants which would have already accounted for a more realistic foliar application interception factor. No refinement was needed to better characterize the risk.

² In the absence of field residue data generated for pollinator studies, field residue data on fenamidone that was submitted for the health risk assessment were used in a Tier I refined risk assessment. The data was published in PRD2007-07 Proposed Registration Decision; Appendix I; Table 1 on page 26. The application rate in most of the residue studies was 1.2 kg a.i./ha, which is higher than the maximum cumulative rate of 900 g a.i./ha on the registered labels and the residues are considered conservative in the pollinator risk assessment. To derive a chronic EEC value for use in the refined chronic oral risk assessment, the highest daily mean residue value was selected from residue trials. The highest daily mean was considered the most relevant for the chronic risk assessment as bees in the Tier I chronic studies are typically exposed to fenamidone over a prolonged period of time (3-4 days for larvae and 10 days for adults).

Table 8 Tier II Semi-field/tunnel studies on pollinators

Organism	Test substance	Study type	Study design	Study results	PMRA No.
Honey bee (<i>Apis mellifera</i>)	Fenamidone SC 500 G (43% purity)	Tier II tunnel	Test crop: <i>Phacelia tanacetifolia</i> (flowering bee attractive plant) Test species: medium-sized honey bee hives Test chemical: Fenamidone SC 500 G (43% purity) Application rate: 147.5 g a.i./ha × 1 applied during full flowering (0 DAT), bees had been introduced into tunnels 3 days prior to treatment. Number of hives tested: 3 tunnels (3 replicates each) for control, treatment and reference item (fenoxycarb). Plot size: 85 m ² Exposure and observation period: 28 days Effect parameters: Mortality (dead bee traps and sheets), foraging activity, behaviour, colony condition (brood nest, different brood stages, and stores); colony strength (# of bees per colony), brood development success (brood termination rate, brood index, and brood compensation index). Residue samples: No. Location: Switzerland Year: 2013	Fenamidone SC 500 G did not cause any adverse effects on the survival of adult bees and immature honey bee life stages, foraging activity and behaviour at a rate of 150 g a.i./ha. Furthermore, no adverse effects on colony strength, condition of the colony, brood termination, brood index and brood compensation index were observed. There were significant effects to adults and brood in the positive control hives (300 g a.i./ha fenoxycarb).	3197498
	Fenamidone SC 500 G (45.1% fenamidone)	Tier II brood feeding test	Test crop: N/A Test species: honey bee colonies Test chemical: Fenamidone SC 500 G (45.1% fenamidone) Application rate: 1 single application of 0.333 g product (0.15 g a.i.)/L for Fenamidone SC 500 treatment group. Number of hives tested:	Fenamidone SC 500 G did not cause any adverse effects to adults, young and old larvae or of pupae at a feeding rate of 0.15 g a.i./L (150 ppm). There was an increase in brood termination rate of eggs. Honey bee brood (including larvae, eggs and pupae) and adults were negatively	3197529

Organism	Test substance	Study type	Study design	Study results	PMRA No.
			3 bee colonies for control, treatment and for reference item (fenoxycarb). Plot size: N/A Exposure and observation period: 21 days Effect parameters: Mortality of adult bees as well as pupae or larvae, bee brood development (eggs, young and old larvae); changes in behaviour. Residue samples: No Location: Germany Year: 2012	affected by the positive control (fenoxycarb).	

Table 9 Screening level risk assessment for birds and small wild mammals

Organism	Effects metric ¹ (mg a.i./kg bw/d)	Feeding guild (food item)	EDE ² (mg a.i./kg bw)	RQ	LOC	LOC exceeded?
Birds						
Fenamidone						
Small-sized bird (0.02 kg)						
Acute oral	> 200	Insectivore	53.7	< 0.3	1	No
Reproduction	120	Insectivore	53.7	0.4	1	No
Medium-sized bird (0.1 kg)						
Acute oral	> 200	Insectivore	42.2	< 0.2	1	No
Reproduction	120	Insectivore	42.2	0.4	1	No
Large-sized bird (1 kg)						
Acute oral	> 200	Herbivore (short grass)	27.2	< 0.1	1	No
Reproduction	120	Herbivore (short grass)	27.2	0.2	1	No
TP RPA 412708						
Small-sized bird (0.02 kg)						
Acute dietary	72.3	Insectivore	51.6	0.7	1	No
Medium-sized bird (0.1 kg)						
Acute dietary	72.3	Insectivore	40.5	0.6	1	No

Organism	Effects metric ¹ (mg a.i./kg bw/d)	Feeding guild (food item)	EDE ² (mg a.i./kg bw)	RQ	LOC	LOC exceeded?
Large-sized bird (1 kg)						
Acute dietary	72.3	Herbivore (short grass)	26.1	0.4	1	No
Mammals						
Fenamidone						
Small-sized small wild mammal (0.015 kg)						
Acute oral	202.8	Insectivore	30.7	0.2	1	No
Reproduction	3.9	Insectivore	30.7	7.9	1	Yes
Medium-sized small wild mammal (0.035 kg)						
Acute oral	202.8	Herbivore (short grass)	58.4	0.3	1	No
Reproduction	3.9	Herbivore (short grass)	58.4	15	1	Yes
Large-sized small wild mammal (1 kg)						
Acute oral	202.8	Herbivore (short grass)	32.1	0.2	1	No
Reproduction	3.9	Herbivore (short grass)	32.1	8.2	1	Yes
TP RPA 412708						
Small-sized small wild mammal (0.015 kg)						
Acute oral	17.6	Insectivore	29.5	1.7	1	Yes
Medium-sized small wild mammal (0.035 kg)						
Acute oral	17.6	Herbivore (short grass)	56.1	3.2	1	Yes
Large-sized small wild mammal (1 kg)						
Acute oral	17.6	Herbivore (short grass)	30.9	1.8	1	Yes
TP RPA 410193						
Small-sized small wild mammal (0.015 kg)						
Acute oral	> 200	Insectivore	37.7	< 0.2	1	No
Medium-sized small wild mammal (0.035 kg)						
Acute oral	> 200	Herbivore (short grass)	71.7	< 0.4	1	No
Large-sized small wild mammal (1 kg)						
Acute oral	> 200	Herbivore (short grass)	39.5	< 0.2	1	No
TP RPA 412636						
Small-sized small wild mammal (0.015 kg)						

Organism	Effects metric ¹ (mg a.i./kg bw/d)	Feeding guild (food item)	EDE ² (mg a.i./kg bw)	RQ	LOC	LOC exceeded?
Acute oral	115.4	Insectivore	25.5	0.2	1	No
Medium-sized small wild mammal (0.035 kg)						
Acute oral	115.4	Herbivore (short grass)	48.5	0.4	1	No
Large-sized small wild mammal (1 kg)						
Acute oral	115.4	Herbivore (short grass)	26.7	0.2	1	No

¹ Uncertainty factors of 10 and 1 were applied to the acute oral (or acute dietary) and reproduction endpoints, respectively.

² EDE = Estimated daily exposure (mg a.i./kg bw/d). EDEs were calculated using the following formula: (FIR/body weight) × EEC, where:

FIR: Food Ingestion Rate (Nagy, 1987). For generic birds with body weight less than or equal to 200 g, the “passerine” equation was used; for generic birds with body weight greater than 200 g, the “all birds” equation was used:

Passerine Equation (body weight < or = 200 g): FIR (g dry weight/day) = 0.398 (body weight in g)^{0.850}

All birds Equation (body weight > 200 g): FIR (g dry weight/day) = 0.648 (body weight in g)^{0.651}

For small wild mammals, the “all mammals” equation was used: FIR (g dry weight/day) = 0.235 (body weight in g)^{0.822}

EEC: Concentration of pesticide on food item based on Hoerger and Kenaga (1972) and Kenaga (1973) and modified according to Fletcher et al. (1994). At the screening level, relevant food items representing the most conservative EEC for each feeding guild are used. The EECs for birds and small wild mammals were calculated based on 3 × 300 g a.i./ha with a 5-day re-application interval and a default foliar half-life of 10 days.

Table 10 Further characterization of foliar risk to small wild mammals

Exposure type	Effects metric (mg a.i./kg bw/d)	Feeding guild	Maximum nomogram residues		Mean nomogram residues	
			EDE ¹ (mg a.i./kg bw)	RQ	EDE ¹ (mg a.i./kg bw)	RQ
Fenamidone						
Small-sized wild mammal (0.015 kg)						
On-field						
Reproduction	3.9	Insectivore	30.7	7.9	21.4	5.5
	3.9	Granivore	4.75	1.2	2.29	0.6
	3.9	Frugivore	9.6	2.5	4.58	1.2
Off-field						
Reproduction	3.9	Insectivore	1.84	0.5	1.27	0.3
	3.9	Granivore	0.28	0.07	0.14	0.04
	3.9	Frugivore	0.57	0.1	0.27	0.07
TP RPA 412708						
Small-sized wild mammal (0.015 kg)						
On-field						
Acute oral	17.6	Insectivore	29.50	1.7	20.4	1.2

Exposure type	Effects metric (mg a.i./kg bw/d)	Feeding guild	Maximum nomogram residues		Mean nomogram residues	
			EDE ¹ (mg a.i./kg bw)	RQ	EDE ¹ (mg a.i./kg bw)	RQ
	17.6	Granivore	4.56	0.3	2.18	0.1
	17.6	Frugivore	9.13	0.5	4.35	0.2
Off-field						
Acute oral	17.6	Insectivore	1.30	0.07	0.90	0.05
	17.6	Granivore	0.20	0.01	0.10	< 0.01 ²
	17.6	Frugivore	0.40	0.02	0.19	0.01

Note: Bolded values indicate risk quotients exceeding the level of concern of 1.

¹ EDEs for birds and small wild mammals were calculated based on the ground boom application on brassica crops at rate of 3 × 300 g a.i./ha with a 5-day re-application interval and a foliar half-life of 10 days.

² Where an RQ is less than 0.01, it is reported as “< 0.01”.

Table 11 Further characterization of aerial application risk to small wild mammals

Exposure type	Effects metric (mg a.i./kg bw/d)	Feeding guild	Maximum nomogram residues		Mean nomogram residues	
			EDE ¹ (mg a.i./kg bw)	RQ	EDE ¹ (mg a.i./kg bw)	RQ
Fenamidone						
Small-sized wild mammal (0.015 kg)						
On-field						
Reproduction	3.9	Insectivore	11.40	2.9	7.87	2.0
	3.9	Granivore	1.76	0.5	0.84	0.2
	3.9	Frugivore	3.53	0.9	1.68	0.4
Off-field						
Reproduction	3.9	Insectivore	2.62	0.7	1.81	0.5
	3.9	Granivore	0.41	0.1	0.19	0.05
	3.9	Frugivore	0.81	0.2	0.39	0.1
TP RPA 412708						
Small-sized wild mammal (0.015 kg)						
On-field						
Acute oral	17.6	Insectivore	19.70	1.1	13.60	0.8
	17.6	Granivore	3.04	0.2	1.45	0.08
	17.6	Frugivore	6.09	0.3	2.90	0.2

Exposure type	Effects metric (mg a.i./kg bw/d)	Feeding guild	Maximum nomogram residues		Mean nomogram residues	
			EDE ¹ (mg a.i./kg bw)	RQ	EDE ¹ (mg a.i./kg bw)	RQ
Off-field						
Acute oral	17.6	Insectivore	1.85	0.1	1.28	0.07
	17.6	Granivore	0.29	0.02	0.14	< 0.01 ²
	17.6	Frugivore	0.57	0.03	0.27	0.02

¹ EDEs for birds and small wild mammals were calculated based on the aerial application (coarse droplet size) on potato at rate of 6 × 100 g a.i./ha with a 7-day re-application interval and a foliar half-life of 10 days.

² Where an RQ is less than 0.01, it is reported as "< 0.01".

Table 12 Screening level risk assessment for non-target aquatic organisms

Organism	Exposure	Test substance	EEC (mg a.i./L)	Endpoint value (mg/L)	UF	Effects metric (mg/L)	RQ	LOC of 1 exceeded?
Freshwater species								
Water flea (<i>Daphnia magna</i>)	48-h Acute	Fenamidone	0.109	0.055	2	0.0275	4.0	Yes
		RPA 412636	0.069	> 97.4	2	> 48.7	< 0.01 ¹	No
		RPA 410193	0.102	> 21.1	2	> 10.55	< 0.01	No
		RPA 221701	0.118	> 10	2	> 5	< 0.02	No
		RPA 411639	0.129	2.5	2	1.25	0.1	No
		RPA 412708	0.08	> 100.8	2	> 50.4	< 0.01	No
		RPA 413255	0.129	9.7	2	4.85	0.03	No
		RPA 413350	0.107	3.78	2	1.89	0.06	No
		RPA 418915	0.118	1.21	2	0.605	0.2	No
		BCS-CV62706	0.224	0.8	2	0.4	0.6	No
		RPA 221607	0.118	> 10	2	> 5	< 0.02	No
		Acetophenone	0.043	162	2	81	< 0.01	No
	21-d Chronic	Fenamidone	0.109	0.0125	1	0.0125	8.7	Yes
		RPA 412708	0.08	16	1	16	< 0.01	No
Midge (<i>Chironomus tentans</i>)	10-d Chronic (water-sediment system; spiked sediment)	Fenamidone	0.109	Overlying water: 0.0415	1	0.0415	2.6	Yes
Harlequin fly (<i>Chironomus riparius</i>)	48-h Acute	BCS-CV62706	0.224	0.78	2	0.39	0.6	No
	24-d Chronic (water-sediment system; spiked water)	Fenamidone	0.109	0.05	1	0.05	2.2	Yes

Organism	Exposure	Test substance	EEC (mg a.i./L)	Endpoint value (mg/L)	UF	Effects metric (mg/L)	RQ	LOC of 1 exceeded?
Rainbow trout (<i>Oncorhynchus mykiss</i>)	96-hr Acute	Fenamidone	0.109	0.74	10	0.074	1.5	Yes
		RPA 412636	0.069	> 34.4	10	> 3.44	< 0.02	No
		RPA 412708	0.08	> 98	10	> 9.8	< 0.01	No
		RPA 413255	0.129	3.61	10	0.361	0.4	No
		RPA 413350	0.107	3.2	10	0.32	0.3	No
Fathead minnow (<i>Pimephales promelas</i>)	Acute	Acetophenone	0.043	155	10	15.5	< 0.01	No
	32-d Chronic (early life stage)	Fenamidone	0.109	0.041	1	0.041	2.7	Yes
Amphibian (fish endpoints used as surrogate data)	96-hr Acute	Fenamidone	0.583	0.74	10	0.074	7.9	Yes
	32-d Chronic (early life stage)	Fenamidone	0.583	0.041	1	0.041	14	Yes
Green alga (<i>Pseudokirchneriella subcapitata</i>)	72-hr Acute	RPA 412636	0.069	> 35	2	> 17.5	< 0.01	No
		RPA 413350	0.107	0.099	2	0.0495	2.2	Yes
Diatom (<i>Navicula pelliculosa</i>)	5-d Acute	Fenamidone	0.109	> 0.9	2	> 0.45	< 0.2	No
Duckweed (<i>Lemna gibba</i>)	14-d Acute	Fenamidone	0.109	> 0.88	2	> 0.44	< 0.2	No
Estuarine/marine species								
Mysid shrimp (<i>Americamysis bahia</i>)	96-hr Acute	Fenamidone	0.109	0.069	2	0.0345	3.2	Yes
	21-d Chronic full life cycle	Fenamidone	0.109	0.0095	1	0.0095	12	Yes
Atlantic oyster (<i>Crassostrea virginica</i>)	96-hr Acute	Fenamidone	0.109	0.12	2	0.06	1.8	Yes
Sheepshead minnow (<i>Cyprinodon variegatus</i>)	96-hr Acute	Fenamidone	0.109	2.5	10	0.25	0.4	No
Diatom (<i>Skeletonema costatum</i>)	72-hr Acute	Fenamidone	0.109	0.08	2	0.04	2.7	Yes

¹ Where an RQ is less than 0.01, it is reported as "< 0.01".

Table 13 Further characterization of foliar ground boom and aerial application risks to aquatic organisms exposed to spray drift of fenamidone

Organism	Exposure	Test substance	Drift EEC ¹ (mg a.i./L)	Endpoint value (mg a.i./L)	UF	Effects metric (mg a.i./L)	RQ	LOC of 1 exceeded?
Freshwater species								
Water flea (<i>Daphnia magna</i>)	48-h Acute	Fenamidone	Ground: 0.0066 Aerial: 0.0116	0.055	2	0.0275	Ground: 0.2 Aerial: 0.4	No
	21-d Chronic	Fenamidone	Ground: 0.0066 Aerial: 0.0116	0.0125	1	0.0125	Ground: 0.5 Aerial: 0.9	No
Midge (<i>Chironomus tentans</i>)	10-d Chronic (water-sediment system; spiked sediment)	Fenamidone	Ground: 0.0066 Aerial: 0.0116	0.0415	1	0.0415	Ground: 0.2 Aerial: 0.3	No
Harlequin fly (<i>Chironomus riparius</i>)	24-d Chronic (water-sediment system; spiked water)	Fenamidone	Ground: 0.0066 Aerial: 0.0116	0.05	1	0.05	Ground: 0.1 Aerial: 0.2	No
Rainbow trout (<i>Oncorhynchus mykiss</i>)	96-hr Acute	Fenamidone	Ground: 0.0066 Aerial: 0.0116	0.74	10	0.074	Ground: 0.09 Aerial: 0.2	No
Fathead minnow (<i>Pimephales promelas</i>)	32-d Chronic (early life stage)	Fenamidone	Ground: 0.0066 Aerial: 0.0116	0.041	1	0.041	Ground: 0.2 Aerial: 0.3	No
Amphibian (fish endpoints used as surrogate data)	96-hr Acute	Fenamidone	Ground: 0.035 Aerial: 0.0616	0.74	10	0.074	Ground: 0.5 Aerial: 0.8	No
	32-d Chronic (early life stage)	Fenamidone	Ground: 0.035 Aerial: 0.0616	0.041	1	0.041	Ground: 0.9 Aerial: 1.5	Yes: Aerial
Estuarine/marine species								
Mysid shrimp (<i>Americamysis bahia</i>)	96-hr Acute	Fenamidone	Ground: 0.0023 Aerial: 0.0021	0.069	2	0.0345	Ground: 0.07 Aerial: 0.06	No

Organism	Exposure	Test substance	Drift EEC ¹ (mg a.i./L)	Endpoint value (mg a.i./L)	UF	Effects metric (mg a.i./L)	RQ	LOC of 1 exceeded?
	21-d Chronic full life cycle	Fenamidone	Ground: 0.0023 Aerial: 0.0021	0.0095	1	0.0095	Ground: 0.2 Aerial: 0.2	No
Atlantic oyster (<i>Crassostrea virginica</i>)	96-hr Acute	Fenamidone	Ground: 0.0023 Aerial: 0.0021	0.12	2	0.06	Ground: 0.04 Aerial: 0.04	No
Diatom (<i>Skeletonema costatum</i>)	72-hr Acute	Fenamidone	Ground: 0.0023 Aerial: 0.0021	0.08	2	0.04	Ground: 0.06 Aerial: 0.05	No

¹ Freshwater drift EECs are calculated using the maximum cumulative application rate. Estuarine/marine drift EECs are calculated on the maximum single application rate. Both values are then multiplied by either a 6% drift for foliar ground boom application of medium droplet size or a 17% drift for aerial application of coarse droplet size

Table 14 Further characterization of foliar ground boom and aerial application plus aerial application risks to aquatic organisms exposed to runoff of fenamidone

Organism	Exposure	Test substance	Runoff EEC ¹ (mg a.i./L)	Endpoint value (mg a.i./L)	UF	Effects metric (mg a.i./L)	RQ	LOC of 1 exceeded?
Freshwater species								
Water flea (<i>Daphnia magna</i>)	48-h Acute	Fenamidone	Ground: 0.0495 Seed piece treatment + aerial: 0.0239	0.055	2	0.0275	Ground: 1.8 Seed piece treatment + aerial: 0.9	Yes: Ground
	21-d Chronic	Fenamidone	Ground: 0.0447 Seed piece treatment + aerial: 0.0225	0.0125	1	0.0125	Ground: 3.6 Seed piece treatment + aerial: 1.8	Yes: Ground
Midge (<i>Chironomus tentans</i>)	10-d Chronic overlying water (water-sediment system; spiked sediment)	Fenamidone	Ground: 0.0486 Seed piece treatment + aerial: 0.0235	0.0415	1	0.0415	Ground: 1.2 Seed piece treatment + aerial: 0.6	Yes: Ground
	10-d Chronic pore water	Fenamidone	Ground: 0.0359	0.285	1	0.285	Ground: 0.1	No

Organism	Exposure	Test substance	Runoff EEC ¹ (mg a.i./L)	Endpoint value (mg a.i./L)	UF	Effects metric (mg a.i./L)	RQ	LOC of 1 exceeded?
	(water-sediment system; spiked sediment)		Seed piece treatment + aerial: 0.018				Seed piece treatment + aerial: 0.06	
Harlequin fly (<i>Chironomus riparius</i>)	24-d Chronic (water-sediment system; spiked water)	Fenamidone	Ground: 0.0447 Seed piece treatment + aerial: 0.0225	0.05	1	0.05	Ground: 0.9 Seed piece treatment + aerial: 0.5	No
Rainbow trout (<i>Oncorhynchus mykiss</i>)	96-hr Acute	Fenamidone	Ground: 0.0486 Seed piece treatment + aerial: 0.0235	0.74	10	0.074	Ground: 0.7 Seed piece treatment + aerial: 0.3	No
Fathead minnow (<i>Pimephales promelas</i>)	32-d Chronic (early life stage)	Fenamidone	Ground: 0.0447 Seed piece treatment + aerial: 0.0225	0.041	1	0.041	Ground: 1.1 Seed piece treatment + aerial: 0.6	Yes: Ground
Amphibian (fish endpoints used as surrogate data)	96-hr Acute	Fenamidone	Ground: 0.1532 Seed piece treatment + aerial: 0.0638	0.74	10	0.074	Ground: 2.1 Seed piece treatment + aerial: 0.9	Yes: Ground
	32-d Chronic (early life stage)	Fenamidone	Ground: 0.1013 Seed piece treatment + aerial: 0.0466	0.041	1	0.041	Ground: 2.5 Seed piece treatment + aerial: 1.1	Yes: Ground
Marine/estuarine species								
Mysid shrimp (<i>Americamysis bahia</i>)	96-hr Acute	Fenamidone	Ground: 0.0486 Seed piece treatment + aerial: 0.0235	0.069	2	0.0345	Ground: 1.4 Seed piece treatment + aerial: 0.7	Yes: Ground
	21-d Chronic full life cycle	Fenamidone	Ground: 0.0447 Seed piece treatment + aerial: 0.0225	0.0095	1	0.0095	Ground: 4.7 Seed piece treatment + aerial: 2.4	Yes: Ground

Organism	Exposure	Test substance	Runoff EEC ¹ (mg a.i./L)	Endpoint value (mg a.i./L)	UF	Effects metric (mg a.i./L)	RQ	LOC of 1 exceeded?
Atlantic oyster (<i>Crassostrea virginica</i>)	96-hr Acute	Fenamidone	Ground: 0.0486 Seed piece treatment + aerial: 0.0235	0.12	2	0.06	Ground: 0.8 Seed piece treatment + aerial: 0.4	No
Diatom (<i>Skeletonema costatum</i>)	72-hr Acute	Fenamidone	Ground: 0.0495 Seed piece treatment + aerial: 0.0239	0.08	2	0.04	Ground: 1.2 Seed piece treatment + aerial: 0.6	Yes: Ground

¹ The maximum application rates were used to generate the most conservative runoff EECs. The foliar ground application is based on 3 × 300 g a.i./ha applied to brassica crops in the PEI regional model scenario. The aerial application is based on 152.75 g a.i./ha seed piece treatment plus 6 × 100 g a.i./ha aerial application to potato in the PEI regional model scenario.

Table 15 Toxic Substances Management Policy Considerations – Comparison to TSMP Track 1 Criteria

TSMP Track 1 Criteria	TSMP Track 1 Criterion value		Active ingredient endpoints	Major transformation product (TP) endpoints
CEPA toxic or CEPA toxic equivalent ¹	Yes		Yes	Yes
Predominantly anthropogenic ²	Yes		Yes	Yes
Persistence: ³	Soil	Half-life ≥ 182 days	No – DT₅₀ = 0.49–10.37 d (aerobic soils) Yes – DT₅₀ could not be calculated due to its stability. (anaerobic soil)	Yes – RPA 412636 DT₅₀ = 84.4 to 1000 d (aerobic soil studies conducted with parent); DT₅₀ = 112 to > 1000 d (aerobic soil studies conducted with TP) RPA 412708 DT₅₀ = 18.7 to 423 d (aerobic soil studies conducted with parent) RPA 413255 DT₅₀ = 73.8 to 201 d (aerobic soil studies conducted with parent) RPA 221607 DT₅₀ = 12.9 to 239.6 d (aerobic soil studies conducted with parent); DT₅₀ = 12.9 to 386 d (aerobic soil studies conducted with TP) RPA 221701 DT₅₀ = 14.1 to 301.4 d (aerobic soil studies conducted with parent); DT₅₀ = 14.1 to 486 d (aerobic soil studies conducted with TP)

TSMPTTrack 1 Criteria	TSMPTTrack 1 Criterion value		Active ingredient endpoints	Major transformation product (TP) endpoints
				No – RPA 410193 DT₅₀ = 0.15 to 0.36 d (aerobic soil studies conducted with parent); DT₅₀ = 3.6 to 8.7 d (aerobic soil studies conducted with TP) RPA 411639 DT₅₀ = 56.6 to 149 d (aerobic soil studies conducted with parent) No data available – RPA 413350 RPA 418915
	Water	Half-life ≥ 182 days	No – DT ₅₀ = 66.81–128.87 d (whole system aerobic aquatic)	Not available.
	Sediment	Half-life ≥ 365 days	Yes – DT ₅₀ = 1105 d (whole system anaerobic aquatic)	
	Air	Half-life ≥ 2 days, or evidence of atmospheric transport to remote regions such as the Arctic	The AOPWIN (v. 1.92) model is not suited for predicting the atmospheric half-life of fenamidone given the large fraction expected to be sorbed to airborne particles.	Yes – RPA 412636, the AOPWIN (v.1.92) predicted half-lives in the gas phase in the atmosphere are 1.6 days, based on the hydroxyl (OH) radical reaction (1.5×10^6 molecules OH/cm³) during 12 hours of daylight. Other major TPs: The AOPWIN (v1.92) model is not suited for predicting the atmospheric half-life of the other major transformation products of fenamidone given the large fraction expected to be sorbed to airborne particles.
Bioaccumulation ⁴	Log K _{ow} ≥ 5		No – Log K _{ow} = 2.8 at 20°C (experimentally derived)	No – Log K_{ow} = 1.02 (RPA 412636 experimentally derived) No – Log K_{ow} = 0.94–3.84 RPA 412636, RPA 412708, RPA 411639, RPA 413255, RPA 221607; RPA 221701, RPA 410193, RPA 418915, RPA 413350 (estimated with KOWWIN model in the Estimation Programs Interface (EPI) Suite™)
	BCF ≥ 5000		Not available.	Not available.

TSMP Track 1 Criteria	TSMP Track 1 Criterion value	Active ingredient endpoints	Major transformation product (TP) endpoints
	BAF $\geq$ 5000	Not available – but low potential for bioaccumulation based on Log K _{ow} value.	Not available.
Is the chemical a TSMP Track 1 substance (all four criteria must be met)?		No, does not meet all of the TSMP Track 1 criteria.	No, does not meet all of the TSMP Track 1 criteria.

¹ All pesticides will be considered CEPA-toxic or CEPA toxic equivalent for the purpose of initially assessing a pesticide against the TSMP criteria. Assessment of the CEPA toxicity criteria may be refined if required (in other words, all other TSMP criteria are met).

² The policy considers a substance “predominantly anthropogenic” if, based on expert judgement, its concentration in the environment medium is largely due to human activity, rather than to natural sources or releases.

³ The pesticide and/or the transformation product(s) is considered persistent when the criterion is met in any one medium.

⁴ Bioaccumulation describes the process by which a substance accumulates in a living organism – either from the surrounding medium or through food containing the substance. A substance’s potential to bioaccumulate can be expressed by the bioaccumulation factor (BAF), the bioconcentration factor (BCF), or the octanol-water partition coefficient (Log K_{ow}). The BAF and the BCF measure the concentration of a substance in a living organism relative to its concentration in the surrounding medium. The BAF accounts for substance intake from both food and the surrounding medium, while the BCF accounts for intake from the surrounding medium only. The Log K_{ow} estimates a substance’s tendency to partition from water to organic media, such as lipids present in living organisms. In the absence of BAF or BCF data, the log K_{ow} may be used.

Appendix IX Proposed label amendment for products containing Fenamidone

The proposed label amendments presented below do not include all label requirements for individual end-use products, such as first aid statements, disposal statements, precautionary statements and supplementary protective equipment. Information on labels of currently registered products should not be removed unless it contradicts the label statements below.

1.0 Proposed label amendments relating to the human health assessment

1.1 Label amendments for end-use products containing fenamidone

1. In all parts of the label:

Remove: “Brassica leafy greens”

Replace with: “Leafy vegetables”

2. Under “**PRECAUTIONS**”, the product label must be amended as follows:

Add:

“For potato seed piece treatment, apply only in a way that this product will not contact workers or other persons, either directly or through drift. Only workers wearing personal protective equipment may be in the area where treating is occurring.”

Remove any references to greenhouses and add:

“For outdoor use only.”

3. Under “**PRECAUTIONS**”, under “Protective Clothing and Equipment”, the product label must be amended as follows:

Remove:

“During mixing, loading, clean-up and repair activities, workers must wear long-sleeved shirts, long pants, shoes plus socks, chemical resistant gloves and safety goggles or a face shield. Applicators and other handlers, as well as workers handling potato seed pieces treated with REASON 500SC Fungicide must wear long-sleeved shirt, long pants, shoes plus socks and chemical-resistant gloves.”

Add the following text and table:

“Follow the personal protective equipment and engineering control requirements for the appropriate task and application scenario. These are required to minimize exposure to the worker. ”

Foliar Applications			
Application Equipment	Personal Protective Equipment and Engineering Controls		
	Mixing/Loading, Clean-up and Repair	Application	
All application equipment ¹	Long-sleeved shirt, long pants, chemical-resistant gloves, socks, shoes and protective eyewear (goggles or face shield).	Long-sleeved shirt, long pants, chemical-resistant gloves ² , socks and shoes.	
Potato Seed Piece			
Treatment	Personal Protective Equipment and Engineering Controls		
	Treating	Cutting, sorting, planting	Back of planter
Potato Seed Pieces	Long-sleeved shirt, long pants, chemical-resistant gloves, socks, shoes and protective eyewear (goggles or face shield).	Long-sleeved shirt, long pants, gloves, socks and shoes. A closed cab tractor is required during planting.	Coveralls over a long-sleeved shirt, long pants, gloves, socks and shoes.

¹ For handheld application equipment, wear eye, head and respiratory protection when applying above waist height, including overhead. Use a fine to very coarse droplet size based on the American Society of Agricultural and Biological Engineers (ASABE) ASABE S572.1 Droplet Size Classification.

² Gloves are not required during application within a closed cab and/or cockpit.

4. Under “**PRECAUTIONS**”, the product label must be amended as follows:

Add the following text and table:

“DO NOT enter or allow worker entry into treated areas during the intervals specified in the following table. Where the REI for harvesting activities and PHI differ, the longer of the two intervals must be followed when harvesting the crop.”

Crop	Pre-harvest Interval (PHI)	Postapplication Activity	Restricted-Entry Interval (REI)
Bulb vegetables (Crop Group 3)	7 days	All activities	12 hours
Leafy vegetables (except turnip greens)	2 days	Hand set/hand line irrigation related activities involving foliar contact	4 days
		Hand harvesting	1 day
		All other activities	12 hours
Brassica head and stem vegetables, Kohlrabi	2 days	All activities	12 hours
Carrot	14 days	Hand set/hand line irrigation related activities involving foliar contact	3 days
		All other activities	12 hours
Cucurbit crops	14 days	All activities	12 hours
Ginseng	14 days	Hand set/hand line irrigation related activities involving foliar contact	3 days
		All other activities	12 hours
Potato	2 days	All activities	12 hours
Basil, Spinach (including baby spinach)	2 days	Hand set/hand line irrigation related activities involving foliar contact	1 day
		All other activities	12 hours
Edible-podded beans, Succulent shelled beans (except cowpea)	3 days	Hand set/hand line irrigation related activities involving foliar contact	3 days
		Hand harvesting, scouting (full foliage)	1 day
		All other activities	12 hours

Crop	Pre-harvest Interval (PHI)	Postapplication Activity	Restricted-Entry Interval (REI)
Tomato	14 days	All activities	12 hours
Turnip greens	2 days	Hand set/hand line irrigation related activities involving foliar contact	3 days
		Hand harvesting	1 day
		All other activities	12 hours
Tobacco	30 days	All activities	12 hours

5. Under “**DIRECTIONS for USE**”, the product label must be amended as follows:

Remove: REI and PHI information

For example, “do not apply within x days of harvest”, “do not re-enter treated field until...”, “do not enter or allow worker entry into treated areas...”

Add the following note:

“Refer to PRECAUTIONs for REIs and PHIs.”

2.0 Proposed label amendments relating to the environmental assessment

2.1 Label amendments for technical grade active ingredient products containing fenamidone

1. Under Directions for Use:

Add:

“DO NOT discharge effluent containing this product into sewer systems, lakes, streams, ponds, estuaries, oceans or other waters.”

2. Under Environmental Precautions:

Add:

“Toxic to aquatic organisms.”

2.2 Label amendments for end-use products containing fenamidone

1. Under Directions for Use:

Add:

“As this product is not registered for the control of pests in aquatic systems, DO NOT use to control aquatic pests.

DO NOT contaminate irrigation or drinking water supplies or aquatic habitats by cleaning of equipment or disposal of wastes.

Field sprayer application: DO NOT apply when wind speed is less than 1 km/h. Avoid application of this product when winds are gusty. DO NOT apply with sprays finer than the American Society of Agricultural and Biological Engineers (ASABE) S572 (572.1–572.3) Medium classification. Boom height must be 60 cm or less above the crop or ground.

Conventional piloted aircraft application: DO NOT apply when wind speed is less than 1 km/h. Avoid application of this product when winds are gusty. DO NOT apply when wind speed is greater than 16 km/h at flying height at the site of application. DO NOT apply with sprays finer than the American Society of Agricultural and Biological Engineers (ASABE) S572 (572.1–572.3) Coarse classification. Reduce drift caused by turbulent wingtip vortices. Nozzle distribution along the spray boom length MUST NOT exceed 65% of the wing - or rotorspan.

Apply only by aircraft equipment which has been calibrated for the atmospheric conditions of the area and the application rates and conditions of this label.

Label rates, conditions and precautions are product specific. Read and understand the entire label before opening this product. Apply only at the rate specified for aerial application on this label. Where no rate for aerial application appears for the specific use, this product cannot be applied by any type of aerial equipment.

Ensure uniform application. To avoid streaked, uneven or overlapped application, use appropriate marking devices or a Global Positioning System (GPS).

Use Precautions

Apply only when meteorological conditions at the treatment site allow for complete and even crop coverage. Apply only under conditions of good practice specific to aerial application as outlined in the relevant manuals, as provided by the provincial or territorial pesticide regulatory authority where the pesticide application is to occur.

Product Specific Precautions

Read and understand the entire label before opening this product. If you have questions, call the registrant at [(XXX)YYY-ZZZZ] or obtain technical advice from the distributor or your provincial or territorial agricultural representative. Application of this specific product must meet and/or conform to the following:

Volume: Apply the specified rate in a minimum spray volume of [X] litres per hectare for conventionally piloted aircraft.

SPRAY BUFFER ZONES

A spray buffer zones is NOT required for:

- Uses with hand-held application equipment permitted on this label.

The spray buffer zones specified in the table below are required between the point of direct application and the closest downwind edge of sensitive terrestrial habitats (such as grasslands, forested areas, shelter belts, woodlots, hedgerows, riparian areas and shrublands), sensitive freshwater habitats (such as lakes, rivers, sloughs, ponds, prairie potholes, creeks, marshes, streams, reservoirs and wetlands) and estuarine/marine habitats.

Method of application	Crop/Site	Spray Buffer Zones (metres) Required for the Protection of:				
		Freshwater Habitat of Depths:		Estuarine/Marine Habitat of Depths:		Terrestrial Habitat:
		Less than 1 m	Greater than 1 m	Less than 1 m	Greater than 1 m	
Field sprayer	Leafy vegetables, beans, tomato, carrot, turnip greens, ginseng	1	1	1	0	0
	Spinach, potato, cucurbits, bulb vegetables, tobacco	1	1	0	0	0
Aerial	Potato	Fixed wing	1	1	0	0
		Rotary wing	1	1	0	0

When tank mixes are permitted, consult the labels of the tank mix partners and observe the largest (most restrictive) spray buffer zone of the products involved in the tank mixture and apply using the coarsest spray (ASABE) category indicated on the labels for those tank mix partners.

Spray buffer zones of 1 m (ground) or 1 m (aerial) CANNOT be modified.”

2. Under Environmental Precautions:

Add:

“Toxic to aquatic organisms. Observe spray buffer zones specified under DIRECTIONS FOR USE.

Toxic to certain beneficial arthropods (which may include predatory and parasitic insects, spiders, and mites). Minimize spray drift to reduce harmful effects on beneficial arthropods in habitats next to the application site such as hedgerows and woodland. Care should be taken when using this product in an integrated pest management program where users are relying on the presence of beneficial arthropods.

To reduce runoff from treated areas into aquatic habitats, avoid application to areas with a moderate to steep slope, compacted soil, or clay. Avoid application when heavy rain is forecast. Contamination of aquatic areas as a result of runoff may be reduced by including a vegetative filter strip between the treated area and the edge of the water body. Additional guidance can be found on the Runoff Mitigation portion of the Canada.ca website.”

3. Under Storage:

Add:

“Store this product away from food or feed.”

References

A. Information considered in the human and animal health assessments

Studies/information submitted by registrant

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777088	1997. RPA 407213 Oral LD50 in the rat. DACO 4.2.1
777089	1997. RPA 407213 Dermal Limit Test in the Rat. DACO 4.21
777090	1998. RPA 407213 An Acute (4 Hour) Inhalation Study in Rats. DACO 4.2.3
777091	1997. RPA 407213. Acute Eye Irritation Test in the Rabbit. DACO 4.2.4
777092	1997. RPA 407213. Acute dermal irritation test in the rabbit. DACO 4.2.5
777093	1997. RPA 407213 skin sensitization test in guinea-pigs (maximization method of magnusson) DACO 4.2.6
777094	1995. RPA 407213. 90-day toxicity study in the rat by dietary administration. DACO 4.3.1
777096	1997. RPA 407213. 90-day toxicity study in the rat by dietary administration. DACO 4.3.1
777098	1997. RPA 407213. 90-day toxicity study in the mouse by dietary administration. DACO 4.3.1
777100	1999. RPA 407213. 13-week toxicity study by oral route (capsules) in beagle dogs. DACO 4.3.2
777102	1999. RPA 407213. 52-week toxicity study by oral route (capsules) in beagle dogs. DACO 4.3.2
777105	1995. RPA 407213. Preliminary 28-day toxicity study in the rat by dietary administration. DACO 4.3.3
777107	1999. RPA 407213. 4-week toxicity study by oral route (capsules) in beagle dogs. DACO 4.3.2
777108, 3197477	1999. A 28-Day Dermal Toxicity Study Of RPA 407213 In Rats. DACO 4.3.5
777110, 1064827	1999. RPA 407213. 80 week oncogenicity study in mice. DACO 4.4.3
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777138	1996. RPA 407213. <i>Salmonella typhimurim</i> reverse mutation assay (Ames test). DACO 4.5.4
777139	1999. RPA 407213. Mutation at the thymidine kinase (tk) locus of mouse lymphoma L5178Y cells (MLA) using the microtitre fluctuation technique. DACO 4.5.5
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777141	1999. RPA 407213. Introduction of Micronuclei in the Bone Marrow of Treated Mice. DACO 4.5.7
777142	1999. RPA 407213. Measurement of Unscheduled DNA Syntheses in Isolated Rat Hepatocytes In Vitro. DACO 4.5.8
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Document number	Reference
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777153	2001. RPA 407213 Neurotoxicity Study by Dietary Administration to CD Rats for 13 weeks. DACO 4.5.13
777156	1999. RPA 412636. (S-Enantiomer of RPA 717879) 90-Day Toxicity Study in the Rat by Dietary Administration. DACO 4.3.1
777158	1999. RPA 412636. (S-Enantiomer of RPA 717879). Reverse mutation in four histidine-requiring strains of <i>Salmonella typhimurium</i> and one tryptophan requiring strain of <i>Escherichia coli</i> . DACO 4.5.4
777159, 3211772	1999. RPA 412636. (S-Enantiomer of RPA 717879). Mutation at the HPRT Locus of L5178Y Mouse Lymphoma Cells using the Microtitre Fluctuation Technique. DACO 4.5.5
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777165	1999. RPA 410193. (S-Enantiomer of RPA 405862). 90-Day Toxicity Study in the Rat by Dietary Administration. DACO 4.3.1
777167	1999. RPA 412708. (S-Enantiomer of RPA 408056). Acute Oral Toxicity in Rats. DACO 4.2.1
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777112, 777113, 777114, 777124, 777125	1999. Chronic toxicity and carcinogenicity study of RPA 407213 (fenamidone) in the Sprague-Dawley rat by dietary administration. DACO 4.4.4
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Document number	Reference
3197508	1995. Preliminary 28-day toxicity study in the dog by dietary administration. DACO 4.3.3
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3197514	1995. RPA407213: 90-day toxicity study in the mouse by dietary administration. DACO 4.3.1
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Additional information considered

Published information

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B. Information considered in the updated dietary assessment

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271273	2002. Fenamidone in/on Lettuce. Health Effects Division (HED) Metabolism Assessment Review Committee (MARC) Briefing Document. DACO 12.5.7
271276	2001. Application of Fenamidone to Potato, Tomato, Bulb Vegetable Crop Group, Cucurbits Crop Group, Head Lettuce, Leaf Lettuce, and Imported Wine Grapes. Petition Method Validation (PMV) Request. DACO 12.5.7
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777178	1999. [14C]-RPA 407213 metabolism in lettuce. DACO 6.3
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1984835	1998. RPA407213 and metabolite (RPA405862) Fosetyl-Al and metabolite (phosphorous acid) Formulations EXP10745D and EXP10745H (WG) South / Italy / 1998 - 1 Decline study trial Residues in lettuce (leaf). DACO 7.4.2
1984837	1998. Residues in grape Trial Greece 1997 Formulation EXP10745D (WG) RPA407213 and RPA405862 (metabolite) Fosetyl-Al and phosphorous acid (metabolite). DACO 7.4.1
1984838	1998. RPA 407213 and metabolite (RPA 405862) Formulation EXP10745D (WG) Trial / Spain / 1997 Residues in grape. DACO 7.4.1
1984839	1998. RPA407213 and RPA405862 (metabolite) Fosetyl-al and phosphorous acid (metabolite) Formulation EXP10745D (WG) Trials / France / 1997 Residues in grape. DACO 7.4.1

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1984840	1998. RPA407213 and RPA405862 (metabolite) Fosetyl-Al and phosphorous acid (metabolite) Formulation EXP10745D (WG) Trial / France / 1997 Residues in grape. DACO 7.4.1
1984842	1998. RPA407213 and RPA405862 (metabolite) Fosetyl-Al and phosphorous acid (metabolite) Formulation EXP10745D (WG) Trial / France / 1997 Residues in grape - Reverse curve. DACO 7.4.1
1984844	1998. RPA407213 and RPA405862 (metabolite) Fosetyl-Al and phosphorous acid (metabolite) Formulation EXP10745D (WG) Trials France 1997 Residues in grape Reverse curve. DACO 7.4.1
1984845	1998. RPA407213 and metabolite (RPA405862) Fosetyl-Al and metabolite (phosphorous acid) Formulation EXP10745D and EXP10745H (WG) North / France / 1998 - 1 Harvest trial Residues in grape (fruit). DACO 7.4.1
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1984849	1998. RPA407213 and metabolite (RPA405862) Fosetyl-Al and metabolite (phosphorous acid) Formulations EXP10745D and EXP10745H (WG) South / Italy / 1998 - 1 Harvest trial Residues in lettuce (leaf). DACO 7.4.1
1984850	1999. RPA407213 and metabolite (RPA405862) Fosetyl-Al and metabolite (phosphorous acid) Formulation EXP10745D (WG) South / France / 1998 - 1 Harvest trial Residues in lettuce (leaf). DACO 7.4.1
1984851	1999. RPA407213 and metabolite (RPA405862) Fosetyl-Al and metabolite (phosphorous acid) Formulation EXP 10745D (WG) South / France / 1998 - 1 Reverse curve trial Residues in lettuce (leaf). DACO 7.4.1
1984852	1998. RPA407213 and metabolite (RPA405862) Fosetyl-Al and metabolite (phosphorous acid) Formulation EXP10745D (WG) South / Italy / 1998 - 1 Harvest trial Residues in lettuce (leaf). DACO 7.4.1
1984856	2000. North / France /1999 - 2 reverse curve trials Residues in lettuce (leaf). Fenamidone and metabolite (RPA405862) Formulation EXP10810A (WG). DACO 7.4.1
1984857	1999. Residues in lettuce (leaf) North / France / 1998 - 1 Reverse curve trial South / France / 1998 - 1 Reverse curve trial Formulation EXP10810A (WG) RPA407213 and metabolite (RPA405862). DACO 7.4.1
1984858	2006. Determination of the residues of Fenamidone and Propamocarb hydrochloride in/on tomato after spraying of AE B066752 03 SC40 A1 (450 SC) in the field in Spain, Italy, Portugal and Greece. DACO 7.4.1
1984859	1999. Residues in tomato (fruit) South / France / 1998 1 Harvest trial Formulation EXP10810A (WG) RPA407213 and metabolite (RPA405862). DACO 7.4.1
1984860	1998. RPA407213 and RPA405862 (metabolite) Fosetyl-Al and phosphorous acid (metabolite) Formulation EXP10745D (WG) Trials / Italy / 1997 Residues in grape. DACO 7.4.1

Document Number	Reference
1984861	1998. RPA407213 and RPA405862 (metabolite) Fosetyl-Al and phosphorous acid (metabolite) Formulation EXP10745D (WG) Trial / Italy / 1997 Residues in lettuce - Decline study. DACO 7.4.2
1984862	1999. RPA407213 and metabolite (RPA405862) Formulation EXP10745D (WG) South / Spain / 1998 - 1 Decline study trial Residues in lettuce (leaf). DACO 7.4.2
1984863	1999. Residues in tomato (fruit) 1 Decline study trial South / France / 1998 Formulation EXP10810A (WG) RPA407213 and metabolite (RPA405862). DACO 7.4.2
1984864	2000. Residues in tomato (fruit) South / Italy / 1999 1 Decline study trial Formulations EXP10846A (WP) and EXP10936B (WG) Fenamidone and metabolite (RPA405862). DACO 7.4.2
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