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Proposed Registration Decision

PRD2025-05

Metamitron, Brevis 150 SC, and Brevis 15 SG

(publié aussi en français)

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Overview

Proposed Registration Decision for Metamitron

Health Canada's Pest Management Regulatory Agency (PMRA), pursuant to subsection 28(1) of the *Pest Control Products Act*, is proposing registration for the sale and use of ADAMA Metamitron Technical, Brevis 150 SC, and Brevis 15 SG, containing the active ingredient metamitron, for thinning of apples and pears.

An evaluation of available scientific information found that, under the approved conditions of use, the health and environmental risks and the value of the pest control products are acceptable.

This Overview describes the key points of the evaluation, while the Science evaluation provides detailed technical information on the human health, environmental and value assessments of metamitron, Brevis 150 SC, and Brevis 15 SG.

What does Health Canada consider when making a registration decision?

The primary objective of the *Pest Control Products Act* is to prevent unacceptable risks to individuals and the environment from the use of pest control products. Health or environmental risk is considered acceptable¹ if there is reasonable certainty that no harm to human health, future generations or the environment will result from use or exposure to the product under its proposed conditions of registration. The Act also requires that products have value² when used according to the label directions. Conditions of registration may include precautionary measures on the product label to further reduce risk.

To reach its decisions, Health Canada's PMRA applies modern, rigorous risk-assessment methods and policies. These methods consider the unique characteristics of sensitive subpopulations in humans (for example, children). They also consider the unique characteristics of organisms in the environment. These methods and policies also consider the nature of the effects observed and the uncertainties when predicting the impact of pesticides. For more information on how Health Canada's PMRA regulates pesticides, the assessment process and risk-reduction programs, please visit the Pesticides and Pest Management portion of Canada.ca.

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

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

Before making a final registration decision on metamitron, Brevis 150 SC, and Brevis 15 SG, Health Canada's PMRA will consider any written comments received from the public directly related to the proposed decision in this consultation document.³ Health Canada will then publish a Registration Decision⁴ on metamitron, Brevis 150 SC, and Brevis 15 SG, which will include the decision, the reasons for it, a summary of comments received on the proposed registration decision and Health Canada's response to these comments.

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

What is metamitron?

Metamitron is a conventional photosynthesis inhibiting herbicide that reduces fruit load in apple and pear when fruit set is higher than optimal.

Health considerations

Can approved uses of metamitron affect human health?

Brevis 150 SC and Brevis 15 SG, containing metamitron, are unlikely to affect your health when used according to the proposed label directions.

Potential exposure to metamitron may occur through the diet (food and drinking water), when handling and applying the end-use products, or when coming into contact with treated surfaces. When assessing health risks, two key factors are considered: the levels at which no health effects occur and the levels to which people may be exposed. The dose levels used to assess risks are selected to protect the most sensitive human population (for example, children and nursing mothers). As such, sex and gender are taken into account in the risk assessment. Only uses for which the exposure is well below levels that cause no effects in animal testing are considered acceptable for registration.

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

In laboratory animals, the active ingredient metamitron was of low to moderate acute toxicity by the oral route of exposure; consequently, the signal word and hazard statement "WARNING – POISON" are required on the label. Metamitron was of low acute toxicity dermally and through inhalation exposure. It was minimally irritating to the eyes, non-irritating to the skin, and did not cause an allergic skin reaction.

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

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

The acute toxicity of the end-use product, Brevis 150 SC, containing metamitron, was low via the oral, dermal, and inhalation routes of exposure. It was minimally irritating to the eyes, non-irritating to the skin, and did not cause an allergic skin reaction.

The acute toxicity of the end-use product, Brevis 15 SG, containing metamitron, was low via the dermal and inhalation routes of exposure. It was of slight acute toxicity via the oral exposure route; consequently, the signal word and hazard statement “CAUTION – POISON” are required on the label. It was non-irritating to the skin and did not cause an allergic skin reaction. It was severely irritating to the eyes; consequently, the signal word and hazard statement “DANGER – EYE IRRITANT” are required on the label.

Registrant-supplied short- and long-term (lifetime) animal toxicity tests, as well as information from the published scientific literature, were assessed for the potential of metamitron to cause neurotoxicity, immunotoxicity, chronic toxicity, cancer, reproductive and developmental toxicity, and various other effects. The most sensitive endpoints for the risk assessment were effects on offspring survival and body weight. There was no evidence of tumourigenicity. There was an indication that the young were more sensitive than the adult animal. The risk assessment protects against the effects noted above and other potential effects by ensuring that the level of exposure to humans is well below the lowest dose level at which these effects occurred in animal tests.

Residues in food and drinking water

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

Aggregate acute dietary (food plus drinking water) intake estimates indicated that the general population and all population subgroups are exposed to less than 16% of the acute reference dose (ARfD), and therefore, are not of health concern.

Aggregate chronic dietary (food plus drinking water) intake estimates indicated that the general population and all population subgroups are exposed to less than 15% of the acceptable daily intake (ADI), and therefore, are not of health concern.

The *Food and Drugs Act* prohibits the sale of adulterated food, that is, food containing a pesticide residue that exceeds the established maximum residue limit (MRL). Pesticide MRLs are established for *Food and Drugs Act* purposes through the evaluation of scientific data under the *Pest Control Products Act*. Given that dietary risks from the consumption of foods are shown to be acceptable when metamitron is used according to the supported label directions, MRLs are being proposed as a result of this assessment (refer to PMRL2025-15, *Metamitron*).

The MRLs for metamitron, determined from the acceptable residue trials conducted throughout Canada and the United States, on apples and pears, can be found in the Science Evaluation section of this consultation document.

Occupational risks from handling Brevis 150 SC and Brevis 15 SG

Occupational risks are not of health concern when Brevis 150 SC and Brevis 15 SG are used according to the proposed label directions, which include protective measures.

Workers mixing, loading, or applying Brevis 150 SC or Brevis 15 SG and workers entering recently treated apple or pear orchards can be exposed to metamitron residues through direct skin contact or through inhalation. Therefore, the label specifies that anyone mixing, loading, and applying Brevis 150 SC or Brevis 15 SG must wear a long-sleeved shirt, long pants, chemical-resistant gloves, chemical-resistant headwear plus socks and shoes. In addition, when handling Brevis 15 SG, workers must wear eye protection when handling the concentrate and when spraying using an open cab sprayer. The labels also require that workers do not enter or be allowed into treated apple or pear orchards during the restricted-entry intervals (REIs) of 12 hours to up to 19 days depending on the activity and the product used. Taking into consideration the label statements, the number of applications, and the duration of exposure for handlers and postapplication workers, the risks to these individuals are not of health concern.

Health risks in residential and other non-occupational environments

Risks in residential and other non-occupational environments are not of health concern when Brevis 150 SC and Brevis 15 SG are used according to the proposed label directions and the REIs are observed.

Residential exposure during pick-your-own (PYO) fruit activities in treated orchards are not of health concern.

Health risks to bystanders

Bystander risks are not of health concern when Brevis 150 SC and Brevis 15 SG are used according to the proposed label directions and spray drift restrictions are observed.

A standard label statement to protect against drift during application is on the label. Therefore, health risks to bystanders are not of concern.

Environmental considerations

What happens when metamitron is introduced into the environment?

When used according to the proposed label directions, environmental risks associated with metamitron and its associated end-use products are acceptable.

Metamitron enters the environment when its end-use products are used as fruit thinners on apple and pear trees.

In the environment, metamitron is readily broken down in water and soil by microorganisms, as well as by sunlight in aquatic systems. In both water and soil, the major transformation product is desamino-metamitron, which also breaks down in soil and surface waters. Two additional major transformation products (M1 and M2) are formed in surface water. High amounts of carbon

dioxide (CO₂) were observed to form in aquatic and terrestrial systems, indicating that complete breakdown of metamitron can occur in the environment. The small amount of metamitron that is not transformed is strongly bound to soil. Overall, metamitron and its transformation products have some potential to leach depending on soil type. Metamitron and its major transformation products are not expected to be found in air or to travel long distances in the atmosphere from the application sites; nor are they expected to accumulate in the tissues of animals. Under field conditions, both metamitron and desamino-metamitron break down and do not carry over to the following growing season.

When used according to the proposed label directions, metamitron and its major transformation products pose acceptable risk to earthworms, beneficial invertebrates, bees, birds, collembola, aquatic invertebrates, fish, aquatic plants, algae, and amphibians. Metamitron may affect non-target terrestrial plants and small wild mammals if they are exposed to high enough levels. Precautionary label statements, best management practice label statements, and spray buffer zones, as described below, are therefore required on the end-use product labels. Risks to the environment are acceptable when the end-use products are used in accordance with the label directions, and when the required risk-reduction measures are applied.

Value considerations

What is the value of Brevis 150 SC and Brevis 15 SG?

Brevis 150 SC and Brevis 15 SG are conventional herbicide products that, when applied post-bloom to apple and pear, will reduce the photosynthetic capacity of the tree, thereby causing excess fruit to fall, which in turn may contribute to an increase in the quality of the remaining fruit.

The use of Brevis 150 SC and Brevis 15 SG can be expected to complement other fruit thinning measures employed by growers and serve as an effective replacement for carbaryl that is under significant global regulatory pressures to restrict and/or eliminate its uses, including its widespread use as a chemical thinning agent in apple and pear.

Measures to minimize risk

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

The key risk-reduction measures being proposed on the labels of ADAMA Metamitron Technical, Brevis 150 SC, and Brevis 15 SG to address the potential risks identified in this assessment are as follows.

Key risk-reduction measures

Human health

To reduce the potential exposure of workers to metamitron through direct skin contact or inhalation, workers mixing, loading, and applying Brevis 150 SC and Brevis 15 SG and

performing cleaning and repair activities must wear a long-sleeved shirt, long pants, chemical-resistant gloves, chemical-resistant headwear plus socks and shoes. In addition, when handling Brevis 15 SG, workers must wear eye protection when handling the concentrate or when spraying using an open cab sprayer. The labels also require that workers do not enter or be allowed entry into treated apple or pear orchards during the REIs of 12 hours to up to 19 days, depending on the activity and the product used. Furthermore, standard label statements to protect against drift during application are present on the labels.

Brevis 150 SC

Restricted-entry intervals (REIs) and Preharvest intervals (PHIs)

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	Preharvest interval (PHI)	Postapplication activity	Restricted-entry interval (REI)
Apples (west of Canadian Rockies)	72 days	Hand thinning fruit	5 days
		All other activities	12 hours
Apples (east of Canadian Rockies), Pears	72 days	All Activities	12 hours

Brevis 15 SG

Restricted-entry Intervals (REIs) and Preharvest Intervals (PHIs)

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	Preharvest interval (PHI)	Postapplication activity	Restricted-entry interval (REI)
Apples (west of Canadian Rockies)	72 days	Hand thinning fruit	19 days
		Hand Harvesting	10 days
		All other activities	12 hours
Apples (east of Canadian Rockies), Pears	72 days	Hand thinning fruit	14 days
		Hand harvesting	5 days
		All other Activities	12 hours

Environment

Standard label statements are required to inform users of the toxicity of metamitron to non-target terrestrial plants, small wild mammals, and aquatic plants.

Standard best management practice label statements are required to instruct users to avoid using Brevis 15 SG and Brevis 150 SC in areas more conducive to leaching to groundwater (in other words, where the soils are permeable and particularly where the water table is shallow).

Standard best management practice label statements are required to instruct users to avoid runoff of Brevis 15 SG and Brevis 150 SC into sensitive aquatic habitats.

Spray buffer zones are required to reduce the risk of spray drift to sensitive non-target terrestrial habitats.

Next steps

Before making a final registration decision on metamitron, Brevis 150 SC, and Brevis 15 SG, Health Canada's PMRA will consider any written comments received from the public that are directly related to this proposed decision, such as comments directed to the science evaluation, in response to this consultation document up to 45 days from the date of publication (8 August 2025) of this document. Please note that, to comply with Canada's international trade obligations, consultation on the proposed MRLs will also be conducted internationally via a notification to the World Trade Organization. Please forward all comments to PMRA Publications, through the Public Engagement Portal (Public Engagement Forms – Consultation Comment). Health Canada will then publish a Registration Decision, which will include its decision, the reasons for it, a summary of comments received on the proposed decision and Health Canada's response to these comments.

Other information

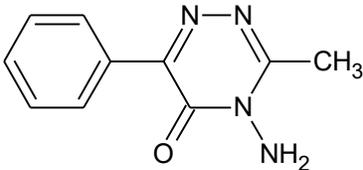
When Health Canada's PMRA makes its registration decision, it will publish a Registration Decision on metamitron, Brevis 150 SC, and Brevis 15 SG (based on the Science evaluation of this consultation document). In addition, the test data referenced in this consultation document will be available for public inspection, upon application, in the PMRA's Reading Room. For more information or if you have questions, please contact the PMRA's Pest Management Information Service.

Science evaluation

Metamitron, Brevis 150 SC, and Brevis 15 SG

1.0 The Active Ingredient, Its Properties and Uses

1.1 Identity of the Active Ingredient

Active substance	Metamitron
Function	Plant growth regulator
Chemical name	
1. International Union of Pure and Applied Chemistry (IUPAC)	4-amino-4,5-dihydro-3-methyl-6-phenyl-1,2,4-triazin-5-one
2. Chemical Abstracts Service (CAS)	4-amino-3-methyl-6-phenyl-1,2,4-triazin-5(4 <i>H</i>)-one
CAS number	41394-05-2
Molecular formula	C ₁₀ H ₁₀ N ₄ O
Molecular weight	202.21
Structural formula	
Purity of the active ingredient	98.66%

1.2 Physical and chemical properties of the active ingredient and end-use products

Technical product—ADAMA Metamitron Technical

Property	Result
Colour and physical state	Light yellow powder
Odour	Nearly odourless
Melting range	166°C
Boiling point or range	Decomposes prior to boiling
Density	1.25–1.29 g/mL
Vapour pressure at 20°C	1.4 × 10 ⁻⁶ Pa at 20°C

End-Use Product—Brevis 15 SG

Property	Result
Colour	Off-white
Odour	Light characteristic
Physical state	Solid
Formulation type	Soluble granules
Label concentration	Metamitron 15%
Container material and description	Plastic bag, bottle, jug, drum or tote, 0.5 kg to bulk
Density	719–757 g/L
pH of 1% dispersion in water	6–8
Oxidizing or reducing action	The product has no oxidizing properties.
Storage stability	The product was shown to be stable when stored in plastic containers for two weeks at 54°C.
Corrosion characteristics	The product did not cause adverse effects when stored in plastic containers for two weeks at 54°C.
Explodability	The product has no explosive properties.

1.3 Directions for use

Brevis 150 SC and Brevis 15 SG are applied using an airblast sprayer at 168–504 g a.i./ha to apple grown west of the Canadian Rockies and at 168–336 g a.i./ha to apple grown east of the Canadian Rockies. In pear, both Brevis end-use products are applied at 168–336 g a.i./ha regardless of geographic area. The rate used in apple and pear is dependent on several factors, including the amount of fruit thinning required, the carbon status of the tree, cultivar sensitivity, tree age, degree of environmental stress, orchard cropping history, orchard management practices, and the use of any other fruit thinning products. West of the Canadian Rockies, a non-ionic surfactant at 0.125% v/v (1.25 L/1000 L water) may be included in the Brevis end-use product spray solution for use in apple when conditions on the day of application favour fast droplet drying. Applications are made when fruit diameter is between 6 and 18 mm. For difficult to thin varieties that typically have high fruit set or in situations where the carbon status of the tree is high, a second treatment may be made 5–10 days after the first, provided fruit diameter does not exceed 20 mm.

1.4 Mode of action

Metamitron is a herbicide that acts as a plant growth regulator when applied to apple and pear through its inhibition of the photosystem II pathway of photosynthesis, which temporarily reduces carbohydrate supply for 7–10 days after application. During this stress period, the decreased production of carbohydrates triggers earlier and enhanced fruit abscission. The degree of thinning is rate-dependent and can also be enhanced under specific conditions, such as strong tree vigour, varietal differences, cloudy weather, and high night temperatures.

Metamitron belongs to the triazinone herbicide family, with the mode of action being classified as a Group 5 herbicide by the Weed Science Society of America (WSSA).

2.0 Methods of analysis

2.1 Methods for analysis of the active ingredient

The methods provided for the analysis of the active ingredient and impurities in the technical product have been validated and assessed to be acceptable.

2.2 Method for formulation analysis

The method provided for the analysis of the active ingredient in the formulations has been validated and assessed to be acceptable for use as enforcement analytical method.

2.3 Methods for residue analysis

Environmental media: High-performance liquid chromatography methods with tandem mass spectrometry (HPLC-MS/MS) were developed and proposed for data generation and enforcement purposes. These methods fulfilled the requirements with regards to selectivity, accuracy, and precision at the respective method limit of quantitation (LOQ). Acceptable recoveries (70–120%) were obtained in environmental media. The methods for residue analysis in environmental media are summarized in Appendix I, Table 1a.

Plant matrices: A HPLC-MS/MS method (Method SGS-17-01-03 in plant matrices) was developed and proposed for data generation and enforcement purposes. This method fulfilled the requirements with regards to specificity, accuracy, and precision at the respective method LOQ. Acceptable recoveries (70–120%) were obtained in plant matrices. The proposed enforcement method was successfully validated in plant matrices by an independent laboratory. Extraction solvents used in the method were similar to those used in the metabolism studies; thus, further demonstration of extraction efficiency with radiolabelled crops was not required for the enforcement method. The method for residue analysis in plant matrices is summarized in Appendix I, Table 1b.

3.0 Impact on human and animal health

3.1 Hazard assessment

3.1.1 Toxicology summary

Metamitron belongs to the 1,2,4-triazine class of pesticides and is used as a plant growth regulator (fruit thinner) on pome fruit. It is a photosystem II inhibitor; as such, it reduces photosynthesis and puts the tree into carbon stress, causing excess fruit to fall, thus contributing to an increase in the quality of fruit production.

A detailed review of the toxicology database for metamitron was conducted. The database is complete, consisting of the full array of toxicity studies currently required for hazard assessment purposes. A number of mechanistic studies were also submitted to explore the potential mode of

action for toxicity. A limited number of studies on select transformation products as well as a manufacturing impurity were also available. The required studies were carried out in accordance with currently accepted international testing protocols and Good Laboratory Practices (GLP). The human health risk assessment also considered any relevant information found in the published scientific literature. The scientific quality of the data is acceptable and the database is considered adequate to characterize the potential health hazards associated with metamitron.

In a series of metabolism and toxicokinetic studies, metamitron was administered to rats either as unlabelled test substance or as test substance uniformly radiolabelled on the phenyl-ring. It was rapidly and almost completely absorbed. Peak plasma concentrations were attained 20–40 minutes after oral administration of a single low dose and one to eight hours after oral administration of a single high dose. Dose-normalised plasma concentration showed a second peak after six hours post-administration, indicating possible enterohepatic circulation. Metamitron was rapidly and evenly distributed between the blood and various organs, with the highest concentrations in the liver and kidneys. Elimination was mainly via the renal and fecal routes. Regardless of the dose level or exposure period, levels of radioactivity in tissues declined to less than 1% of the administered dose (AD) within 48 hours after dosing, indicating a low potential for retention in tissues. Metamitron was rapidly and extensively metabolised. Major metabolites in the urine and feces of rats were metamitron-triazinium acetic acid, metamitron-4-hydroxy-desamino, metamitron-3-hydroxy-desamino, and desamino-metamitron. Metamitron-desamino-dienyl-glutathione and metamitron-desamino-dienyl-cysteinylglycine were major metabolites identified in bile. No significant sex differences were observed on absorption, distribution, elimination, and metabolism, except that females had a higher plasma concentration and a slower decline than males at all dose levels. Compared to single dose administration, repeated dosing did not have a significant influence on absorption, elimination, or distribution of unchanged metamitron or metabolites in tissues. Metabolism studies were also conducted in vitro. Based on comparative metabolism in liver microsomes, no major metabolic inter-species (rat, dog, human) differences were observed, and no unique human metabolites were identified.

Metamitron was of low to moderate acute toxicity by the oral route of exposure and was of low acute toxicity via the dermal and inhalation routes of exposure in rats. It was minimally irritating to the eyes and non-irritating to the skin of rabbits. It was not a dermal sensitizer in guinea pigs in three maximization tests.

The acute toxicity of the end-use product, Brevis 150 SC, was low via the oral, dermal, and inhalation routes of exposure in rats. It was minimally irritating to the eyes and non-irritating to the skin of rabbits. It was not a dermal sensitizer in guinea pigs in a maximization test or a Buehler test.

The acute toxicity of the end-use product, Brevis 15 SG, was slight via the oral route of exposure and low via the dermal and inhalation routes of exposure in rats. It was non-irritating to the skin and severely irritating to the eyes of rabbits. It was not a dermal sensitizer in a Local Lymph Node Assay (LLNA) in mice.

In short-term oral toxicity studies in mice, rats, and dogs treated with metamitron, reductions in body weight and body weight gain were observed in all species. The liver was identified as the primary target organ in all species and liver effects included increased liver weight, elevated cholesterol and triglyceride levels, and hepatic enzyme induction.

Treatment-related hypercholesterolemia was noted in all species. It was more evident in the dog and was often accompanied by hypertriglyceridemia. A mechanistic study in male Beagle dogs revealed that increased cholesterol co-occurred with the induction of hepatic cholesterol 7 α -hydroxylase (CYP7A1). CYP7A1 is a rate-limiting enzyme for cholesterol catabolism and bile acid synthesis and the increase noted in this study is considered secondary to the increased cholesterol levels. Slight reductions in red blood cell parameters and an increase in reticulocytes were observed in most dog studies. An iron-positive pigment within Kupffer cells was observed in the mechanistic study in dogs and an increased incidence of pigment deposit in the liver was also noted in the two-year rat study. The sequestration of iron in the liver resulted in the shortage of iron availability in the circulation, possibly accounting for the reduction in red blood cell parameters.

Following long-term dietary dosing with metamitron, reductions in body weight and body weight gain were observed in both mice and rats. The liver was again identified as a target organ in both species. Evidence of hepatotoxicity included hepatocyte alteration (hypertrophy, condensed cytoplasm, multinucleated) and increased incidences of foci (basophilic, eosinophilic degeneration, and necrotic). In the two rat studies, reductions in red blood cell parameters and elevated hepatic inflammation were noted, evidenced by angiectasis and Kupffer cell and monocyte activation in the liver. Systemic inflammation was also observed, evidenced by lymphoid hyperplasia and sinus histiocytosis. An increased incidence of pigment deposit in the liver was noted in one rat study.

Metamitron was tested for potential genotoxic activity in a standard battery of in vivo and in vitro assays. All assays were negative for genotoxicity, including seven bacterial reverse mutation assays, three forward gene mutation assays in mammalian cells, four in vitro chromosomal aberration assays, and six in vivo micronucleus assays. Therefore, metamitron did not demonstrate any genotoxic potential. Six carcinogenicity studies in mice and rats were conducted to assess tumour incidence and there was no evidence of tumourigenicity.

Four reproductive toxicity studies in the rat were available (one one-generation, two two-generation, and one three-generation) in the PMRA database for metamitron. The most common indications of parental toxicity were decreased body weight and body weight gain and increased liver weight. An increased incidence of urinary incontinence was observed in one two-generation study in both sexes (see discussion below). Reproductive toxicity consisted of decreased numbers of corpora lutea, implantation sites, and live births in one two-generation study and decreased prostate weight and birth weight in the other two-generation study. Offspring exhibited decreased body weight in one two-generation study, and reduced survival index at day 21, decreased body weight, and increased incidence of missing/cannibalized pups in the other two-generation study. No evidence of increased sensitivity of the young was noted in these studies.

Three developmental toxicity studies in the rat were available in the PMRA database for metamitron. An increased incidence of wavy ribs was noted in fetuses at the same dose level in two of the studies. Wavy rib is considered a non-serious effect that may result from a single exposure. At this same dose level, treatment-related effects in parental animals, such as dyspnoea, ventral- and/or dorsal-body position, and decreased food consumption, were observed in one study. In another study, the decreased body weight gain during gestation day (GD) 6–15 and one mortality at this dose level were considered equivocal signs of parental toxicity. An additional rat developmental study for metamitron was also available in the published literature. In this study, treatment with metamitron showed increased incidences of skeletal variations such as shortening of last ribs, wavy ribs, incomplete ossification of all sternbrae, and absence of xiphisternum. These findings were consistent with the observations in the database.

Three developmental toxicity studies in rabbits were available in the PMRA database for metamitron. The first study was performed in 1977 and was considered acceptable with limitations. In the second study, both parental toxicity and developmental toxicity were observed at the highest dose tested. Parental toxicity consisted of changes in urine and feces, decreased food consumption, body weight loss during the gestation period, and decreased gravid uterus weight. Developmental toxicity included a reduction in the number of live fetuses, increased post-implantation loss, and an increased incidence of liver histology changes. In the third study, treatment-related effects in fetuses were observed at the highest dose tested in the absence of maternal toxicity, which included an increased incidence of incomplete/poor ossification and asymmetrical ossification. Increased sensitivity of the young was noted in this study.

Although the available reproductive studies were either conducted according to an older test protocol (the Organisation for Economic Co-operation and Development Test Guideline (OECD TG) 416; 1983) or conducted prior to the implementation of OECD guidelines, most parameters required by the current OECD test guideline (OECD TG 416; 2001), such as oestrus cycle, sperm parameters, time to sexual maturation, and weight of reproductive organs, were measured in one of the two-generation reproductive studies. There was no qualitative or quantitative examination of the ovarian primordial or growing follicle population. This data gap was partially addressed by the decreased number of corpora lutea, implantation sites, and live births noted in one study, suggesting an inadequate number of follicle formulations, or that follicles were not able to ovulate properly. Anogenital distance (AGD) was also not assessed in any of these reproductive toxicity studies. Anogenital distance is known to be regulated by in utero androgenic exposure. Metamitron was screened for androgen and antiandrogen response in rats (Hershberger assay), and was tested for androgenic agonist and antagonist activity, estrogenic agonist activity, and effects on steroidogenesis in vitro. All of these test results were negative, which indicates a low endocrine activity potential of metamitron. The unaltered estrous cycle length and periodicity and sperm parameters further support that metamitron is unlikely to be estrogenic or androgenic. Therefore, metamitron is not anticipated to alter AGD.

The developmental studies were conducted from 1977 to 1997 and they were either conducted prior to the implementation of OECD guidelines or according to an older test protocol (OECD TG 414; 1981). Rats were dosed from GD 6–15, while rabbits were dosed from GD 7–19. As such, a recovery period was included within the study since metamitron was not administered from GD 16–20 in the rat and GD 20–29 in the rabbit. This period of development towards the end of gestation is a critical window of development known to include parts of phenotypic sexual

differentiation (GD 14–19 in the rat; GD 17–28 in the rabbit) and brain development, and, as such, is a requirement for testing under current guidelines (OECD TG 414; 2018). This period of development was covered by the dosing period in the two-generation reproductive toxicity studies in the rat, and there were no indications of effects on sexual maturation, lowering the concern due to the absence of dosing during sexual differentiation.

A guideline acute neurotoxicity study was not provided; however, a series of studies in male rats, each assessing a limited set of parameters, were provided to address the data requirement. In two of the acute oral neurotoxicity studies, a statistically significant, dose-related decrease in body temperature was noted at all dose levels tested. In addition, decreased distance travelled and number of rearings, and increased rest time in the open field test were observed in a dose-related manner, as well as an increase in clinical signs, including sedation and prone posture. Hypothermia was also observed in female rats at week 13 in a 90-day neurotoxicity study. However, as this effect was isolated (limited to one sex at the high dose level and only at study termination), and without any accompanying behavioural changes, it was not considered evidence of selective neurotoxicity. Urinary incontinence was observed in rats in a developmental toxicity study, a 90-day oral toxicity study, and a two-generation reproductive study. There was insufficient information available in the metamitron database to definitively conclude on the underlying mechanism for the observed urinary incontinence. Therefore, a potential neurotoxic mechanism could not be ruled out. In a 90-day dietary toxicity study in rats, increased cholinesterase activity (the enzyme that catalyzes the hydrolysis of the neurotransmitter acetylcholine) in plasma and erythrocytes, but not in the brain, was noted. In the absence of a clear dose-response relationship and the low number of animals tested, this finding was considered only equivocally related to treatment. Although some of the findings in the acute studies, including hypothermia, number of rearings, and clinical signs, suggest potential neurotoxicity, with the exception of isolated hypothermia in the high-dose females, the effects were not observed in the 90-day study. Overall, concern for neurotoxicity was limited, and the requirement for a developmental neurotoxicity study was not triggered.

Evidence of local immune activation was noted in long-term studies in rats. Lymphoid hyperplasia in the mesenteric, mediastinal, and mandibular lymph nodes and lymph node edema in mesenteric lymph nodes were observed in male rats in one combined chronic and carcinogenicity study. In another combined chronic and carcinogenicity study, angiectasis in the hepatic sinus and subcapsular area and Kupffer cell activation were observed in both sexes of rats. In one study from the published literature, metamitron was shown to induce the production of pro-inflammatory cytokine TNF- α in human peripheral blood mononuclear cells. No other effects on immune system function were identified in the metamitron database.

The identification of select metabolites is presented in Appendix I, Table 2. The toxicology reference values for use in the human health risk assessment are summarized in Appendix I, Table 3. Results of the toxicology studies conducted on laboratory animals with metamitron and relevant metabolites and with its associated end-use products are summarized in Tables 4 and 5, respectively, of Appendix I.

3.1.2 *Pest Control Products Act* hazard characterization

For assessing risks from potential residues in food or from products used in or around homes or schools, the *Pest Control Products Act* requires the application of an additional 10-fold factor to 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.⁵

With respect to the completeness of the toxicity database as it pertains to the toxicity to infants and children, the standard complement of studies was available, including gavage developmental toxicity studies in the rabbit and rat, and dietary reproductive toxicity studies in the rat. Despite the limitations based on the age of the studies, as discussed above, they were considered adequate to address the effects on the young.

With respect to concerns regarding potential prenatal and postnatal toxicity, evidence of increased sensitivity of the young was observed in one rabbit developmental toxicity study. In that study, a delay in ossification, observed as an increased incidence of incomplete/poor ossification and asymmetrical ossification, occurred in fetuses at the highest dose level tested in the absence of maternal toxicity. Although this study provided evidence of increased sensitivity of the young, the concern for this finding was low, given the non-serious nature of the developmental endpoint. In another rabbit developmental toxicity study, serious effects, such as a reduction in the number of live fetuses and increased post-implantation loss, were observed in the presence of maternal toxicity. No evidence of increased sensitivity of the young was observed in the dietary two-generation reproductive toxicity studies in rats with metamitron or in the gavage developmental toxicity studies in rats. In one two-generation reproductive toxicity study, reduced survival and decreased body weight were noted in offspring in the presence of maternal toxicity. The reduced survival was considered as a serious effect. An increased incidence of wavy ribs was observed in two rat developmental toxicity studies; however, this effect was considered non-serious in nature and it occurred in the presence of maternal toxicity.

Overall, the database was adequate for determining the sensitivity of the young. There was a low level of concern (LOC) for sensitivity of the young, as effects either occurred in the presence of maternal toxicity or the effects were non-serious in nature. The decreased survival of offspring in the reproductive toxicity study and decreased live fetuses and increased post-implantation loss in the rabbit developmental study were considered serious endpoints, although the concern was tempered by the presence of maternal toxicity. Therefore, the *Pest Control Products Act* (PCPA) factor was reduced to three-fold when using either of these studies to establish the point of departure for the risk assessment; otherwise, a PCPA factor of onefold is warranted.

⁵ SPN2008-01. The Application of Uncertainty Factors and the Pest Control Products Act Factor in the Human Health Risk Assessment of Pesticides.

3.2 Toxicology reference values

3.2.1 Route and duration of exposure

Occupational exposure to Brevis 150 SC and Brevis 15 SG is expected to occur predominantly via the dermal and inhalation routes of exposure for mixers, loaders, and applicators, and through the dermal route of exposure for postapplication workers. Exposure is expected to be intermittent over a short-term duration for farmers and an intermediate-term duration for custom applicators and postapplication workers, as there are up to two applications made 5–10 days apart and various postapplication activities occurring during that time period (which can result in exposure for greater than 30 days).

3.2.2 Occupational toxicology reference values

Short- and intermediate-term dermal and inhalation exposure

For short- and intermediate-term occupational exposures via the dermal and inhalation routes, the no observed adverse effect level (NOAEL) of 11 mg/kg body weight (bw)/day from the two-generation dietary reproductive toxicity study was selected for the risk assessment. Offspring toxicity was observed in this study in the form of reduced survival, decreased body weight, and increased incidence of missing and cannibalised pups. Worker populations could include pregnant or lactating women; therefore, these endpoints were considered relevant for the occupational risk assessment. The available 20-day and 28-day dermal toxicity studies did not assess the relevant endpoints of concern (that is, decreased survival in pups following prenatal or postnatal exposure). A valid short-term inhalation toxicity study was not available.

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, as well as a PCPA factor of threefold for the reasons outlined in the *Pest Control Products Act* hazard characterization Section. The selection of this study and target MOE is considered to be protective of all populations, including nursing infants and unborn children of exposed female workers.

3.2.3 Acute reference dose (ARfD)

General population

To estimate acute dietary risk, the NOAEL of 10 mg/kg bw from an acute neurotoxicity study in the rat was selected for the risk assessment. At the lowest observed adverse effect level (LOAEL) of 30 mg/kg bw, decreased body temperature and decreased motor activity were observed. These effects were the result of 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 PCPA factor was reduced to onefold. The composite assessment factor (CAF) is thus 100.

The ARfD was calculated according to the following formula:

$$\text{ARfD} = \frac{\text{NOAEL}}{\text{CAF}} = \frac{10 \text{ mg/kg bw}}{100} = 0.1 \text{ mg/kg bw of metamitron}$$

The ARfD provides a margin of 250 to the NOAEL for developmental toxicity in the rat and a margin of 400 to the NOAEL for the developmental toxicity in the rabbit and is thus considered protective of pregnant women and their fetuses.

3.2.4 Acceptable daily intake (ADI)

To estimate risk following repeated dietary exposure, the NOAEL of 11 mg/kg bw/day from the two-generation reproductive toxicity study in the rat was selected. At the LOAEL of 54 mg/kg bw/day, reduced survival and decreased body weight of offspring, as well as an increased incidence of missing and cannibalized pups were observed. As discussed in the *Pest Control Products Act* hazard characterization Section, the PCPA factor was reduced to threefold when using this study to establish the point of departure for the risk assessment. This study provides the lowest NOAEL in the database once the PCPA factor of threefold is applied, and is comparable to the NOAEL of 3.9 mg/kg bw/day from another two-generation reproductive toxicity study where the three-fold PCPA factor would not apply. Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability were applied. The CAF is thus 300.

The ADI was calculated according to the following formula:

$$\text{ADI} = \frac{\text{NOAEL}}{\text{CAF}} = \frac{11 \text{ mg/kg bw/day}}{300} = 0.04 \text{ mg/kg bw/day of metamitron}$$

3.2.5 Cancer assessment

There was no evidence of tumourigenicity; therefore, a cancer risk assessment was not necessary.

3.2.6 Aggregate toxicology reference values

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 metamitron, the aggregate assessment consisted of combining food and drinking water exposure only, since residential exposure is not expected. The most relevant toxicology endpoints and assessment factors for acute and chronic oral aggregate exposure are the same as those selected for the ARfD (see Section 3.2.3) and ADI (see Section 3.2.4), respectively.

3.3 Dermal absorption

An in vivo dermal absorption study in rats was conducted with AG-M4-700 OF1 (Goltix Gold). The Goltix Gold formulation is similar to that of Brevis 150 SC with the only difference being that the proportion of formulants is proportionally lower when compared to the proposed Brevis

150 SC formulation. The concentration of active ingredient is much higher in the tested product (700 g/L) compared to the proposed product (150 g/L).

In vitro dermal absorption studies were conducted using both AG-M4-150 SG (Brevis 15 SG) and AG-M4-700 OF1 (Goltix Gold, same as above). Results of dermal absorption studies are summarized in Appendix I, Tables 6 and 7.

For worker exposure to Brevis 150 SC, a dermal absorption value of 17% for all exposure scenarios was established from the rat in vivo study, using the low dose of AG-M4-700 OF1 at the 144-hour sacrifice. Derivation of this dermal absorption value did not consider the tape strips (in other words, stratum corneum), as residues remained constant across 24-, 72-, and 144-hour sampling times, indicating a complete dermal absorption.

For Brevis 15 SG, dermal absorption values of 4% for mixer/loaders (from the human in vitro study conducted with the AG-M4-150 SG formulation concentrate) and 54% for all other exposure scenarios (applicators, postapplication, etc.), from the human in vitro study conducted with the AG-M4-150 SG low dose concentration, were established. Residues in the stratum corneum were included in these dermal absorption values, since the in vitro study was conducted for only 24 hours, which did not allow enough time to characterize the fate of skin-bound residues.

3.4 Occupational and residential exposure assessment

3.4.1 Acute hazards of end-use products and mitigation measures

3.4.1.1 Brevis 150 SC

The acute hazard assessment indicated that Brevis 150 SC was of low toxicity via the oral, dermal, and inhalation routes of exposure in rats. It was minimally irritating to the skin of rabbits and did not cause an allergic skin reaction in mice according to both the Buehler and maximization methods. Based on these acute hazards, a long-sleeved shirt, long pants, socks, and shoes are required for workers during mixing, loading, application, clean-up, and repair.

3.4.1.2 Brevis 15 SC

The acute hazard assessment indicated that Brevis 15 SG was of slight oral toxicity in rats, and of low acute toxicity via the dermal and inhalation routes of exposure. In rabbits, Brevis 15 SG was found to be corrosive to the eyes. Brevis 15 SG was not irritating to the skin and was not a skin sensitizer in the LLNA. Based on these acute hazards, a long-sleeved shirt, long pants, socks, shoes, and eye protection (goggles or face shield) are required for workers during mixing, loading, application, clean-up, and repair.

3.4.2 Occupational exposure and risk assessment

3.4.2.1 Mixer, loader, and applicator exposure and risk assessment

Individuals have potential for exposure to metamitron during mixing, loading, application, clean-up, and repair. Dermal and inhalation exposure estimates were generated from the Agricultural Handlers Exposure Task Force (AHETF) database, for mixers, loaders, and applicators applying

Brevis 150 SC or Brevis 15 SG to apples or pears using airblast equipment wearing a long-sleeved shirt, long pants, socks, shoes, and chemical-resistant gloves plus a chemical-resistant hat (unless inside a closed-cab tractor or cockpit) (Appendix I, Table 8).

Dermal exposure was estimated by coupling the unit exposure values with the amount of product handled per day and the dermal absorption value of 4% for mixer/loaders and 54% for applicators handling Brevis 15 SG, and 17% for mixer/loaders/applicators handling Brevis 150 SC. Inhalation exposure was estimated by coupling the unit exposure values with the amount of product handled per day with 100% inhalation absorption. Exposure was normalized to mg/kg bw/day by using 80 kg adult body weight.

Exposure estimates were compared to the selected toxicology reference value to obtain the MOE; the target MOE is 300. Dermal and inhalation MOEs were combined, since the dermal and inhalation endpoints are based on the same toxicological effects. Calculated MOEs are greater than the target MOE of 300 for all chemical handler scenarios for agriculture crops and are therefore not of health concern (Appendix I, Table 9).

3.4.2.2 Postapplication exposure and risk assessment

There is potential for exposure to workers entering areas treated with Brevis 150 SC or Brevis 15 SG to complete tasks such as scouting, hand thinning, hand harvesting, pruning, hand weeding, and transplanting. Given the nature of the activities performed, exposure should be primarily via the dermal route based on dermal contact with treated foliage. Inhalation exposure is not expected, as metamitron is considered non-volatile with a vapour pressure of $1.4\text{--}2.8\text{E-}9$ kPa (at 20–25°C), which is less than the North American Free Trade Agreement (NAFTA) criterion for non-volatile products for outdoor scenarios. As such, a quantitative inhalation risk assessment was not required. Inhalation risk is not of health concern for postapplication workers, as metamitron is considered to be non-volatile and the REI of at least 12 hours will allow residues to dry, suspended particles to settle, and vapours to dissipate.

Chemical-specific data for assessing human exposures during postapplication activities specific to apples were reviewed. The relevant study was designed to collect data to calculate dislodgeable foliar residue (DFR) dissipation curves for metamitron on apple leaves at three test sites: New York, Ontario, and Washington. Each site received two uniform airblast spray applications at 560 g a.i./ha of AG-M4-150 SC (a suspension concentration formulation containing 150 g metamitron/L), 5 ± 1 days apart, and was monitored for up to 35 days after the last application. Geographical and climatic conditions were relevant to Canadian growing regions. The application method, application rates, frequency, and monitoring times were relevant to the proposed use pattern.

Samples were presented as an average of three replicates and expressed as a percentage of the actual dose. Residues measured in treated samples were corrected for field recovery when recovery was lesser than 95%. Values lesser than or equal to the LOQ were not corrected for recovery but were set to half of the LOQ. The dissipation rate for all the three geographic locations was modeled using three models to fit DFR datasets: LnDFR linear, exponential, and biphasic. The models are evaluated using visual analysis and are considered acceptable when a good fit is observed in the dissipation graph and when there are no patterns found in the residual plot. If multiple models are considered acceptable, then the simplest model is recommended.

New York

The recoveries of metamitron were all above 95% and were not corrected for recovery prior to fitting to the linear, exponential, or biphasic models. All three models produced a poor fit with data from the New York trial and it was recommended to use the actual data from the trial instead of the equations. The actual peak residue was 0.938 $\mu\text{g}/\text{cm}^2$ at day 0 (17% of the application rate).

Ontario

The recoveries of metamitron were below 95% at the low fortification level; therefore, samples that fell below the midpoint of the low and mid fortification levels were corrected for recovery prior to fitting to the linear, exponential, or biphasic models. The exponential and biphasic models had good fits; therefore, the exponential model was used, as it was the simplest model. The predicted peak residue using the exponential model method was 0.875 $\mu\text{g}/\text{cm}^2$ at day 0 (15.63% of the application rate) and the daily dissipation rate was 29%.

Washington

The recoveries of metamitron were below 95% at the low fortification level; therefore, samples that fell below the midpoint of the low and mid fortification levels were corrected for recovery prior to fitting to the linear, exponential, or biphasic models. All models had good fits; the linear model was used, as it was the simplest model. The predicted peak residue was 1.225 $\mu\text{g}/\text{cm}^2$ at day 0 (22% of the application rate) and the daily dissipation rate was 8%.

Overall, the three studies were acceptable with no major limitations. Considering the regression analyses, the geographic relevance of each site, and the impact of rainfall, the Washington site was the most appropriate for deriving DFR values for use in Canada. This site is located in North America Free Trade Agreement (NAFTA) Growing Zone 11, which also includes British Columbia's Okanagan Valley – one of Canada's major apple-producing regions – making the data geographically and climatically relevant. Additionally, the Washington study results were unaffected by rainfall and produced the most conservative residue values, providing a protective approach for human health assessments. Results of the DFR study are presented in Appendix I, Table 10.

Dermal exposure to workers entering treated areas is estimated by coupling DFR values with activity-specific transfer coefficients (TCs). Activity TCs are based on data from the Agricultural Re-entry Task Force (ARTF). As chemical-specific DFR data were submitted, a DFR value of 24% of the application rate coupled with 8% daily dissipation of residues were used in the exposure assessment.

Exposure estimates were compared to the toxicology reference value to obtain the MOE; the target MOE is 300. Only exposures and risks to the activities with the highest TCs are presented, as MOEs for these activities exceed the target MOE of 300, and are thus, not of health concern (Appendix I, Tables 11 and 12). For Brevis 150 SC, a five-day REI for hand thinning apples is required west of the Canadian Rockies to meet the target MOE of 300. For all other postapplication activities, the REI of 12 hours is adequate. For Brevis 15 SG, a 19-day REI for hand thinning and an 11-day REI for hand harvesting are required for apples west of the

Canadian Rockies; a 14-day REI for hand thinning and a five-day REI for hand harvesting are required for pears and apples east of the Canadian Rockies to meet the target MOE of 300. For all other postapplication activities, the REI of 12 hours is adequate.

3.4.3 Residential exposure and risk assessment

3.4.3.1 Handler exposure and risk assessment

Brevis 150 SC and Brevis 15 SG are not domestic class products and are not permitted for use in residential settings; therefore, a residential handler exposure assessment was not required.

3.4.3.2 Postapplication exposure and risk assessment

Pick-your-own activities

Given that apple and pear can be treated with metamitron, there is potential for exposure during PYO activities. The postapplication occupational risk assessment is protective of the risk associated with dermal exposure to the patrons in a PYO facility; therefore, a quantitative risk assessment was not required.

Trees in residential areas treated with Brevis 150 SC and Brevis 15 SG

Neither Brevis 150 SC nor Brevis 15 SG are anticipated to be used in residential areas, as fruit thinning is not typically done chemically on residential orchard crops. As such, a postapplication residential risk assessment was not required for this scenario.

3.4.4 Bystander exposure and risk assessment

Bystander exposure is considered negligible, as application is limited to agricultural crops only when there is low risk of drift to areas of human habitation or activity such as houses, cottages, schools and recreational areas, taking into consideration wind speed, wind direction, temperature inversions, application equipment, and sprayer settings. Therefore, bystander exposure and risk are not of health concern, since the potential for drift is expected to be minimal.

3.5 Dietary exposure and risk assessment

3.5.1 Exposure from residues in food of plant origin

The residue definition for risk assessment in apples and pears is metamitron and the metabolite desamino-metamitron. The residue definition for enforcement in apples and pears is metamitron. The data gathering and enforcement analytical method is valid for the quantitation of metamitron and desamino-metamitron residues in these crop matrices. The residues of metamitron and desamino-metamitron are stable in high-water content commodities (in other words, apple processed commodities (juice, wet pomace, and applesauce) and sugar beet leaves) for up to 15 months, in high-acid content commodities (in other words, strawberries) for up to 12 months, in high-starch commodities (sugar beet roots) for up to 24 months, and in dry apple pomace for up to 15 months when stored in a freezer at -18 to -20°C. Metamitron residues concentrated in the following processed commodity: apple dry pomace (2.3-fold). Crop field trials conducted throughout Canada and the United States using end-use products containing metamitron at

slightly exaggerated rates in or on apples and pears were sufficient to support the proposed MRLs. Rotational crop studies were not required since apples and pears cannot be rotated with other crops. Residue chemistry data in livestock commodities were not required since apples and pears are not considered as livestock feed items.

3.5.2 Exposure from residues in drinking water

3.5.2.1 Concentrations in drinking water

For the human health risk assessment, estimated environmental concentrations (EECs) of metamitron and relevant transformation products in potential drinking water sources are calculated for both groundwater and surface water using the Pesticide Water Calculator (PWC; version 2.001). For surface water, the PWC calculates the amount of pesticide entering the water body by runoff and drift, and the subsequent degradation of the pesticide in the water system. Estimated environmental concentrations are calculated by modelling a total land area of 173 ha draining into a 5.3-ha reservoir with a depth of 2.7 m. Groundwater EECs are calculated by simulating leaching through a layered soil profile and reporting the average concentration in the 1 m below a water table.

Drinking water modelling follows a tiered approach consisting of progressive levels of refinement. Level 1 EECs are conservative values intended to screen out pesticides that are not expected to pose any concern related to drinking water. These are calculated using conservative inputs with respect to application rate, application timing, and geographic scenario. Level 2 EECs are based on a narrower range of application timing, methods, and geographic scenarios, and are not considered conservative values that cover all regions of Canada.

Residues modelled and fate inputs

The residue definition for drinking water included metamitron (parent compound), desamino-metamitron, M1 (6-Methyl-3-phenyl-1,2,4,5-tetrazine), and M2 (2-(acetylhydrazinylidene)-2-(phenyl) acetic acid (Appendix I, Table 13).

Estimated environmental concentrations (EECs) in drinking water

For metamitron and its transformation products, modelling was performed at Level 1. The use pattern selected for the modelling was the highest cumulative yearly rate (total application rate accumulated over a year accounting for dissipation between applications) of two applications of 504 g a.i./ha with a five-day interval. The EECs for surface water were calculated based on a single standard scenario. The EECs in groundwater were calculated for several scenarios representing different regions of Canada; only the highest EECs from across these scenarios are reported. Most scenarios were run for 50 years, but the British Columbia scenario was run for 100 years to more closely approach steady-state concentrations. The resulting drinking water EECs are found in Appendix I, Table 14.

3.5.3 Dietary risk assessment

Acute and chronic dietary risk assessments were conducted using the Dietary Exposure Evaluation Model (DEEM-FCID™, Version 4.02, 05-10-c), which incorporates consumption data from the National Health and Nutrition Examination Survey/What We Eat in America (NHANES/WWEIA) for the years 2005–2010.

3.5.3.1 Acute dietary exposure results and risk characterization

The following assumptions were applied in the basic acute analysis for metamitron: 100% crop treated, default processing factors, residues in/on crops at MRL levels, and American tolerances for imported commodities. The basic acute dietary exposure (food alone) from all supported metamitron registered and imported food commodities is estimated to be less than 1% (<0.000473 mg/kg bw) of the ARfD for all representative population subgroups, including females 13–49 years old (95th percentile, deterministic). Aggregate exposure from food and drinking water is considered acceptable at less than 5% (0.004482 mg/kg bw) of the ARfD for females 13–49 years old and less than 16% (0.015576 mg/kg bw) of the ARfD for all infants (less than 1 year old), the highest exposed subpopulation.

3.5.3.2 Chronic dietary exposure results and risk characterization

The following assumptions were applied to the basic chronic analysis for metamitron: 100% crop treated, default processing factors, residues in/on crops at MRL levels, and American tolerances for imported commodities. The basic chronic dietary exposure (food alone) from all supported metamitron registered and imported food commodities for all representative population subgroups, including infants and children, is less than 1% (<0.000132 mg/kg bw/day) of the ADI. Aggregate exposure from food and drinking water is considered acceptable. The PMRA estimates that chronic dietary exposure to metamitron from food and drinking water is 4% (0.001513 mg/kg bw/day) of the ADI for the total population. The highest exposure and risk estimate is for all infants (less than one year old) at less than 15% (0.005659 mg/kg bw/day) of the ADI.

3.6 Aggregate exposure and risk assessment

For metamitron, the aggregate assessment consisted of combining food and drinking water exposure only, since residential exposure is not expected.

3.7 Cumulative assessment

The *Pest Control Products Act* requires the PMRA to consider the cumulative health effects of pest control products that have a common mechanism of toxicity. Accordingly, an assessment of a potential common mechanism of toxicity with other pesticides was undertaken for metamitron. Metamitron belongs to a class of herbicides known as asymmetrical triazines. Within this class, there is one other herbicide registered in Canada and internationally: metribuzin. Reduced body temperature and elevated cholesterol were noted in both the metamitron and metribuzin toxicology databases. As these rare and specific toxic effects were observed in same class of pesticides, and although not fully elucidated, they are very likely elicited via a common mechanism of toxicity. The liver is the primary target organ for both active ingredients.

In addition to identifying a common mechanism of toxicity, other important considerations must be explored as part of the process in determining the need to conduct a cumulative risk assessment (CRA). These considerations include defining and comparing the use patterns of the different chemicals belonging to a class of pesticides with a common mechanism of toxicity such as registered uses, residential uses, potential routes of exposure, and the potential for co-occurrence of exposure to the different chemicals. In addition, food residue monitoring data from the Canadian Food Inspection Agency (CFIA) and/or the United States Department of Agriculture (USDA) Pesticide Data Program (PDP), as well as drinking water monitoring information, are important sources of real-world data for dietary exposure assessment, and are key in order to conduct realistic CRAs.

3.7.1 Exposure pathways and co-occurrence of exposure

Table 3.7.1.1 presents the summary of uses and exposure pathways for the asymmetrical triazines, metribuzin and metamitron.

Table 3.7.1.1 Summary of uses and exposure pathways for registered and proposed asymmetrical triazines

Active ingredient	PMRA published document	Pesticide uses	Potential exposure pathways		
			Food	Drinking water	Residential
Metribuzin	PACR2005-07, RRD2006-15	Various field crops, vegetables, fruit (including apples and pears) and fallow land as an herbicide to be applied pre- or post-emergent to weeds	Yes	Yes (water monitoring data)	No
Metamitron	Current assessment	Apples and pears for the purpose of fruit thinning	Yes	Yes (EEC ¹)	No

¹ EEC = estimated environmental concentration; based on conservative modelling of pesticide residues in drinking water sources.

There is a potential for co-occurrence of exposure of these pesticide residues through dietary exposure. As no residential uses are registered or proposed for asymmetrical triazines, no residential (non-dietary) exposure is anticipated. Accordingly, the potential contribution to the cumulative exposure of asymmetrical triazines is through dietary exposure alone.

3.7.2 Dietary exposure

3.7.2.1 Exposure to metribuzin from food

The most recent dietary risk assessment for metribuzin was conducted in 2015. No other expansion of use has been approved for metribuzin since then. Only a dietary chronic risk assessment was conducted, and an acute dietary exposure assessment was not required, as no appropriate endpoint attributable to a single dose for the general population (including children and infants) was identified.

The risk assessment was refined with available monitoring data from the PDP. The refined chronic dietary exposure from all supported metribuzin food uses for the representative population subgroups ranged from 3.5% to 15.3% of the ADI.

3.7.2.2 Exposure to metribuzin from drinking water

There was no estimated EEC value modelled for metribuzin in drinking water; therefore, the aggregate risk assessment from food and drinking water was not conducted.

However, water monitoring data are currently available for metribuzin through the Canadian Water Monitoring Program for Pesticides (CWMPP) and Atlas de l'eau. Available information on all water monitoring data was used, as sites have not been fully assessed for relevancy to the drinking water assessment (in other words, streams and creeks in agricultural areas are included) at this time. This dataset may also include sites in areas where there are no crops on which metribuzin is registered for use.

In the CWMPP data available as of February 25, 2025, metribuzin was detected in 768 of 6233 samples (12.3%) collected from 2022 to 2024. Metribuzin was detected in 16 of 218 groundwater samples (7.3%). All groundwater detections were at a single site in PEI. The highest detected groundwater concentration was 0.035 µg/L, well below the human health reference value (HHRV) of 53 µg/L. Metribuzin was detected in surface water samples in Manitoba, Nova Scotia, Ontario, Prince Edward Island, Quebec, and Saskatchewan. Metribuzin was detected in 753 of 6015 surface water samples (12.5%), and the maximum concentration detected was 13 µg/L. At the site with the highest detected concentration (Wigle Creek, Ontario), the maximum concentration was a peak in concentration, and the three smaller peaks that occurred over the two years of sampling were no higher than 5.4 µg/L. This surface water site is surrounded by high agricultural density, with the dominant crops being soybean, corn, and winter wheat (metribuzin is registered for use on these crops). This stream is not a drinking water source.

In the water monitoring data from Quebec (Atlas de l'eau), from 2010 to 2023, metribuzin was detected in 1292 of 3355 samples (38.5%). The maximum concentration detected was 43 µg/L in 2013. The next highest concentration was 8.6 µg/L, at the same site and in the same year. This site is in a high-density vegetable crop area and is sampled twice weekly during the growing season. In 2013, the average concentration at the site was 2.5 µg/L. Elevated concentrations were preceded and followed by lower concentrations, suggesting the peaks resulted from runoff events. This stream is not a drinking water source. Focusing on the most recent data, metribuzin was detected in 308 of 1031 (30%) of Quebec samples from 2020 to 2023. The highest concentration detected in that period was 1.6 µg/L.

Based on the water monitoring data summarized above, drinking water concentrations of metribuzin are expected to be no higher than 13 µg/L, since the maximum detected concentrations in the two databases (13 µg/L and 43 µg/L) are not drinking water sources.

3.7.3 Qualitative risk assessment of asymmetrical triazines

When considering the estimated risks from the individual dietary exposure assessments, exposure was low, and represented 14% of the ADI in the basic chronic dietary exposure assessment (food + drinking water) for metamitron and 15% in the refined chronic dietary exposure assessment (food only) for metribuzin. Median residue concentrations are considered appropriate for the chronic dietary risk assessment. For the purpose of this qualitative assessment, a high exposure scenario was assumed. Based on the water monitoring data available, as summarized above, drinking water concentrations of metribuzin are expected to be no higher than 13 µg/L, which is less than 25% of the HHRV of metribuzin. A simple sum of these exposure estimates would not exceed the risk cup.

These risk estimates from the individual dietary exposure assessments were calculated using the most conservative points of departure, that are not necessarily based on common effects of reduced body temperature and elevated cholesterol (which are likely to be higher). As a result, the summing of these individual risk estimates overestimates the cumulative risk of asymmetrical triazines.

Therefore, based on this qualitative assessment, the cumulative risks from potential co-exposure to asymmetrical triazines, metamitron and metribuzin, through food, and drinking water where relevant, are acceptable.

3.8 Maximum residue limits

Dietary risks from the consumption of food commodities listed in Table 3.8.1 were shown to be acceptable when metamitron is used according to the supported label directions. Therefore, foods containing residues at these levels are safe to eat, and the PMRA recommends that the following MRLs be specified for residues of metamitron.

Table 3.8.1 Recommended maximum residue limits

MRL (ppm)	Food commodity
0.01	Apples
0.01	Pears

The MRLs proposed for metamitron in Canada are the same as corresponding tolerances in the United States. For additional information on MRLs in terms of the international situation and trade implications, refer to Appendix II.

The nature of the residues in plant commodities, analytical methodologies, field trial data, and acute and chronic dietary risk estimates are summarized in Appendix I, Tables 1b, 15, and 16.

3.9 Health incident reports

As of 13 February 2025, no human or domestic animal incidents involving the active ingredient metamitron had been submitted to the PMRA.

4.0 Impact on the environment

4.1 Fate and behaviour in the environment

A summary of the transformation products of metamitron is provided in Appendix I. The environmental fate parameters for metamitron and its transformation products are provided in Appendix I, Tables 17–22.

Terrestrial environment

The main dissipation pathways for metamitron in the terrestrial environment are hydrolysis and biotransformation in soil. Phototransformation on soil is not expected to be a significant route of degradation in terrestrial environments.

The rate of hydrolysis for metamitron is temperature- and pH-dependant. Hydrolysis is quicker at higher temperatures and at pH 9, and slower at pH 4 and 7. Metamitron transformed to three major hydrolysis transformation products at pH 9: benzonitrile, phenylglyoxylic acid, and benzoic acid. Biotransformation in soil is a major route of transformation for metamitron. Metamitron is non-persistent to slightly persistent and transformed with dissipation time 50% (DT₅₀) values ranging from 3.4 to 42 days, depending on soil type. In most studies, metamitron transformed into major transformation products of desamino-metamitron and CO₂. The main transformation product, desamino-metamitron, is slightly persistent and dissipated with DT₅₀ values ranging from 18.7 to 53 days, depending on soil type. Some residues were bound strongly to soil.

Metamitron is slightly persistent to persistent in flooded soils. In flooded soils, the DT₅₀ values ranged from 28 to 279 days, depending on the soil system. These types of studies have short periods of aerobic soil conditions before flooding occurs, and in the studies with longer aerobic conditions, more desamino-metamitron was formed before flooding. Other major transformation products formed and detected in flooded soils included M2a and CO₂. Similar to the soil studies, some residues were bound strongly to soil and were not considered bioavailable.

Field conditions

Two terrestrial field dissipation studies on bare soil were conducted in Canadian-relevant ecoregions (New York and Washington). Metamitron was applied twice at 550 g a.i./ha with a five-day interval (slightly higher rate than the proposed Canadian rate), followed by water inputs equalling 120% of historical averages. Between both sites, metamitron and the major transformation product, desamino-metamitron, were found mainly in the 0–30.5 cm of top three layers, and their residues declined by 180 days. Under field conditions among the two sites, the DT₅₀ values of metamitron were 7.44 and 12.8 days, and DT₅₀ values of desamino-metamitron were 11.8 and 21.1 days, with longer half-lives in the Washington location.

Metamitron and desamino-metamitron are not expected to carry over to the following growing season.

Aquatic environments

In water, phototransformation in surface waters is expected to be a major route of transformation for both metamitron and desamino-metamitron. Photolysis of metamitron occurs more quickly than hydrolysis. In natural pond water at pH 7 with light, metamitron transformed rapidly (DT₅₀: 0.487 and 1.86 hours) to form desamino-metamitron, which also declined after a few days. Other major transformation products formed included M4, M8, and benzoic acid, which all declined by 14 days. Studies were also conducted in pure water with light at pH 7 and pH 5, where metamitron transformed rapidly (DT₅₀: 8.52 to 12.7 minutes). The transformation of desamino-metamitron from both direct and indirect photolysis was also investigated. These studies showed that desamino-metamitron transformed with maximum half-lives of 53 days, and that photolysis increased with increasing pH. The addition of humic substances led to further dissipation from water, with a half-life of 23 hours.

In the studies with water and sediment, metamitron was slightly persistent to moderately persistent, and dissipated with total system DT₅₀ values ranging from 8.9 to 50.1 days. The major transformation product formed was desamino-metamitron, which did not decline significantly during the studies. Hydrolysis may also have played a role in dissipation in studies with higher pH values.

Under anaerobic aquatic conditions with water and sediment, metamitron was not persistent, and dissipated with a half-life of 3.8 to 6.1 days. The main transformation product was desamino-metamitron. Some residues were bound and not considered bioavailable.

Under aerobic aquatic conditions with no sediment (in other words, surface water from aquatic environment with no sediment included), metamitron was non-persistent to slightly persistent (DT₅₀: 15.4 to 24.6 days). Two major transformation products were formed: M1 (6-methyl-3-phenyl-1,2,4,5-tetrazine) and M2 [2-(acetylhydrazinylidene)-2-(phenyl) acetic acid]. There was also a high amount of CO₂ formed (up to 40%).

Dissipation into air

Metamitron and its major transformation products are not expected to be found in the air near the application site based on their low vapour pressures and Henry's law constants. This is also supported by the laboratory fate studies, which did not find significant amounts of radioactivity in the organic traps used to collect volatile compounds.

Bioaccumulation

Metamitron is not expected to build up in the tissues of organisms based on low bioconcentration factor values determined in a bioconcentration study in fish. The major transformation products, desamino-metamitron, M1, and M2, are also not expected to build up in the tissue of organisms based on low predicted log *K*_{ow} values.

Mobility in soil

Based on batch equilibrium studies with radiolabelled metamitron, the mobility of metamitron in soil ranged from moderately mobile to highly mobile, depending on soil type (organic carbon normalized adsorption coefficient (K_{oc}) / organic carbon normalized Freundlich adsorption coefficient (K_{FOC}) range from 31.5 to 396 mL/g). In most cases, Freundlich desorption coefficient (K_{F-DES}) and organic carbon normalized Freundlich desorption coefficient ($K_{FOC-DES}$) values were greater than the corresponding adsorption values, indicating that adsorption was only partially reversible (Appendix I, Table 20). Overall, metamitron transforms and mineralizes, and also forms irreversibly bound residues.

According to the criteria of Cohen et al. (1984), metamitron meets the criteria for leaching based on solubility, adsorption properties, and soil and water half-lives depending on soil type (in other words, meets the criteria for some soils and not others). It does not meet the criteria for leaching based on pK_a and volatilization criteria (Appendix I, Table 21).

Based on groundwater ubiquity score (GUS) values for leachability, considering laboratory aerobic soil DT_{50} or half-life values and K_{OC} mobility values, metamitron is considered a non-leacher/borderline leacher. Considering laboratory soil half-lives (DT_{50}) and K_{OC} mobility values, desamino-metamitron is considered a borderline leacher/leacher.

Overall, the mobility of metamitron and its transformation products have some potential to leach depending on soil type. As such, label statements are included on the label indicating leaching and runoff potential.

4.2 Environmental risk characterization

An environmental risk assessment was conducted as described in the PMRA 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 EECs to effects-based values used to assess risk (effects metrics). The 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 I, Tables 22, 27, 28, 31, and 32.

Acute and chronic ecotoxicological data for non-target terrestrial, freshwater, and marine organisms are summarized in Appendix I, Tables 23 and 24. In the risk assessment, toxicity endpoints were adjusted via an uncertainty factor 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). The effects metrics and uncertainty factors used in the risk assessment are presented in Appendix I, Table 25.

Initially, a screening level risk assessment was performed to identify specific uses that do not pose a risk to non-target organisms. The screening level risk assessment used 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 LOC. When

the screening level RQ was below the LOC, the risk was considered to be 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 evaluated additional and more realistic exposure scenarios, including consideration of spray drift, exposure estimates, as well as effects metrics that were more reflective of potential exposure in the environment. 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, pollinators, beneficial arthropods, birds, small wild mammals, and terrestrial non-target vascular plants can be exposed to metamitron through direct contact with spray, spray drift, run-off, contact with sprayed surfaces, or from ingestion of contaminated food.

For terrestrial organisms, the risks of metamitron were assessed at the maximum application rate: two applications of 504 g a.i./ha with a five-day interval. Risks of the major transformation product, desamino-metamitron, was assessed by assuming 100% conversion (considering molecular w/w) from metamitron. When applicable, drift off-field was also assessed, assuming 59% drift for late airblast application. Although metamitron can be applied as early or late airblast, applications are made as a fruit thinner when there are leaves present on the trees, which is more accurately represented by 59% late application drift. The airblast drift estimates are based on fine droplet size, as the proposed label specifies that droplets no smaller than the American Society of Agricultural and Biological Engineers (ASABE) medium are permitted.

Exposure to bees at the maximum application rate is based on one application at 504 g a.i./ha. This is because the major exposure routes for bees are from nectar and pollen in flowers and the same flowers are unlikely to be exposed multiple times to the foliar application. As well, the application interval is typically longer than the blooming span of a single flower.

The conservative screening level and refined risk assessment (including endpoints and EECs/estimated daily exposures (EDEs)) for terrestrial organisms is summarized below and in Appendix I, Tables 26–33. Overall, the screening level LOC was not exceeded for soil-dwelling organisms, leaf-dwelling arthropods, and pollinators. The screening level LOC was exceeded for mammals, birds and terrestrial plants, and a refined risk assessment was conducted to further characterize the risk.

Soil dwelling organisms (earthworms and collembola): The screening level risk for soil-dwelling invertebrates is calculated by using the most sensitive effect metrics, and conservative soil exposure concentrations. The acute and chronic screening level RQs for soil-dwelling invertebrates (earthworms and collembola) exposed to metamitron, its major soil transformation product, desamino-metamitron, or end-use product formulation, did not exceed the LOC (RQ < LOC). No further risk characterization was performed.

Leaf dwelling beneficial arthropods: The screening level risk for leaf-dwelling invertebrates is calculated by using the most sensitive effect metrics, and maximum cumulative yearly application field rates accounting for dissipation between applications. The screening level RQ for leaf-dwelling invertebrates (beneficial arthropods) exposed to metamitron as an end-use product did not exceed the LOC. No further risk characterization was performed.

Pollinators: The screening level risk for pollinators is calculated by using the most sensitive acute and chronic effect metrics for larval and adult bees, and conservative contact and oral exposure concentrations. The screening level RQs did not exceed the LOC from acute oral and contact exposure to adult honey bees, or acute and chronic exposure to larval bees. Despite the RQ (5) exceeding the LOC (1) for adult chronic exposure, there are no applications during bloom, as only post-bloom applications are allowed. As such, no exposure from ingestion of contaminated pollen and/or nectar is expected. No further risk characterization was performed.

Terrestrial plants: The screening level risk for terrestrial plants is calculated by using the most sensitive effects metrics and the maximum cumulative yearly application field rates accounting for dissipation between applications. In the case of terrestrial plants, the seedling emergence effect metrics for lettuce was the most sensitive (considering vegetative vigour as well). The RQs for on-field (14) and off-field, considering 59% drift (8.3), both exceeded the LOC (1). In order to mitigate the risks to terrestrial organisms, a terrestrial spray buffer zone up to 15 metres is required on the label.

Birds and mammals: A screening level risk assessment was conducted to evaluate acute and reproductive risks to birds and mammals based on the estimated concentration of metamitron in various food items in the diet (the EDE). Exposure is dependent on the body weight of the organism, and the amount and type of food consumed. As such, a set of generic body weights was used to represent a range of species (20, 100, and 1000 g for birds and 15, 35, and 1000 g for mammals), and specialized feeding guilds (in other words, herbivore, frugivore, insectivore, and granivore) were considered for each category of animal weights.

The screening level risk assessment evaluated a conservative exposure scenario based on:

- The maximum metamitron residue concentrations in food items;
- A diet that is composed entirely (100%) of a particular metamitron-contaminated food item; and
- The feeding guild assumed to have the highest exposure for each animal weight category.

If a concern was identified at the screening level (in other words, $RQ > LOC$ of 1), the risk was then further characterized.

Birds

Screening level risk assessment: For birds, the screening level risk is calculated by using the most sensitive effect metrics, and assuming 100% consumption of contaminated food items with maximum residues from on-field exposure for the most conservative food guilds (in other words, insectivores for small and medium birds, and herbivores [short grass] for large birds).

The on-field screening level RQs did not exceed the LOC for acute effects for small-, medium-, or large-sized birds, or for reproductive effects to large birds.

The screening level RQs (up to 1.8) exceeded the LOC (1) for reproductive effects for small- and medium-sized birds (Appendix I, Table 27). To further characterize risk of reproductive effects to small and medium birds, additional food guilds, off-field exposure with maximum residues, and mean residues on dietary items for both on- and off-field exposure are considered, as well as comparison of effects using the LOAEL from the same toxicity study. The percent contaminated daily diet required to reach the effect metric was also considered.

Sub-lethal effects: A number of avian studies showed sublethal effects, such as diarrhea, lethargy, unsteadiness, and post mortem observations of pale organs, hemorrhaging, and reduction in body weight gain. As these sublethal effects were observed in several studies, and could have impacts on survival, they were considered in the risk assessment. Sublethal effects from the acute and dietary studies with Japanese quail, canary, and mallard duck were observed at levels as low as 196 mg/kg bw/d. The acute LD₅₀/10 of 132.6 mg a.i./kg bw is the lowest effect metrics in the avian risk assessment and covers off observed sublethal effects.

Further characterization – birds

Additional food guilds: To further characterize the risk to birds, RQs were calculated for additional food guilds (in other words, granivores and frugivores) in addition to the most conservative food guild for small- and medium-sized birds (in other words, insectivores). The RQs only exceeded the LOC for small and medium insectivorous birds and did not exceed the LOC for granivores or frugivores (Appendix I, Table 28).

Off-field assessment: To further characterize the risk to birds, the off-field risk was calculated assuming 59% drift for late airblast application. The proposed label requires droplets no smaller than ASABE medium, which are expected to result in less drift than what was considered in the risk assessment. As such, off-field estimates are likely overly conservative in the risk assessment. The resulting off-field RQs (1.1) were exceeded for reproductive effects for small-sized birds, considering maximum residues in food (Appendix I, Table 28).

Mean residues: In the screening level assessment, the potential risk to birds comes from the assumption that 100% of their diet is from peak residues in insects. To further characterize the risk, the mean residue concentration in diet was considered for both on- and off-field exposure. Based on mean nomogram residue levels, the RQ still exceeded the LOC for on-field exposure for small birds for reproduction (RQ of 1.23) but did not exceed the LOC for small-sized birds for off-field exposure, or for medium-sized birds for on- or off-field exposure (Appendix I, Table 28).

Considering the LOAEL: In the screening level and refined assessments, the NOAEL is considered for reproductive effects. For exploratory purposes, the LOAEL endpoints can be considered in the risk assessment to determine if RQs are exceeded at the LOAEL. In the screening level risk assessment considering the NOAEL (NOAEL of 39.2 mg a.i./kg bw/day), the only feeding guild RQ that exceeded the LOC was for insectivores, with the assumption that 100% of their diet consisted of contaminated food (maximum residues resulted in exceedances for small and medium birds on-field, and for small birds off-field; mean residues resulted in

exceedances only for small birds on-field). To further explore potential risk, the LOAEL was considered in the assessment (LOAEL of 85.7 mg a.i./kg bw/day; the concentration which elicited a reduction in body weight of hatchlings and 14-day old chicks compared to controls of 6.93% and 6.72%, respectively). Based on maximum residues and the LOAEL, the RQs did not exceed the LOC for on- or off-field exposure for any sized birds (Appendix I, Table 29).

Considering percent of diet required to reach the NOAEL: The percent of estimated daily diet required to reach an effect metric can be calculated by dividing $1/RQ \times 100$ (Appendix I, Table 30). As mentioned, in the screening level risk assessment considering the NOAEL (NOAEL of 39.2 mg a.i./kg bw/day), the only feeding guild RQ that exceeded the LOC was for insectivores, with the assumption that 100% of their diet consisted of contaminated food. Considering maximum residues, small-sized birds would require 56% of diet on-field and 81% of diet off-field to reach the NOAEL, and medium-sized birds would require 72% of diet on-field and >100% of diet off-field to reach the NOAEL. Considering mean residues, small birds would require 81% of diet on-field to reach the NOEL, but small birds off-field and medium birds on- and off-field would require >100% of diet to reach the NOEL, thus they would not consume enough food to reach the NOAEL. As well, neither small- or medium-sized birds would consume enough food to reach the LOAEL, considering either maximum or mean residues, as >100% of diet would be required to reach the LOAEL. In all cases, the percentage of diet required to reach the NOEL is very high, and unlikely to be reached.

Other considerations for consumption of contaminated diet is the potential for overestimation related to method OF application. The nomogram/residue unit dose used to estimate residues on feed items is based on field sprayer data, for which applications would be directed towards the ground. With respect to the chronic risk for bird populations, residue estimates on arthropods are based on measures taken after direct spray. Airblast to canopy would be subject to foliar interception and, if arthropods were not immobilized by the application, they would likely continue to move in and out of the treated area, with subsequent generations emerging. As such, the exposure estimate is an extreme worst-case scenario that is unlikely to impact a sizeable fraction of an entire bird population.

Summary of risk conclusions – Birds:

- Screening level RQ exceedances of the LOC were identified for reproduction for birds (RQs up to 1.8), considering maximum residues in the field. Further characterization of risk was completed considering on- and off-field exposure to both mean and maximum residues, percent contaminated diet to reach LOC, and considering the LOAEL.
- When considering mean residues and the NOAEL, the RQ for reproduction was reduced to 1.23 on-field and >81% of the diet would need to be contaminated to reach the LOC. The RQ was <1 off-field when considering the NOAEL.
- When the LOAEL (6.93% reduction in body weight for hatchlings compared to control) and maximum residues were considered, the RQ did not exceed the LOC for on- or off-field exposure.
- Risk of reproductive effects in birds from exposure to metamitron is considered unlikely when label directions are followed given that (i) RQs for off-field scenarios were below the LOC, (ii) birds would need to consume a large proportion of a single contaminated food item to reach the effects metric, and (iii) insectivores were the only feeding guild to

exceed the NOAEL, considering maximum residues, and their diet would likely consist of food sources foraged from different areas.

- Based on the acute oral and dietary lethal dose 50% (LD₅₀) values, and overall acceptable risk to birds, there is no requirement for a hazard-based toxicity statement on the label.

Mammals

Screening level risk assessment: For mammals, the screening level risk is calculated by using the most sensitive effect metrics, and assuming 100% consumption of contaminated food items with maximum residues from on-field exposure for the most conservative food guilds (in other words, insectivores for small mammals, and herbivores [short grass] for medium and large mammals).

The RQs, which ranged from 1.21 to >10.7, exceeded the LOC (1) for small-, medium-, and large-sized mammals. The RQ of >10.7 is based on a non-definitive reproduction endpoint (there were effects at the lowest test dose in the reproduction study; therefore, the NOAEL is a < value). The RQs did not exceed the LOC for small- or large-sized mammals, considering acute endpoints, but did exceed the LOC for medium-sized mammals (RQ of 1.21). The reproductive RQ exceeded the LOC for all sized mammals (Appendix I, Table 31).

To further characterize risk of acute and reproductive effects to mammals, additional food guilds, off-field exposure with maximum residues, and mean residues for both on- and off-field exposure are considered. Comparison of effects using the LOAEL from the same toxicity study was considered. The percent contaminated daily diet required to reach the effect metric was also considered.

Further characterization – mammals:

Additional food guilds: To further characterize the risk to mammals, RQs were calculated for additional food guilds. RQs exceeded the LOC for the reproductive NOAEL in small insectivorous and frugivorous mammals, medium insectivorous, frugivorous, and herbivorous mammals, and large insectivorous and herbivorous mammals. In addition, RQs exceeded the LOC for acute effects in medium herbivorous (short grass) mammals (Appendix I, Table 32). RQs did not exceed the LOC for granivorous mammals of any size, or for large frugivorous mammals.

Off-field assessment: To further characterize the risk to mammals, the off-field risk was calculated assuming 59% drift for late airblast application and maximum residues in food. The proposed label specifies that droplets no smaller than ASABE medium are permitted, which are expected to result in less drift than what was considered in the risk assessment. As such, off-field estimates were likely overly conservative in the risk assessment. The off-field RQs were exceeded for the reproductive NOAEL for small, medium, and large mammals with a maximum RQ of > 6.31 (Appendix I, Table 32). RQs did not exceed the LOC for any acute effects for any sized mammal.

Mean residues: In the screening level assessment, the potential risk to mammals comes from the assumption that 100% of their diet is from peak residues on various food items. To further characterize the risk, the mean residue concentration in diet was considered for both on- and off-

field exposure. Based on mean nomogram residue levels, the RQs still exceeded the LOC for small- and medium-sized mammals for the reproductive NOAEL from on- and off-field exposure, with maximum RQs of > 3.8 for on-field exposure and > 1.2 for off-field exposure (Appendix I, Table 32).

Considering the LOAEL and NOAEL: In the screening level and refined assessments, the NOAEL is considered for reproductive effects. The most sensitive effect metric was based on a rat study, with effects at the lowest test concentration including a decrease in body weight and body weight gain during pre-mating, gestation, and lactation, and decreased food consumption (with a LOAEL of 7.3 mg/kg bw/day and a non-definitive NOAEL < 7.3 mg/kg bw/day). For exploratory purposes, the LOAEL endpoints can be considered in the risk assessment to determine if RQs are still exceeded at the effect level (compared to the no effect level). The maximum RQs considering the LOAEL from mean residue exposure is 3.8 on-field and 1.2 off-field.

Considering percent of diet: The percent of estimated daily diet required to reach an effect metric can be calculated by dividing $1/RQ \times 100$. For small mammals consuming mean residues on contaminated food items to reach the reproductive LOAEL, it would require between 26% contaminated diet on-field and 44% contaminated food off-field.

For medium-sized mammals to reach the acute effect metric from maximum residues, they would need to consume > 83% contaminated diet. No risk was identified from the consumption of contaminated food, considering mean residues on- or off-field (in other words, > 100% consumption of contaminated diet required). For medium-sized mammals to reach the reproductive LOAEL from mean residues, they would need to consume between 26 and 47% contaminated diet on-field, and 45 and 79% contaminated diet off-field, depending on the food item.

For large mammals to reach the reproductive LOAEL based on mean residues, they would need to consume 56% contaminated diet on-field, and < 100% contaminated diet off-field (in other words, likely no risk identified) (Appendix I, Table 33).

Another consideration for consumption of contaminated diet is the potential for overestimation related to method of application. The nomogram/residue unit dose used to estimate residues on feed items is based on field sprayer data, for which applications would be directed towards the ground. Airblast applications are directed towards the canopy, and therefore, concentrations on feed items below the trees (such as broadleaf plants and grasses), would likely be less than what the nomogram/residue unit dose values predict. Other considerations regarding chronic risk to mammalian populations include that residue estimates on arthropods are based on measures taken after direct spray. Airblast to canopy would be subject to foliar interception and, if arthropods were not immobilized by application, they would likely continue to move in and out of the treated area, with subsequent generations emerging. The same argument would apply to the interception of ground cover, such as grasses, that would occur during a canopy application. Therefore, actual chronic exposure for mammals is likely to be far lower than predicted. It is recognized that long-term effects could occur due to an acute exposure. However, that is an extreme worst-case scenario that is unlikely to impact a sizeable fraction of an entire mammalian population.

Summary of risk conclusions – Mammals:

- Screening level risks were identified for acute oral exposure (RQs up to 1.2) and reproduction (RQs up to > 10.7, based on a NOAEL endpoint of < 7.3 mg/kg bw/day) for mammals when considering maximum residues in the field. Further characterization of risk was completed considering on- and off-field exposure to both mean and maximum residues, percent contaminated diet to reach the LOC, and considering the LOAEL (7.3 mg/kg bw/day).
- When considering mean residues, the RQ for reproduction considering the NOAEL was reduced to > 3.8 for reproduction on-field and > 2.2 off-field. When considering mean residues, the RQ was < 1 for acute oral exposure for both on- and off-field exposure.
- For mammals, there were effects observed in the reproduction study (decreased body weight gain and food consumption) at the lowest dose tested; therefore, the NOAEL is lower than the lowest dose tested, and is a non-definitive value (NOAEL < 7.3 mg/kg bw/day). The lowest dose tested is also equivalent to the LOAEL (7.3 mg/kg bw/day).
- Risk of reproductive effects in mammals from exposure to metamitron is considered low when label directions are followed given that (i) based on typical exposure using mean residues and definitive LOAEL endpoints, the RQs are 3.80 on-field and 2.24 off-field, (ii) RQs exceeding the LOCs for reproductive effects to small and medium mammals are expected to be overestimates based on the interception anticipated from canopy applications to contaminated food sources in the understory, such as grasses, and (iii) there is limited acute risk identified for small, medium and large mammals, with more than 83% of daily diet required to reach effects metrics for medium-sized mammals based on maximum on-field exposure, and > 100% for small and large mammals.
- Risks are acceptable with a label statement informing the user of the toxicity of metamitron to small wild mammals.

4.2.2 Risks to aquatic organisms

Aquatic organisms, such as invertebrates, fish, plants, and algae can be exposed to metamitron through spray drift or runoff. A risk assessment of metamitron and the associated end-use products was undertaken based on available toxicity data for freshwater and marine invertebrates, fish, plants, and algae. Acute toxicity data for the major transformation product, desamino-metamitron, was available for daphnia, diatom, and duckweed, and were included in the risk assessment.

For aquatic organisms, the risks of metamitron were assessed following two applications at 504 g a.i./ha with a five-day interval, and the conservative assumption of the pesticide going directly into water at the screening level. Risk of desamino-metamitron, was assessed by assuming 100% conversion (considering molecular w/w) from metamitron.

The conservative screening level and refined risk assessments (including endpoints and EECs/EDEs) for aquatic organisms is summarized below and in Appendix I, Table 34. Overall, the screening level LOC was not exceeded for any freshwater or marine organism.

Invertebrates: The screening level risk for aquatic invertebrates is calculated by using the most sensitive effect metrics, and conservative water exposure concentrations. The acute and chronic screening level RQs for daphnia, exposed to metamitron and desamino-metamitron, did not exceed the LOC. No further risk characterization was performed.

Fish (including amphibians): The screening level risk for freshwater and marine fish is calculated by using the most sensitive effect metrics, and conservative water exposure concentrations. The acute screening level RQs for fish (including bluegill sunfish, golden orfe, rainbow trout, and common carp) and chronic screening level RQ for the freshwater fish (fathead minnow) and the saltwater fish (sheepshead minnow), exposed to metamitron, did not exceed the LOC. No further risk characterization was performed.

The screening level risk for amphibians is based on using the most sensitive acute and chronic endpoints for fish, and a conservative water exposure concentration for amphibian habitat. The acute and chronic screening level RQ for amphibians, exposed to metamitron, did not exceed the LOC. No further risk characterization was performed.

Algae and aquatic vascular plants: The screening level risk for algae and vascular plants (duckweed) are based on using the most sensitive endpoints, and a conservative water exposure concentration. Since algae were the most sensitive aquatic organisms (in comparison to fish and invertebrates), additional studies were conducted with desamino-metamitron, for consideration in the freshwater risk assessment. The screening level RQs did not exceed the LOC for freshwater or marine algae. Based on some of the values of effective concentration on 50% of the population (EC₅₀) of < 1 mg/L for freshwater algae and aquatic plants in laboratory studies, a toxicity statement (toxic to aquatic plants) is required on the labels.

Other than desamino-metamitron, only two other major transformation products (M1 and M2) were formed in the aquatic environment (only formed in a surface water study). Based on the lack of toxicity from the parent compound and desamino-metamitron, a lack of toxicity is expected for M1 and M2. A lack of exposure is possible in the environment, as they are not formed in water/sediment systems, not formed from hydrolysis at relevant pH and temperatures, and not formed in photolysis studies. As well, based on ECOSAR estimations, the acute lethal concentration 50% (LC₅₀) for M1 for fish, daphnid, and algae are 5866, 2829, and 1056 mg/L; and the corresponding acute LC₅₀ for M2 are 2015, 1024, and 488 mg/L, which all indicate they are not toxic.

Based on fate information and the screening level ecological risk assessment, the ecological residue definition included the parent compound, metamitron, only. However, no refinements were required for the aquatic risk assessment, such as drift or ecological modelling, because the screening level RQs for aquatic organisms did not exceed the LOC for the parent compound or transformation products.

4.3 Environmental Incident Reports

As of 3 March 2025, no environmental incident reports involving metamitron have been submitted to the PMRA

5.0 Value

Value information was submitted as efficacy, crop tolerance, and fruit quality data generated in small-scale research trials conducted in apple and pear. Additionally, information from a published manuscript and registrations for Brevis end-use products in foreign jurisdictions were also taken into consideration. The conclusions listed below are the result of a thorough review of the entirety of this information:

- One or two post-bloom applications of Brevis 150 SC or Brevis 15 SG at a rate of 168-504 g a.i./ha (rate is dependent on many factors as described in Appendix I, Table 35) when fruitlets are between 6 and 20 mm in diameter would be expected to provide effective fruit thinning in both apple and pear.
- The use of a non-ionic surfactant at 0.125% v/v may improve the efficacy of either Brevis end-use product for fruit thinning in apple grown west of the Canadian Rockies.
- Apple and pear would both be expected to exhibit adequate tolerance to one or two post-bloom applications of Brevis 150 SC or Brevis 15 SG when applied in accordance with label instructions.
- As a consequence of fruit thinning, larger and heavier fruit that have greater market value may be produced.
- The use of either Brevis end-use product would not be expected to negatively impact fruit quality parameters in the year of application or return bloom in the year following application.

Both Brevis 150 SC and Brevis 15 SG applied in accordance with their use directions are expected to provide effective post-bloom fruit thinning in apple and pear. These products complement other fruit thinning measures employed by growers and serve as an effective replacement for carbaryl that is under significant global regulatory pressures to restrict and/or eliminate its uses, including its widespread use as a chemical thinning agent in apple and pear.

Supported uses are summarized in Appendix I, Table 35.

6.0 Pest Control Product Policy considerations

6.1 Assessment of the active ingredient under the Toxic Substances Management Policy

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* (CEPA). The *Pest Control Products Act* requires that the TSMP be given effect in evaluating the risks of a product.

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

Please refer to Appendix I, Table 36 for further information on the TSMP assessment.

6.2 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 PMRA 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 CEPA, 1999, (substances designated under the *Montreal Protocol*).

The PMRA has reached the conclusion that metamitron and its end-use products, Brevis 150 SC and Brevis 15 SG, 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 PMRA formulant initiatives and Regulatory Directive DIR2006-02.

7.0 Proposed regulatory decision

Health Canada's PMRA, pursuant to subsection 28(1) of the *Pest Control Products Act*, is proposing registration for the sale and use of ADAMA Metamitron Technical, Brevis 150 SC and Brevis 15 SG, containing the technical grade active ingredient metamitron, for thinning of apples and pears.

An evaluation of available scientific information found that, under the approved conditions of use, the health and environmental risks and the value of the pest control products are acceptable.

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

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 New Pest Control Products Act.

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

Additional information being requested

Since this technical product is manufactured only at pilot scale before registration, five-batch data representing commercial-scale production will be required as post-market information after registration.

List of abbreviations

♀	female
♂	male
λ	wavelength
\pm	plus-or-minus
\uparrow	increased
\downarrow	decreased
=	equal to
>	greater than
<	lesser than
\geq	greater than, or equal to
\leq	lesser than, or equal to
μg	microgram
μm	micrometre
μM	micromolar
μPa	micropascal
%	percent
#	number
$^{\circ}\text{C}$	degree Celsius
$^{\circ}\text{N}$	degree North
1/n	exponent for the Freundlich isotherm
a.i.	active ingredient
ACN	acetonitrile
AD	administered dose
ADI	acceptable daily intake
AGD	anogenital distance
AHETF	Agricultural Handlers Exposure Task Force
ALT	alanine aminotransferase
AOPWIN	Atmospheric Oxidation Estimation Program for Windows
AR	applied radioactivity
ARfD	acute reference dose
ARTF	Agricultural Re-entry Task Force
AST	aspartate aminotransferase
atm	atmosphere
ATPD	area treated per day
BAF	bioaccumulation factor
BBCH	Biologische Bundesanstalt, Bundessortenamt and Chemical industry (scale is used to identify the phenological development stages of plants)
BCF	bioconcentration factor
BDC	bile duct cannulation
BE-label	[benzene ring- ^{14}C]metamitron
MBq	megabecquerel
bw	body weight
bwg	body weight gain
CAF	composite assessment factor
CAS	Chemical Abstracts Service
CEC	cationic exchange capacity

CEPA	<i>Canadian Environmental Protection Act</i>
CFIA	Canadian Food Inspection Agency
ChE	cholinesterase
cm	centimetre
cm ²	square centimetre
cm ³	cubic centimetre
C _{max}	maximum concentration
CO ₂	carbon dioxide
CRA	cumulative risk assessment
CWMPP	Canadian Water Monitoring Program for Pesticides
d	day
DACO	data code
DAT	days after treatment
DEEM	Dietary Exposure Evaluation Model
DFOP	double first order in parallel
DFR	dislodgeable foliar residue
DIR	Directive
DOC	dissolved organic carbon
DT ₅₀	dissipation time 50% (the dose required to observe a 50% decline in concentration)
dw	dry weight
EC ₅₀	effective concentration on 50% of the population
ECOSAR	Ecological Structure Activity Relationships Predictive Model (USEPA)
EDE	estimated daily exposure
EEC	estimated environmental concentration
ER ₂₅	effective rate for 25% of the population
F0	parental generation
F1	first filial generation
F2	second filial generation
FC	food consumption
FDA	<i>Food and Drugs Act</i>
g	gram
GAP	Good Agricultural Practice
GD	gestation day
GIT	gastrointestinal tract
GLP	Good Laboratory Practices
GUS	groundwater ubiquity score
ha	hectare
HAFT	highest average field trial
HC ₅	hazard concentration for 5% of the species
HCT	hematocrit
Hb	hemoglobin
HHRV	human health reference value
HLC	Henry's law constant
HPLC	high performance liquid chromatography
HPLC-MS/MS	high performance liquid chromatography method with tandem mass spectrometry
hr	hour

ID	identification
IORE	indeterminate order rate equation
IUPAC	International Union of Pure and Applied Chemistry
kg	kilogram
K_d	soil adsorption coefficient
K_F	Freundlich adsorption coefficient
K_{FOC}	organic carbon normalized Freundlich adsorption coefficient
K_{F-DES}	Freundlich desorption coefficient
$K_{FOC-DES}$	organic carbon normalized Freundlich desorption coefficient
K_{OC}	organic carbon normalized adsorption coefficient
K_{ow}	<i>n</i> -octanol-water partition coefficient
KOWWIN	log K_{ow} estimation program for Windows
kPa	kilopascal
L	litre
LAFT	lowest average field trial
LC ₅₀	lethal concentration 50%
LD ₅₀	lethal dose 50%
LD _{50/10}	lethal dose 50% with an uncertainty factor of 10
LLNA	local lymph node assay
LOAEC	lowest observed adverse effect concentration
LOAEL	lowest observed adverse effect level
LOC	level of concern
LOD	limit of detection
LOEC	low observed effect concentration
LOED	lowest-observed effect dose
LOEDD	lowest-observed effect daily dose
LOQ	limit of quantitation
LR ₅₀	lethal rate 50%
m	metre
m ³	cubic metre
MAS	maximum average score
meq	milliequivalent
MIS	maximum irritation score
mg	milligram
mL	millilitre
mm	millimetre
MOE	margin of exposure
mol	mole
MRID	US Master Record Identification Number
MRL	maximum residue limit
MS	mass spectrometry
MS/MS	tandem mass spectrometry
MW	molecular weight
NA	not applicable
NAFTA	North American Free Trade Agreement
NC	not calculated
ND	not detected
NER	non-extractable residue

NHANES/	
WWEIA	National Health and Nutrition Examination Survey/What We Eat in America
nm	nanometres
NOAEC	no observed adverse effect concentration
NOAEL	no observed adverse effect level
NOEC	no observed effect concentration
NOED	no observed effect dose
NOEDD	no observed effect dietary dose
NOEL	no observed effect level
NOER	no observed effect rate
NR	not required
OECD	Organisation for Economic Co-operation and Development
OECD TG	OECD Test Guideline
Pa	pascal
PACR	Proposed Acceptability for Continuing Registration
PCE/NCE	ratio of polychromatic erythrocytes to normochromatic erythrocytes
PCPA	<i>Pest Control Product Act</i>
PD	post dosing
PDP	Pesticide Data Program
PHI	preharvest interval
pK_a	dissociation constant
PMRA	Pest Management Regulatory Agency
PND	postnatal day
PPE	personal protective equipment
ppm	parts per million
PWC	Pesticide in Water Calculator
PYO	pick-your-own
QA	Quality Assurance
R-squared	coefficient of determination
RAC	raw agricultural commodity
RBC	red blood cells
REI	restricted entry interval
RQ	risk quotient
RRD	Re-evaluation Decision Document
S9	mammalian metabolic activation system
SC	soluble concentrate
SDEV	standard deviation
SFO	single first order
SG	soluble granule
SPN	Science Policy Note
SSD	species sensitivity distribution
TC	transfer coefficient
T_{max}	time to maximum concentration
TNF	tumor necrosis factor
TOC	total organic carbon
TP	transformation product
TRR	total radioactive residue
TSMP	<i>Toxic Substances Management Policy</i>

TZ-label	[triazine-5,6- ¹⁴ C]metamitron
UR	unextracted residue
USDA	United States Department of Agriculture
USEPA	United States Environmental Protection Agency
UV	ultraviolet
v/v	volume per volume dilution
w/w	weight for weight
wk	week
WSSA	Weed Science Society of America
wt	weight

Appendix I Tables and figures

Table 1a Residue analysis in environmental media

Matrix	Method ID	Analyte	Method type	LOQ	Reference
Soil / Sediment	P/B 1355 G	Metamitron	HPLC-MS/MS	0.05 mg/kg	PMRA# 3304599
		Desamino-metamitron	HPLC-MS/MS	0.05 mg/kg	PMRA# 3304600
Water	20071119/ 01-RVW	Metamitron	HPLC-MS/MS	0.05 µg/L	PMRA# 3304605
		Desamino-metamitron	HPLC-MS/MS	0.05 µg/L	PMRA# 3304606

Table 1b Residue analysis in plant matrices

Analytical methods	Matrix	Analytes	Method ID/Type	LOQ	Reference
Plant commodities					
Enforcement/ data-gathering method	Apple fruit, juice, wet pomace, dry pomace, and sauce	Metamitron, desamino-metamitron, metamitron-N- glycoside, and desamino-metamitron- N-glycoside	QuEChERS HPLC- MS/MS [SGS-17-01- 03]	0.01	Study No. SGS-17-01-03 PMRA# 3305205
Independent laboratory validation of enforcement method	Apple fruit and dry pomace	Metamitron, desamino-metamitron, metamitron-N- glycoside, and desamino-metamitron- N-glycoside	QuEChERS HPLC- MS/MS [SGS-17-01- 03]	0.01	Study No. 19C0304 PMRA# 3305208
Radiovalidation	A radiovalidation study per se was not submitted. Extractable total radioactive residues (TRRs) in the apple metabolism studies using extraction solvents similar to those used in the proposed enforcement method (in other words, acetonitrile:water, minus the QuEChERS salts) demonstrated extraction efficiencies ranging from 76 to 99% for both radiolabels. The use of QuEChERS salts is widely known to increase extractabilities, and therefore, extraction efficiencies of the proposed enforcement method are acceptable.				

Table 2 Identification of select metabolites of metamitron

Metabolite/Impurity	Chemical name	Source
MTM/004	Metamitron-triazinium acetic acid	Rat metabolite
MTM/002	Metamitron-4-hydroxy-desamino	Rat metabolite
MTM/003	Metamitron-3-hydroxy-desamino	Rat metabolite

Metabolite/Impurity	Chemical name	Source
MTM/001 (MH1)	Desamino-metamitron	Rat metabolite/environmental degradate
MTM/009	Metamitron-desamino-dienyl-glutathione	Rat metabolite
MTM/008	Metamitron-desamino-dienyl-cysteinylglycine	Rat metabolite
MTM/029	N-[(Z)-(2-hydrazino-2-oxo-1-phenylethylidene)amino] acetamide	Environmental degradate

Table 3 Toxicology reference values for use in the health risk assessment for metamitron

Exposure scenario	Study	Point of departure and endpoint	CAF ¹ or target MOE
Acute dietary general population	Acute oral neurotoxicity studies in rats	NOAEL = 10 mg/kg bw ↓ body temperature, ↓ motor activity	100
ARfD = 0.1 mg/kg bw			
Repeated (chronic) dietary	Two-generation reproductive toxicity study in rats	Offspring NOAEL = 11 mg/kg bw/d ↓ survival, ↓ bw, and ↑ incidence of missing and cannibalised pups	300
ADI = 0.04 mg/kg bw/d			
Short- and intermediate-term dermal ²	Two-generation reproductive toxicity study in rats	Offspring NOAEL = 11 mg/kg bw/d ↓ survival, ↓ bw, and ↑ incidence of missing and cannibalised pups	300
Short- and intermediate-term inhalation ³	Two-generation reproductive toxicity study in rats	Offspring NOAEL = 11 mg/kg bw/d ↓ survival, ↓ bw, and ↑ incidence of missing and cannibalised pups	300
Cancer	No evidence of tumourigenicity; a cancer risk assessment was not required.		

¹ CAF refers to a total of uncertainty and PCPA factors for dietary assessments; MOE refers to a target MOE for occupational assessments.

² Since an oral NOAEL was selected, a dermal absorption factor 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 4 Toxicity profile of technical metamitron

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. Effects seen above the LOAEL(s) have not been reported in this table for most studies for reasons of brevity.

Study type / Animal / PMRA#	Study results																																												
Toxicokinetics																																													
Toxicokinetics – Single and repeat oral dose (gavage) Wistar rats PMRA# 3304753	<p>[Phenyl-UL-¹⁴C] labelled metamitron was administered as single gavage doses to intact and bile duct-cannulated rats at dose levels shown in table below. Unless otherwise indicated below, there were no significant differences in toxicokinetic parameters between sexes, dose level, or radiolabel position.</p> <table border="1" data-bbox="596 643 1304 1053"> <thead> <tr> <th>#</th> <th>#/sex</th> <th>Rat</th> <th>Dose (mg/kg)</th> <th>Duration</th> </tr> </thead> <tbody> <tr> <td>1</td> <td>4 ♂</td> <td rowspan="5">Intact</td> <td>2</td> <td>48 hrs</td> </tr> <tr> <td>2</td> <td>4 ♂</td> <td>2</td> <td>48 hrs</td> </tr> <tr> <td>3</td> <td>4 ♀</td> <td>2</td> <td>48 hrs</td> </tr> <tr> <td>4</td> <td>4 ♂</td> <td>200</td> <td>48 hrs</td> </tr> <tr> <td>7</td> <td>4 ♀</td> <td>200</td> <td>48 hrs</td> </tr> <tr> <td>5*</td> <td>4 ♂</td> <td></td> <td>2</td> <td>48 hrs</td> </tr> <tr> <td>6</td> <td>5 ♂</td> <td rowspan="3">BDC</td> <td>2</td> <td>24 hrs</td> </tr> <tr> <td>8</td> <td>8 ♂</td> <td>20</td> <td>8 hrs</td> </tr> <tr> <td>9</td> <td>6 ♂</td> <td>2</td> <td>24 hrs</td> </tr> </tbody> </table> <p>BDC = bile duct cannulation *Pre-treated with 2 mg/kg non-labelled metamitron for 14 d.</p> <p>Metamitron was absorbed rapidly. It reached peak concentration in plasma at 20–40 minutes after a single low dose administration and 1–8 hrs after a single high dose administration. It was almost completely absorbed based on excretion in urine (34–56%) and bile (56–64%). The estimated oral absorption, considering the renal and bile excretion and residues found in the carcass without gastrointestinal tract (GIT), amounted to 91–105%. A second plasma concentration peak occurred 6 hrs after a single low dose and is suggestive of a possible enterohepatic circulation pathway.</p> <p>Metamitron was rapidly and evenly distributed between blood and various organs. Forty-eight hrs after administration, less than 1% of the AD was found in organs and tissues. The highest tissue</p>	#	#/sex	Rat	Dose (mg/kg)	Duration	1	4 ♂	Intact	2	48 hrs	2	4 ♂	2	48 hrs	3	4 ♀	2	48 hrs	4	4 ♂	200	48 hrs	7	4 ♀	200	48 hrs	5*	4 ♂		2	48 hrs	6	5 ♂	BDC	2	24 hrs	8	8 ♂	20	8 hrs	9	6 ♂	2	24 hrs
#	#/sex	Rat	Dose (mg/kg)	Duration																																									
1	4 ♂	Intact	2	48 hrs																																									
2	4 ♂		2	48 hrs																																									
3	4 ♀		2	48 hrs																																									
4	4 ♂		200	48 hrs																																									
7	4 ♀		200	48 hrs																																									
5*	4 ♂		2	48 hrs																																									
6	5 ♂	BDC	2	24 hrs																																									
8	8 ♂		20	8 hrs																																									
9	6 ♂		2	24 hrs																																									

Study type / Animal / PMRA#	Study results
	<p>residues were found in the liver and the kidneys. There was no evidence of a potential for tissue retention.</p> <p>Excretion was almost complete within 48 hrs after single low or high doses and after repeated low dose administration. Elimination was mainly via the renal (45–61%) and fecal (46–53%) routes. Experiments with bile duct-cannulated rats showed that the biliary excretion amounted to 56–64% of the AD after 24 hrs. Between 93% and 107% of the AD were excreted via urine, bile, and feces. Excretion via expired air was negligible.</p> <p>Metamitron was rapidly and extensively metabolised with less than 4.3% of the AD recovered unchanged in the excreta. Very similar metabolic profiles were determined in urine and feces, which include metamitron-triazinium acetic acid (MTM/004), metamitron-4-hydroxy-desamino (MTM/002), metamitron-3-hydroxy-desamino (MTM/003), and desamino-metamitron (MTM/001). Metamitron-desamino-dienyl-glutathione (MTM/009) and metamitron-desamino-dienyl-cysteinylglycine (MTM/008) are major metabolites identified in bile.</p> <p>Females had a higher plasma concentration and a slower decline than males at both low and high dose levels.</p> <p>Repeated dosing did not have a significant influence on absorption, elimination, or distribution of the parent compound and metabolites in tissues.</p>
<p>Toxicokinetics – Single oral dose (gavage) Wister rats (♂) PMRA# 3304755</p>	<p>[Phenyl-UL-¹⁴C] labelled metamitron was administered as a single gavage dose of 2 mg/kg bw to Wistar rats. Animals were sacrificed at 0.5, 2, or 6 hrs post dosing (PD).</p> <p>The highest concentrations of radioactivity were detected in kidney and liver at 0.5 hrs PD. Similar concentrations were measured in plasma, carcass, and skin, suggesting a rapid equilibration of radioactivity between plasma and the tissue. Desamino-metamitron (MTM/001) was identified as the most prominent metabolite in plasma, liver, and kidneys at 0.5 hrs PD. Other major metabolites detected in plasma were metamitron-triazinium acetic acid (MTM/004), metamitron-desamino-dienyl-cysteine (MTM/006), and metamitron-4-hydroxy-desamino (MTM/002); in the liver were metamitron-triazinium acetic acid (MTM/004), metamitron-desamino-dienyl-cysteine (MTM/006), and metamitron-dienyl-glutathione (MTM/010); and in the kidneys were metamitron-triazinium acetic acid (MTM/004) and metamitron-desamino-dienyl-cysteine (MTM/006). The percentage of the parent compound and the metabolites desamino-metamitron (MTM/001), metamitron-desamino-dienyl-glutathione (MTM/009), and metamitron-desamino-N-oxide (MTM/011a,b) decreased with time, while the percentage of most other metabolites increased or remained at a constant level. The</p>

Study type / Animal / PMRA#	Study results																				
	metabolites identified accounted for 72–96%, 63–87%, and 74–94% of the TRRs in plasma, liver, and kidney, respectively. About 4–28%, 11–21%, and 5–22% of the TRR was characterised in plasma, liver, and kidney, respectively. All unidentified metabolites were at levels < 9% of the TRR in plasma, liver, or kidney.																				
Toxicokinetics – Single dose (gavage or intravenous) Sprague Dawley rats PMRA# 3304756	<p>[Phenyl-UL-¹⁴C] labelled metamitron was administered as a single dose via the routes and levels shown in the table below.</p> <table border="1" data-bbox="600 477 1318 732"> <thead> <tr> <th data-bbox="600 477 772 565">Dose mg/kg bw</th> <th data-bbox="772 477 940 565">Route</th> <th data-bbox="940 477 1094 565">#</th> <th data-bbox="1094 477 1318 565">Duration</th> </tr> </thead> <tbody> <tr> <td data-bbox="600 565 772 607">1</td> <td data-bbox="772 565 940 607">Intravenous</td> <td data-bbox="940 565 1094 607">4/sex</td> <td data-bbox="1094 565 1318 607">7 d</td> </tr> <tr> <td data-bbox="600 607 772 649">1</td> <td data-bbox="772 607 940 649">Gavage</td> <td data-bbox="940 607 1094 649">4/sex</td> <td data-bbox="1094 607 1318 649">7 d</td> </tr> <tr> <td data-bbox="600 649 772 691">200</td> <td data-bbox="772 649 940 691">Gavage</td> <td data-bbox="940 649 1094 691">4/sex</td> <td data-bbox="1094 649 1318 691">7 d</td> </tr> <tr> <td data-bbox="600 691 772 732">1</td> <td data-bbox="772 691 940 732">Intravenous</td> <td data-bbox="940 691 1094 732">8 ♀</td> <td data-bbox="1094 691 1318 732">1, 4, 24 hrs, 7 d</td> </tr> </tbody> </table> <p>After a single application, metamitron was rapidly absorbed and then eliminated. The absolute bioavailability was found to be 98% comparing intravenous and oral administration. At the high dose, absorption was not saturated and remained linear. Elimination was mainly via renal and fecal routes within 48 hrs PD. The highest concentration was detected in the kidney and liver. Only 2% of the parent compound could be detected in urine, and the major metabolites in urine were desamino-metamitron (MTM/001) at 29% and phenylhydroxylated desamino-metamitron (MTM/002 or MTM/003) at 17% of the AD.</p>	Dose mg/kg bw	Route	#	Duration	1	Intravenous	4/sex	7 d	1	Gavage	4/sex	7 d	200	Gavage	4/sex	7 d	1	Intravenous	8 ♀	1, 4, 24 hrs, 7 d
Dose mg/kg bw	Route	#	Duration																		
1	Intravenous	4/sex	7 d																		
1	Gavage	4/sex	7 d																		
200	Gavage	4/sex	7 d																		
1	Intravenous	8 ♀	1, 4, 24 hrs, 7 d																		
Toxicokinetics – Repeat oral dose (gavage) Sprague Dawley rats (♀) PMRA# 3304757	<p>0.94 mg/kg bw unlabelled metamitron was administered daily via gavage for 14 d, followed by 0.94 mg/kg bw [phenyl-UL-¹⁴C]-labelled metamitron on d 15.</p> <p>The cumulative total excretion in urine and feces over 7 d was 100.8% of the AD. Approximately 60.6% and 40.3% of the AD was from urine and feces, respectively. Most of the excreted radioactivity was found in the first 24 hrs. Seven d after the last oral administration, radioactivity was only detectable in the kidney, liver, and fat samples of one animal. There was no evidence of tissue retention. In urine, only 0.4% of the AD was identified as the parent compound. In total, 18 metabolites were detected in urine. The major metabolites found were desamino-metamitron (MTM/001) (up to 11% of the AD), hydroxyphenyl (up to 11% of the AD), and hydroxymethyl-derivates (up to 11% of the AD). No conjugates were detected.</p>																				

Study type / Animal / PMRA#	Study results
<p>Toxicokinetics – Single oral dose (gavage) Wistar rats Non-guideline PMRA# 3304758</p>	<p>Acceptable with limitations</p> <p>Wistar rats were administered orally by gavage at a single dose of 2000/1360 mg/kg bw (♂/♀), and the concentration of metamitron in blood, tissues, and excrement samples, and toxicokinetic parameters were analyzed by high performance liquid chromatography (HPLC).</p> <p>Absorption: Metamitron was detectable in the blood at 5 minutes PD. The time to maximum concentration (T_{max}) was 2/3.5 hrs (male ♂/♀). The maximum concentration (C_{max}) was 66/40 mg/L (♂/♀). The absorption half-lives were shorter than the elimination half-lives in both sexes, which indicated rapid elimination, unlikely resulting in tissue retention. The clearance rate of 2.59/0.78 L/(hr•kg) (♂/♀) suggested slower elimination in females.</p> <p>Tissue distribution: The apparent volume of distribution was large, with 8.33/10.76 L/kg (♂/♀), suggesting a wide distribution. The highest concentrations were detected in the liver and kidney. The tissue concentrations declined rapidly within 24 hrs, with no evidence of tissue retention.</p> <p>Excretion: Elimination was mainly via the renal and fecal routes. The highest concentrations detected in urine and feces was on the first d PD, following a decreasing trend and becoming undetectable on the 5th d in the urine and 6th d in feces. The average cumulative content in feces and urine in 7 d accounted for 71.4% and 8.9% of the AD, respectively.</p> <p>Study Limitations: Non-GLP study. No raw data were provided.</p>
<p>Comparative in vitro metabolism Human, rat, or dog liver microsomes Non-guideline PMRA# 3304760 and 3304761</p>	<p>Acceptable</p> <p>75 μM [¹⁴C]-metamitron incubated with various concentrations of human, rat, or dog liver microsomes at 37 °C between 10–45 minutes.</p> <p>Metabolite formation was nicotinamide adenine dinucleotide phosphate-dependent.</p> <p>Low amount of administered radioactivity attached to microsomal protein (2.4%/3.9% of AD for 0.2/1.0 mg/mL).</p> <p>Enzymatic reaction was linear with time up to 30 minutes for rat and up to 45 minutes for dog and human.</p> <p>Desamino-metamitron (MTM/001) was identified at 6%/5%/5% 10 minutes after incubation and 14%/11%/8% 30 minutes after incubation with rat/dog/human liver microsomes. No unique human, dog, or rat metabolite was observed.</p>

Study type / Animal / PMRA#	Study results
Toxicokinetics – Single oral dose (gavage) Wistar rats PMRA# 3304754	<p>Acceptable with limitations</p> <p>Wistar rats were administered [phenyl-UL-¹⁴C]-metamitron orally by gavage at a single dose of 5 mg/kg bw, and then 1/sex were sacrificed at 1, 4, 8, 24, or 48 hrs after dosing. The distribution of metamitron and its metabolites over time within the animals was investigated by whole body autoradiography.</p> <p>Metamitron was absorbed rapidly from the GIT and fairly equally distributed within the blood and most organs and tissues with preference to the liver and the kidney. Low concentrations of radioactivity were detected in adrenal, thyroid, ovary, uterus, and testes. Very low concentrations of radioactivity were observed in the brain and spinal cord. One hr PD, maximum concentrations were detected in all tissues with a rapid decline thereafter. The concentrations dropped below the limit of detection (LOD) or LOQ for most organs and tissues within 48 hrs. There was no evidence of retention of radioactivity in any of the organs or tissues. Elimination was mainly via the renal (55–63% of AD) and fecal (42–49% of AD) routes.</p> <p>Female rats showed slightly higher levels of radioactivity in most organs and tissues compared to male rats. High concentrations of radioactivity were detected in the extra-orbital gland and the infra-orbital gland of females but not males at 1 to 24 hrs PD.</p> <p>Study Limitations: Only data for tissue distribution and excretion were measured in this study.</p>
Acute toxicity studies	
Acute oral toxicity NMRI mouse PMRA# 3303530	LD ₅₀ ♂/♀ = 691/644 mg/kg bw Moderate acute toxicity
Acute oral toxicity Swiss albino mouse PMRA# 3303531	LD ₅₀ ♂/♀ = 863 mg/kg bw Moderate acute toxicity
Acute oral toxicity Wistar rats PMRA# 3303527	LD ₅₀ ♂/♀ = 1183/1482 mg/kg bw Slight acute toxicity Clinical signs included piloerection, decreased reactivity and motility, poor reflexes, uncoordinated gait, spastic gait, lateral position, spasmodic state, tonical cramps, laboured breathing, breathing

Study type / Animal / PMRA#	Study results
	sounds, diarrhea, narrowed palpebral fissure, and closed eyelids. All signs occurred from 20 minutes to 7 hrs PD and resolved within 3 d.
Acute oral toxicity Wistar rats PMRA# 3303528	LD ₅₀ ♂♀ = 3340 mg/kg bw Low acute toxicity
Acute oral toxicity Sprague Dawley rats PMRA# 3303529	LD ₅₀ ♂♀ > 2000 mg/kg bw Low acute toxicity
Acute dermal toxicity Wistar rats PMRA# 3303534	LD ₅₀ ♂♀ > 4000 mg/kg bw Low acute toxicity
Acute dermal toxicity Wistar rats PMRA# 3303535	LD ₅₀ ♂♀ > 5000 mg/kg bw Low acute toxicity
Acute dermal toxicity Sprague Dawley rats PMRA# 3303536	Acceptable with limitations LD ₅₀ ♂♀ > 2000 mg/kg bw Study limitations: Purity of test substance was not reported.
Acute inhalation toxicity (nose-only) Wistar rats PMRA# 3303537	LC ₅₀ ♂/♀ > 5/3.17 mg/L Low acute toxicity
Acute inhalation toxicity (nose-only) Wistar rats PMRA# 3303538	Acceptable with limitations LC ₅₀ ♂♀ > 3.91 mg/L Study limitations: Mass median aerodynamic diameter 6.9 µm (acceptable range 1–4 µm).
Primary eye irritation Himalayan rabbits	Maximum average score (MAS) = 0/110 Maximum irritation score (MIS) = 0/110

Study type / Animal / PMRA#	Study results
PMRA# 3303541	Non-irritating
Primary eye irritation New Zealand white rabbits PMRA# 3303542	MAS = 2.9/110 MIS = 6/110 at 24 hrs Minimally irritating
Primary eye irritation New Zealand white rabbits PMRA# 3303543	MAS = 0/110 MIS = 5.67/110 at 1 hr Non-irritating
Primary skin irritation Himalayan rabbits PMRA# 3303544	MAS = 0/8 MIS = 0/8 Non-irritating
Primary skin irritation New Zealand white rabbits PMRA# 3303545	MAS = 0/8 MIS = 0/8 Non-irritating
Primary skin irritation New Zealand white rabbits PMRA# 3303546	MAS = 0/8 MIS = 0/8 Non-irritating
Dermal sensitization (maximisation test) Dunkin-Hartley guinea pigs PMRA# 3303547	Negative
Dermal sensitization (maximisation test) Dunkin-Hartley guinea pigs PMRA# 3303548	Negative
Dermal sensitization (maximisation test) Dunkin-Hartley guinea pigs	Acceptable with limitations In the test substance group, 18 out of 20 animals showed slight to well-defined erythema 49 hrs after topical induction, which was resolved at 72 hrs. No animal in this group showed skin reaction 48 and

Study type / Animal / PMRA#	Study results
PMRA# 3303550	72 hrs after challenge exposure. Study limitations: Missing information on the purity of the test substance.
Short-term toxicity studies	
90-d oral toxicity study (dietary) CrI:CD-1(ICR)BR mice PMRA# 3303558 and 3303559	NOAEL = 55/93 mg/kg bw/d (♂/♀) LOAEL = 367/568 mg/kg bw/d (♂/♀) Effects at the LOAEL: ↓ bwg, ↑ liver wt, ↑ incidence of hepatic hypertrophy, karyomegaly, and cytoplasmic change (♂/♀); ↓ bw (♂); ↑ spleen wt (♀)
28-d oral toxicity study (gavage) Wistar rats PMRA# 3303568	Acceptable with limitations Effects at ≥ 100 mg/kg bw/d: ↑ urea and creatinine, ↑ liver wt (♂/♀) Study Limitations: Missing information for test substance and experimental conditions. Limited data reported.
28-d oral toxicity study (dietary) Wistar rats PMRA# 3303565, 3303566 and 3303567	Acceptable with limitations Effects at ≥ 51.4 mg/kg bw/d: ↓ bw and bwg (♀); Effects at 208.6/206.9 mg/kg bw/d: ↑ liver wt and ↑ alkaline phosphatase (♂/♀); ↓ bw and bwg (♂) Study Limitations: Missing measurements in clinical chemistry. Missing a control group for recovery test. All data were presented by mixing sexes.
90-d oral toxicity study (dietary) Sprague Dawley rats PMRA# 3303560	Acceptable with limitations Test 1 Effects at ≥ 46 mg/kg bw/d: ↑ plasma cholinesterase (ChE) activity (♂/♀); ↑ cholesterol wk 13 (♀) Test 2 Effects at ≥ 14 mg/kg bw/d: ↑ red blood cell (RBC) ChE activity (♂) and plasma ChE activity (♀); Effects at 140 mg/kg bw/d: ↓ bw, bwg and ↑ liver wt (♂/♀); ↑ plasma ChE activity, ↑ cholesterol wk 6 (♂); ↑ cholesterol wk 13 (♀) Study Limitations: Test substance batch and purity, diet preparation, environmental conditions were not reported. Missing some clinical chemistry and histopathology parameters, only 5/sex/dose were assessed for histopathology.

Study type / Animal / PMRA#	Study results
90-d oral toxicity study (dietary) Wistar rats PMRA# 3303555 and 3303556	NOAEL = 34.4/42.9 mg/kg bw/d (♂/♀) LOAEL = 182.7/201.8 mg/kg bw/d (♂/♀) Effects at the LOAEL: ↑ urinary incontinence, ↓ bw and bwg (♂/♀); ↓ glucose (♀)
90-d oral toxicity study (dietary) Wistar rats PMRA# 3303554	NOAEL = 46.6/42.8 mg/kg bw/d (♂/♀) LOAEL = 78.0/88.3 mg/kg bw/d (♂/♀) Effects at the LOAEL: ↓ bw and bwg, ↑ cholesterol wk 5 and wk 14 (♂/♀); ↓ adrenal wt (♀)
84-d oral toxicity study (dietary) Beagle dogs Non-guideline PMRA# 3303563	Acceptable with limitations Effects at 187.5 mg/kg bw/d: Exsiccotic (dehydrated), pale anemic mucosa, occasionally apathic behaviour in all animals, ↑mortality, ↓ bw, bwg and food consumption (FC), impaired reflexes, ↓ RBC and hemoglobin (Hb) (♂/♀); ↑ alanine aminotransferase (ALT) at wk 6 and wk 13 (♂) Study Limitations: Non-GLP study and no Quality Assurance (QA) study. The information of test substance and experimental conditions were not provided. The initial body weights were not comparable between groups. All animals had severe parasite infection, which masked the effects of the test substance.
90-d oral toxicity study (dietary) Beagle dogs PMRA# 3303562	LOAEL = 25.1/22.8 mg/kg bw/d (♂/♀) NOAEL = 7.0/7.8 mg/kg bw/d (♂/♀) Effects at the LOAEL: ↑ triglyceride and cholesterol (♂/♀); ↑ incidence of lymphoid hyperplasia in small and large intestine (♂); ↓ FC (♀)
90-d oral toxicity study (dietary) Beagle dogs PMRA# 3303561	LOAEL = 65.4/55.7 mg/kg bw/d (♂/♀) NOAEL = 16.8/16.3 mg/kg bw/d (♂/♀) Effects at the LOAEL: ↓ bwg, ↑ cholesterol, and triglyceride, ↑ liver wt, ↑ incidence of hepatocytomegaly (♂/♀); ↑ bile acid (♂); ↓ FC (♀)
One-year oral toxicity study (dietary) Beagle dog	LOAEL = 31.6/32 mg/kg bw/d (♂/♀) NOAEL = 13.6/12.7 mg/kg bw/d (♂/♀) Effects at the LOAEL: ↑ cholesterol and ALT (♂/♀); ↓ glucose (♂); ↓ RBC, Hb, and hematocrit

Study type / Animal / PMRA#	Study results
PMRA# 3303564	(HCT) and ↑ reticulocytes (♀)
Two-year oral toxicity study (dietary) Beagle dogs Non-guideline PMRA# 3304697	<p>Acceptable with limitations</p> <p>Effects at ≥ 3.2/3.2 mg/kg bw/d: ↑ cholesterol (♀); Effects at ≥ 12.5/13.3 mg/kg bw/d: ↑ cholesterol (♂);</p> <p>Effects at 56/51 mg/kg bw/d: ↓ bw, bwg, and FC, ↓ RBC and Hb, ↑ reticulocytes, ↑ ALT, bilirubin, and glutamate dehydrogenase, ↑ liver, spleen, and kidney wt, viscous bile containing black concretions, liver yellowish-brown color and brittle to coarse texture, hepatocyte morphological changes, deposition of bilirubin and ↑ interstitial connective tissue, ↑ iron deposition and ↓ glycogen in the liver, ↑ extramedullary erythropoiesis (♂/♀)</p> <p>Study Limitations: Missing signed and dated GLP, QA, and data confidentiality statements. Missing dose selection rationale. Study author raised the dose from 1600 ppm to 3200 ppm in the high-dose group from wk 57. Missing measurements for some urinalysis parameters. Histopathology was not performed for some organs. Analytical data on stability and homogeneity of the preparation were not provided and the actual doses were not stated.</p>
20-d dermal toxicity study New Zealand white rabbits PMRA# 3303569	<p>Acceptable with limitations</p> <p>Effects at ≥ 50 mg/kg bw/d: ↓ liver wt (♂/♀);</p> <p>Effects at 250 mg/kg bw/d: ↓ bwg (♂/♀); bw loss (abraded) (♂); ↑ aspartate aminotransferase (AST) and ALT (♀)</p> <p>Study Limitations: Vehicle (Cremophor EL) has skin irritation potential. Insufficient number of animals were tested. Histology analysis results were not reported properly. Skin was abraded. Purity of the test substance was not stated.</p>
28-d dermal toxicity study + 14-d recovery period Sprague Dawley rats PMRA# 3303570	<p>LOAEL = 1000 mg/kg bw/d (♂/♀) NOAEL = 300 mg/kg bw d (♂/♀)</p> <p>Main Test Effects at the LOAEL: ↑ cholesterol, ↑ liver wt (♂/♀); ↑ thyroid + parathyroid wt (♀)</p> <p>Recovery Group Effects at 1000 mg/kg bw/d: ↓ bw (-9%), ↓ bwg (-40%) at d 28 (♂), after 14-d recovery: bw (-3.7%), bwg 14-d recovery (+96%) (♂/♀)</p> <p>Toxicokinetic Test</p>

Study type / Animal / PMRA#	Study results
	Metamitron was rapidly absorbed via the dermal route and metabolized to desamino-metamitron. Both metamitron and desamino-metamitron reached T _{max} between 8-12 hrs PD. The increases of metamitron and desamino-metamitron concentrations in the blood (C _{max} and area under the curve) were not proportional to the dosing concentrations. Repeated dosing for 28 d resulted in tissue retention at 1000 mg/kg.
Waiver for the 90-d inhalation study PMRA# 3303571	Submitted waiver request based on low acute oral and inhalation toxicity of active ingredient and low potential for exposure via the inhalation route of exposure (metamitron is non-volatile). Waiver considered acceptable and 90-d inhalation study was not required.
Chronic toxicity and oncogenicity studies	
20-month chronic toxicity study (dietary) CD-1 Swiss mice Non-guideline PMRA# 3304691	Acceptable with limitations Effects at ≥ 50 mg/kg bw/d: ↓ mean corpuscular volume and HCT at 6 months (♀); Effects at ≥ 84 mg/kg bw/d: ↑ incidence of chronic hepatitis (♂/♀); ↑ ALT and ↑ AST (♀); Effects at 168 mg/kg bw/d: ↓ bw and ↓ bwg (♀) Study limitations: The analytical concentration of the test substance was low between months 15 to 20 (down to 63.8% of nominal concentrations). Pooled samples were used for most hematology and clinical chemistry parameters. Solvent was changed from acetone to methanol after wk 56.
18-month oncogenicity study (dietary) CD-1 mice PMRA# 3304692	NOAEL = 7.1/9.3 mg/kg bw/dy (♂/♀) LOAEL = 35.9/46.3 mg/kg bw/d (♂/♀) Effects at the LOAEL: ↑ incidence of liver degeneration, centrilobular hypertrophy, condensed cytoplasm, and mitotic figures (♂/♀); ↑ liver wt (♂) No evidence of tumourigenicity.
18-month carcinogenicity study (dietary) Swiss albino mice PMRA# 3304693	NOAEL = 46.2/46.5 mg/kg bw/d (♂/♀) LOAEL = 178.7/193.0 mg/kg bw/d (♂/♀) Effects at the LOAEL: ↓ bw, bwg, and FC, ↑ liver and gall bladder wt (♂/♀) No evidence of tumourigenicity.
Two-year combined chronic toxicity study (dietary)	Acceptable with limitations Effects at ≥ 2.7/3.4 mg/kg bw/d: ↑ cholesterol in month 1 (♂); ↑ cholesterol in months 6 and 24 (♀);

Study type / Animal / PMRA#	Study results
Wistar rats Non-guideline PMRA# 3304690	Effects at $\geq 13.3/17.4$ mg/kg bw/d: \uparrow cholesterol in month 12 (♀); Effects at 74.6/96.7 mg/kg bw/d: \downarrow bw and bwg, \downarrow RBC and Hb, \uparrow cholesterol in months 1 and 3, \uparrow incidence of bile duct alteration ($\text{♂}/\text{♀}$); \downarrow adrenal wt (♀) Study Limitations: Insufficient number of animals were used for blood sampling. Missing histopathological examination for some organs. Missing information for stability, homogeneity, or concentration of metamitron in the diet.
Combined chronic toxicity / carcinogenicity study (dietary) Wistar rats PMRA# 3304694	NOAEL = 19.1/27.0 mg/kg bw/d ($\text{♂}/\text{♀}$) LOAEL = 114/139 mg/kg bw/d ($\text{♂}/\text{♀}$) Effects at the LOAEL for the chronic (1-year) study: \downarrow bw, bwg, and FC ($\text{♂}/\text{♀}$). Effects at the LOAEL for the carcinogenicity (2-year) study: \downarrow bw and bwg, \downarrow liver wt, \uparrow incidence of liver ecchymoses, cyst, and necrotic foci ($\text{♂}/\text{♀}$); \uparrow incidence of liver basophilic foci, \uparrow incidence of lymphoid hyperplasia in the mesenteric, mediastinal, and mandibular lymph nodes, \uparrow incidence of mesenteric lymph node edema (♂); \uparrow incidence of enlarged mammary gland, \downarrow adrenal wt (♀). No evidence of tumourigenicity.
Combined chronic toxicity / carcinogenicity study in rats (dietary) Wistar rats PMRA# 3304695 and 3304696	NOAEL = 4.9/6.0 mg/kg bw/d ($\text{♂}/\text{♀}$) LOAEL = 19.5/24.9 mg/kg bw/d ($\text{♂}/\text{♀}$) Effects at the LOAEL for 1-year study: \uparrow incidence of reduced glycogen in the liver ($\text{♂}/\text{♀}$). Effects at the LOAEL for 2-year study: \uparrow incidence of kidney early papillary necrosis, \uparrow incidence of liver eosinophilic focus, single cell necrosis, focal degeneration, angiectasis (sinus and subcapsular), increased fat marrow in sternum ($\text{♂}/\text{♀}$); \uparrow incidence of liver basophilic focus, Kupffer cell activation, mandibular lymph node lymphoid hyperplasia (♂); \downarrow bw and bwg, \downarrow RBC, Hb, and HCT, \uparrow incidence of liver hypertrophy and hepatocyte alteration, \uparrow incidence of uterine cervix squamous cell hyperplasia and keratinization (♀). No evidence of tumourigenicity.
Developmental and reproductive toxicity studies	
Reproductive toxicity (dietary) Wistar rats	Acceptable with limitations Parental effects $\geq 62.2/67.8$ mg/kg bw/d: \uparrow testes wt (♂); \downarrow bw, \uparrow liver wt (♀);

Study type / Animal / PMRA#	Study results
Range-finding study PMRA# 3304705	119.6/125 mg/kg bw/d: ↓ bw, bwg, and FC (♂/♀). Reproductive effects 119.6/125 mg/kg bw/d: ↓ fertility rate (♂/♀). Offspring effects ≥ 16.4/17.4 mg/kg bw/d: ↓ pup bw at birth and up to postnatal day (PND) 28 (♂/♀); ≥ 62.2/67.8 mg/kg bw/d: ↓ pup bw. Study Limitations: Range-finding study, primarily designed to inform dose selection; limited animal number and parameters assessed.
Two-generation reproduction toxicity (dietary) Wistar rats PMRA# 3304702 and 3304704	Parental NOAEL = 8.4/ND (♂/♀) Parental LOAEL = 41/12.0 mg/kg bw/d (♂/♀) Effects at the LOAEL: ↓ bw, bwg, and FC Reproductive NOAEL = 36.4/59.3 mg/kg bw/d (♂/♀) Reproductive LOAEL = 239.1/354.3 mg/kg bw/d (♂/♀) Effects at the LOAEL: ↓ mean # of corpora lutea and mean # of implantations in parental generation (F0) and first filial generation (F1), ↓ # of live births and litter size in F1 Offspring NOAEL = 11.3 mg/kg bw/d Offspring LOAEL = 53.8 mg/kg bw/d Effects at the LOAEL: ↓ PND 21 survival index in F1 pups, ↓ bw in second filial generation (F2) pups, ↑ incidence of missing/cannibalised pups in F1 and F2 No evidence of sensitivity of the young.
Two-generation reproductive toxicity (dietary) Wistar rats PMRA# 3304706	Parental NOAEL = 3.9/4.6 mg/kg bw/d (♂/♀) Parental LOAEL = 19.8/22.9 mg/kg bw/d (♂/♀) Effects at the LOAEL: ↓ bw and bwg (F1♂/♀) Reproductive NOAEL = 3.9/4.6 mg/kg bw/d (♂/♀) Reproductive LOAEL = 19.8/22.9 mg/kg bw/d (♂/♀) Effects at the LOAEL: ↓ birth wt (F1) Offspring NOAEL = 4.6 mg/kg bw/d Offspring LOAEL = 22.9 mg/kg bw/d Effects at the LOAEL: ↓ bw at PND 4–28 (5–11%) F2 pups

Study type / Animal / PMRA#	Study results
	No evidence of sensitivity of the young.
Developmental toxicity study (gavage) FB30 (Long Evans) rats Non-guideline PMRA# 3304699	Acceptable with limitations Maternal effects ≥ 30 mg/kg bw/d: ↓ bwg; 100 mg/kg bw/d: one dam with total litter loss Developmental effects 100 mg/kg bw/d: one dam with total litter loss Study Limitations: Non-GLP, no QA, missing measurements.
Developmental toxicity study (gavage) Wistar rats PMRA# 3304700	Maternal NOAEL = 30 mg/kg bw/d Maternal LOAEL = 100 mg/kg bw/d Effects at the LOAEL: Clinical signs on first day of treatment (dyspnoea, ventral, and/or dorsal body position), ↓ FC GD 6–11. Developmental NOAEL = 30 mg/kg bw/d Developmental LOAEL = 100 mg/kg bw/d Effects at the LOAEL: ↑ incidence of wavy ribs No evidence of sensitivity of the young.
Developmental toxicity study (gavage) Wistar rats PMRA# 3304701 and 3304703	Maternal NOAEL = 25 mg/kg bw/d Maternal LOAEL = 100mg/kg bw/d Effects at the LOAEL: ↓ bwg, ↑ mortality Developmental NOAEL = 25 mg/kg bw/d Developmental LOAEL = 100 mg/kg bw/d Effects at the LOAEL: ↑ incidence of wavy ribs No evidence of sensitivity of the young.
Developmental toxicity study (gavage) Himalayan rabbits Non-guideline PMRA# 3304723	Acceptable with limitations Maternal effects 100 mg/kg bw/d: ↑ bw loss (GD 6–18), ↑ post-implantation loss. Developmental effects 100 mg/kg bw/d: ↑ post-implantation loss.

Study type / Animal / PMRA#	Study results
	Study Limitations: No information on stability, FC, gross pathology, limited reporting of fetal examinations, no individual data on clinical signs or bw.
Developmental toxicity study (gavage) New Zealand white rabbits PMRA# 3304722 and 3304720	Maternal NOAEL = 100 mg/kg bw/d Maternal LOAEL = not determined Developmental NOAEL = 25 mg/kg bw/d Developmental LOAEL = 50 mg/kg bw/d Effects at the LOAEL: ↑ incidence of incomplete/poor ossification of sternebrae, ↑ incidence of asymmetrically ossified sternebrae and incomplete/poor ossification of parietal, intraparietal. Evidence of sensitivity of the young.
Developmental toxicity study (gavage) Himalayan rabbits PMRA# 3304721	Maternal NOAEL = 40 mg/kg bw/d Maternal LOAEL = 160 mg/kg bw/d Effects at the LOAEL: ↑ incidence of discoloured urine, ↓ feces and urine, ↓ FC GD 6–16, bw loss GD 6–19, ↓ gravid uterus wt, ↑ post-implantation loss, one dam with total litter loss Developmental NOAEL = 40 mg/kg bw/d Developmental LOAEL = 160 mg/kg bw/d Effects at the LOAEL: ↓ # live fetuses/dam, ↑ post-implantation loss, liver histology changes (discoloration, mottled and borders dark discolored and distinct liver lobulation), slightly thickened ribs No evidence of sensitivity of the young.
Genotoxicity studies	
Bacterial reverse mutation assay <i>Salmonella</i> Typhimurium, <i>Escherichia coli</i> PMRA# 3304724	Negative ± metabolic activation Tested up to the limit concentration

Study type / Animal / PMRA#	Study results
Bacterial reverse mutation assay <i>Salmonella</i> Typhimurium, <i>Escherichia coli</i> PMRA# 3304725	Negative ± metabolic activation Tested up to the limit concentration Evidence of cytotoxicity at ≥ 2500 µg/plate for TA 1537 (-metabolic activation).
Bacterial reverse mutation assay <i>Salmonella</i> Typhimurium PMRA# 3304726	Acceptable with limitations The number of revertant mutants in the treated groups were comparable to controls at all doses in all cell lines in two experiments except in one experiment, at 500 µg/plate in TA1535 with mammalian metabolic activation system (S9) activation for which the number of revertant colonies was two-fold greater than control. Evidence of cytotoxicity: 5000 and 10000 µg/plate (±S9) Tested up to the limit concentration ± metabolic activation. Study Limitations: Appropriate positive controls were not included.
Bacterial reverse mutation assay <i>Salmonella</i> Typhimurium PMRA# 3304727	Acceptable with limitations The number of revertant mutants in the treated groups were comparable to controls at all doses in all cell lines in two experiments except in one experiment, at 333 µg/plate in TA1535 with S9 activation for which the number of revertant colonies was two-fold greater than control. Tested up to the limit concentration ± metabolic activation. Study Limitations: Purity not stated. Missing test strains
Bacterial DNA damage or repair test <i>Bacillus subtilis</i> PMRA# 3304728	Negative ± metabolic activation. Tested up to the limit concentration
Bacterial DNA damage or repair test <i>Escherichia coli</i> PMRA# 3304729	Acceptable with limitations No growth inhibition zones were induced by metamitron up to the highest dose tested (5000 µg/plate). Tested up to the limit concentration ± metabolic activation. Study Limitations: Information on bacterial growth, media composition were not available.

Study type / Animal / PMRA#	Study results
Mitotic gene conversion in <i>Saccharomyces cerevisiae</i> PMRA# 3304730	<p>Acceptable with limitations</p> <p>Increased mutant frequency was noted at 12500 µg/mL (±S9) in two experiments but not at 18000 µg/mL.</p> <p>Tested up to precipitating concentrations ± metabolic activation.</p> <p>Evidence of cytotoxicity at ≥ 2500 µg/mL (±S9)</p> <p>Study Limitations: Spontaneous rate of conversion not tested. Dimethyl sulfoxide is not the recommended vehicle for this type of study.</p>
Dominant lethal test (gavage) Wistar rats PMRA# 3304737	<p>Acceptable with limitations</p> <p>Effects at 2000 mg/kg bw: ↑ incidence of urinary incontinence and watery discharge of the nose, ↓ bw, ↓ pregnancy rate and live implants, ↑ fetal resorption, pre-implantation loss, and post-implantation loss, ↑ early resorption.</p> <p>Study Limitations: Insufficient number of animals were tested in the study. Housing conditions did not meet the criteria of the guideline. Initial bw had high variations. The number of total implantations was considerably lower in most intervals. The treatment scheme did not follow the test guideline. There were missing measurements such as FCs and fetus weights. The data from the range finding study were not reported.</p>
In vitro mammalian chromosomal aberration test Human lymphocytes PMRA# 3304739	<p>Acceptable with limitations</p> <p>Tested up to limit concentration ± metabolic activation.</p> <p>-S9: Cytotoxicity at all concentrations</p> <p>+S9: Cytotoxicity at 5250 µg/mL and above</p> <p>↑ aberrations at 1250 µg/mL (-S9) and 6000 µg/mL (+S9)</p> <p>Study Limitations: Cytotoxicity was noted in all dose levels without S9.</p>
In vitro mammalian chromosomal aberration test Chinese hamster ovary cells PMRA# 3304740	<p>Acceptable with limitations</p> <p>Tested up to limit concentration ± metabolic activation.</p> <p>Precipitation: 5000 µg/mL (-S9), ≥ 1250µg/mL (+S9)</p> <p>Cytotoxicity: Test 1 ≥ 1250 µg/mL (+S9)</p>

Study type / Animal / PMRA#	Study results
	Test 2 \geq 2500 $\mu\text{g}/\text{mL}$ (-S9) (18 hrs exposure) \geq 312.5 $\mu\text{g}/\text{mL}$ (+S9) (18 hrs exposure) $=$ 2500 $\mu\text{g}/\text{mL}$ (\pm S9) (32 hrs exposure) \uparrow aberrations at 5000 $\mu\text{g}/\text{mL}$ (-S9) Study Limitations: Short-term treatment without S9 activation was not tested. The top concentration exceeded the highest concentration required by guideline. The concurrent control data was not in the range of the historical control data.
In vitro mammalian chromosomal aberration test Chinese hamster V79 cell PMRA# 3304741	Negative \pm metabolic activation. Tested up to limit concentration. Cytotoxicity \geq 1000 $\mu\text{g}/\text{mL}$ (-S9) 21 hrs
Gene mutations in mammalian cells in vitro Chinese hamster V79 cell PMRA# 3304742	Negative \pm metabolic activation. Tested up to precipitating concentration.
Gene mutations in mammalian cells in vitro Chinese hamster V79 cell PMRA# 3304743	Equivocal Tested up to a limit concentration \pm metabolic activation. Evidence of cytotoxicity at \geq 750 $\mu\text{g}/\text{mL}$ (-S9) -S9: \uparrow mutation frequency at 50, 750, 1000, 1500 $\mu\text{g}/\text{mL}$ +S9: \uparrow mutation frequency at 50, 100, 250 and 1500 $\mu\text{g}/\text{mL}$, all within historical control data
Mammalian erythrocyte micronucleus test (gavage) Swiss albino mice PMRA# 3304744	Negative \downarrow bw at 500 mg/kg bw
Mammalian erythrocyte micronucleus test (gavage) CD-1 mice	Acceptable with limitations The micronucleus occurrence rates in polychromatic erythrocytes and normochromatic erythrocytes were comparable between the treatment groups and the control. Effects at 800 mg/kg bw: One ♀ died within 24 hrs. Clinical signs (piloerection, slight to severe

Study type / Animal / PMRA#	Study results
PMRA# 3304745	<p>lethargy, waddling, decreased respiration, gasping for air, loss of righting reflex, and ptosis) resolved by 48 hrs.</p> <p>Study limitations: The test doses exceeded the maximum tolerated dose. Bone marrow exposure was not addressed. Less than 3 dose levels were investigated as the guideline required.</p>
<p>Mammalian erythrocyte micronucleus test (intraperitoneal injection)</p> <p>Hsd/Win NMRI mice</p> <p>PMRA# 3304747</p>	<p>Acceptable with limitations</p> <p>Decreased ratio of polychromatic to normochromatic erythrocytes was noted in treatment groups. The micronucleus occurrence rate in polychromatic erythrocytes was comparable between the treatment groups and the control.</p> <p>Study limitations: The route of administration is not an intended route of human exposure. The number of immature erythrocytes scored is not sufficient. Body weight at the end of the study was not recorded.</p>
<p>Mammalian erythrocyte micronucleus test (gavage)</p> <p>NMRI mice</p> <p>PMRA# 3304748</p>	<p>Acceptable with limitations</p> <p>The micronucleus occurrence rate in polychromatic erythrocytes and normochromatic erythrocytes was comparable between the treatment groups and the control.</p> <p>Study Limitations: Cell harvest time did not follow guideline. Test substance information was missing, clinical signs, mortality/morbidity, and bw were not recorded. Bone marrow exposure was not addressed. Less than 3 dose levels were investigated as the guideline required. No historical control data was provided.</p>
<p>Mammalian erythrocyte micronucleus test (gavage)</p> <p>Han Wistar rats</p> <p>PMRA# 3304749</p>	<p>Negative</p> <p>Effects at 125 mg/kg bw: lethargy, ptosis, and diarrhea;</p> <p>Effects at 250 mg/kg bw: hunched posture.</p>
<p>Mammalian erythrocyte micronucleus test (gavage)</p> <p>Non-guideline</p> <p>Swiss albino mice</p> <p>PMRA# 3304751</p>	<p>Acceptable with limitations</p> <p>The chromosomal aberration frequency and rates at 500 mg/kg bw group were not higher than the control group.</p> <p>Study Limitations: Bone marrow exposure was not addressed. Insufficient number of cells used for determining the mitotic index and scored for aberrations. Only the high-dose group was counted. Historical control data were missing.</p>

Study type / Animal / PMRA#	Study results
Validity of bone marrow micronucleus testing with metamitron PMRA# 3304750	<p>In 5 Mammalian Erythrocyte Micronucleus Tests (PMRA# 3304747, 3304748, 3304744, 3304745 and 3304751), blood samples were not collected to confirm the bone marrow exposure. In a toxicokinetics study (PMRA# 3304753), rats dosed 2 or 200 mg/kg bw metamitron via gavage, showed a broad range of maximum concentrations with plasma levels of 102–141 µg/mL (1–8 hrs PD). The results at 200 mg/kg bw are considered relevant to the doses used in the tests mentioned above (200–800 mg/kg bw). NMRI male mice treated with 200 mg/kg twice had a strong suppression on the ratio of polychromatic erythrocytes to normochromatic erythrocytes (PCE/NCE) (1.16 versus 2.49) (PMRA# 3304747). Swiss albino mice treated with 500 mg/kg twice had a slight reduction in PCE/NCE (0.56 versus 0.83).</p> <p>Conclusion of study author: Bone marrow exposure is evident and the bone marrow genotoxicity assays are valid.</p>
Neurotoxicity studies	
Acute neurotoxicity study (gavage) HsdWin:NMRI mice Non-guideline PMRA# 3304708	<p>Acceptable with limitations</p> <p>Effects at 100 mg/kg bw: ↑ incidence of sedation, prone position, ptosis, and piloerection. All behaviour changes were resolved within 120 minutes post-treatment.</p> <p>Study Limitations: Only males were tested. Limited observations and tests were performed (no motor activity, gross, or histopathology). No positive control was included to validate the test system.</p>
Acute neurotoxicity study (gavage) NMRI mice Non-guideline PMRA# 3304709	<p>Acceptable with limitations</p> <p>Effects at 100 mg/kg bw: ↑ incidence of impaired balance</p> <p>Study Limitations: Only males were tested. No positive control was included to validate the test system.</p>
Acute neurotoxicity study (gavage) Wistar rats Non-guideline PMRA# 3304707	<p>Acceptable with limitations</p> <p>No difference in the isometric force after direct or indirect stimulation in animals treated with metamitron compared to controls.</p> <p>Study Limitations: Only males were tested. No positive control was included to validate the test system.</p>

Study type / Animal / PMRA#	Study results
Acute neurotoxicity study (gavage) Wistar rats Non-guideline PMRA# 3304710	Acceptable with limitations Effects at 100 mg/kg bw: ↓ body temperature; ↓ travelled distance, ↑ resting time, and ↓ # of rearing in open-field test Evidence of neurotoxicity Study Limitations: Only males were tested. No positive control was included to validate the test system. Only limited parameters were tested.
Acute neurotoxicity study (gavage) Wistar rats Non-guideline PMRA# 3304712	Acceptable with limitations Effects at 30 mg/kg: ↓ body temperature; ↓ travelled distance, ↑ resting time, and ↓ # of rearing in open-field test Evidence of neurotoxicity Study Limitations: Only males were tested. No positive control was included to validate the test system. Only limited parameters were tested.
Acute neurotoxicity study (gavage) Wistar rats Non-guideline PMRA# 3304711	Acceptable with limitations Effects at 100 mg/kg: reduced intestinal motility (measured by distance travelled by charcoal in small intestine) Study Limitations: Only males were tested. The travelled distance was not calibrated by the total length of small intestine. No positive control was included to validate the test system.
Effects of DRW 1139* on the isolated guinea pig ileum Guinea pig ileum Non-guideline PMRA# 3304713 *metamitron	Acceptable with limitations Acetylcholine, barium, chloride, histamine, serotonin induced ileum spasm was not influenced by metamitron at dose up to 10 ⁻⁶ g/mL. Study Limitations: No rationale for dose selection, no positive control, data on direct effect of metamitron not provided.

Study type / Animal / PMRA#	Study results
Waiver for acute neurotoxicity study PMRA# 3304714	Submitted waiver request was based on available non-guideline acute neurotoxicity studies, which evaluated endpoints relevant to autonomic and neurobehavioral effects, neuromuscular effects, body temperature, motor activity, and sensory effects. Fore- and hind-limb grip strength were measured in a subchronic neurotoxicity study. Neurotoxicity endpoints were assessed in acute, subacute, subchronic, and chronic toxicity, carcinogenicity, reproduction, and developmental toxicity studies. Waiver considered acceptable and an additional acute neurotoxicity study was not required.
90-d neurotoxicity study (dietary) Sprague Dawley rats PMRA# 3304719	NOAEL = 28.2/35.3 mg/kg bw/d ♂/♀ LOAEL = 84.0/96.8 mg/kg bw/d ♂/♀ Effects at the LOAEL: ↓ bw (♂/♀) No evidence of neurotoxicity.
Special studies (or mechanistic studies)	
Effects of a single oral administration on diuresis and blood pharmacological parameters of rats (gavage) Wistar rats Non-guideline PMRA# 3304762	Acceptable with limitations Effects at 100 mg/kg: ↑ urinary excretion of sodium, potassium, and chloride without change in urine volume, ↓ Hb without changes in osmotic tolerability in erythrocyte. Effects at 300 mg/kg: Prolonged thromboplastin time. Study Limitations: Limited parameters assessed.
Effects of a single oral administration on diuresis in rats (gavage) Wistar rats Non-guideline PMRA# 3304763	Effects at 30 mg/kg: ↑ urine volume, ↑ urinary excretion of sodium, potassium, and chloride. Study Limitations: Limited parameters assessed.

Study type / Animal / PMRA#	Study results
Hershberger bioassay in rats (gavage) CrI:CD(SD) rats PMRA# 3304765 and 3304766	No evidence of androgen agonism or antagonism.
Waiver for immunotoxicity study PMRA# 3304767	No systemic immunotoxicity identified in the toxicology database. However, some localized immune activation was noted, such as Kupffer cell activation. Waiver was accepted.
A mechanistic investigation of bile composition, liver- related clinical chemistry, and liver and gall bladder histopathology (4-wk dietary) Beagle dogs Non-guideline PMRA# 3303573	<p>Acceptable with limitations</p> <p>Effects at 63 mg/kg/bw/d: ↓ bwg, ↑ ALT, ↑ glutamate dehydrogenase, ↑ cholesterol (blood), ↑ liver CYP7A, ↑ incidence of apoptotic hepatocytes and centrilobular cytoplasmic eosinophilia, deposition of an iron-positive pigment within Kupffer cells, ↑ biliary glutathione conjugates, non-conjugated cholic acid in one dog</p> <p>Study Limitations: Limited parameters assessed.</p>
Stably transfected human androgen receptor transcriptional activation assay AR-EcoScreen™ cell line PMRA# 3304687	Negative in the androgen receptor agonist and antagonist assays
Stably transfected human estrogen receptor- α transactivation assay Human hER α -HeLa-9903 cell line PMRA# 3304688	Negative in the estrogen receptor agonist and antagonist assays

Study type / Animal / PMRA#	Study results
H295R steroidogenesis assay Human H295R cell line PMRA# 3303552	Negative Tested up to the highest non-precipitating concentration
Aromatase assay (human recombinant) Human recombinant microsomes PMRA# 3304752	Negative Tested up to precipitating concentrations. The average aromatase activity was above 100% in all of the concentrations tested (> 75% non-inhibitor).
Metabolite studies	
Derek and Sarah Nexus structural activity relationship evaluation: MTM-237-3C3O (metabolite QSAR) In silico PMRA# 3303551	MTM-237-3C3O was predicted to be inactive for mutagenicity in vitro in bacterium and a non-sensitizer to the skin in mammals; no firing alerts for the other endpoints were reported in the DEREK model.
Bacterial reverse mutation assay (desamino-metamitron) <i>Salmonella</i> Typhimurium, <i>Escherichia coli</i> PMRA# 3304732	Negative ± metabolic activation Tested up to the limit concentration. Cytotoxicity <i>Escherichia coli</i> strain WP2 uvrA in the standard plate test and pre-incubation plate test ±S9 at 5000 µg/plate and pre-incubation test at 2500 µg/plate
Bacterial reverse mutation assay (M-N-glycoside) <i>Salmonella</i> Typhimurium, <i>Escherichia coli</i> PMRA# 3304733	Negative ± metabolic activation Tested up to the limit concentration. Evidence of cytotoxicity at 5000 µg/plate (-S9) for <i>Salmonella</i> Typhimurium strain TA1535

Study type / Animal / PMRA#	Study results										
Bacterial reverse mutation assay (DAM-N-glycoside) <i>Salmonella</i> Typhimurium, <i>Escherichia coli</i> PMRA# 3304734	Negative ± metabolic activation Tested up to limit concentration.										
In vitro mammalian cell gene mutation test (desamino-metamitron) Chinese hamster V79 cell PMRA# 3304738	Negative ± metabolic activation Tested up to precipitating concentration.										
In vitro mammalian chromosomal aberration test (desamino-metamitron) Human lymphocytes PMRA# 3304746	Negative ± metabolic activation Tested up to precipitating concentration. Evidence of cytotoxicity at 2500 µg/mL (-S9), 24 hrs, 2500 µg/mL (+S9), 4 hrs.										
Additional data from the open scientific literature											
Effects of selected herbicides on cytokines production in vitro Life Sciences, 66(26): 2519-2525; May 2000 Human peripheral blood mononuclear cell PMRA# 3502031	<table border="1" data-bbox="598 938 1297 1144"> <thead> <tr> <th colspan="2" data-bbox="598 938 1297 982">TNF-α</th> </tr> <tr> <th data-bbox="598 982 947 1026">Metamitron (µM)</th> <th data-bbox="947 982 1297 1026">% of Control</th> </tr> </thead> <tbody> <tr> <td data-bbox="598 1026 947 1062">0.8</td> <td data-bbox="947 1026 1297 1062">102 ± 15</td> </tr> <tr> <td data-bbox="598 1062 947 1097">8</td> <td data-bbox="947 1062 1297 1097">98 ± 14</td> </tr> <tr> <td data-bbox="598 1097 947 1133">80</td> <td data-bbox="947 1097 1297 1133">118 ± 16**</td> </tr> </tbody> </table> <p data-bbox="598 1144 730 1182">**p<0.01</p> <p data-bbox="598 1214 1780 1292">Metamitron induced proinflammatory cytokine TNF-α production in human peripheral blood mononuclear cells at 80 µM.</p>	TNF- α		Metamitron (µM)	% of Control	0.8	102 ± 15	8	98 ± 14	80	118 ± 16**
TNF- α											
Metamitron (µM)	% of Control										
0.8	102 ± 15										
8	98 ± 14										
80	118 ± 16**										
Metabolism and toxicity of metribuzin in mouse liver Pesticide Biochemistry and	Liver glutathione content was significantly depleted by intraperitoneal 200 mg/kg metribuzin. Metribuzin caused much less glutathione depletion.										

Study type / Animal / PMRA#	Study results
Physiology, 23(1): 123-130; February 1985 Swiss Webster albino mice ♂ PMRA# 3502030	

Table 5 Toxicity profile of products Brevis 150 SC and Brevis 15 SG containing metamitron

Effects are known or assumed to occur in both sexes unless otherwise noted; in such cases, effects observed in both sexes are presented first followed by sex-specific effects in males, then females, each separated by semi-colons.

Study type / Animal / PMRA#	Study results
Brevis 150 SC	
Acute oral toxicity (gavage) Wistar (albino) rats PMRA# 3305182	LD ₅₀ ♀ > 2000 mg/kg bw No clinical signs of toxicity. Low acute toxicity
Acute oral toxicity (up and down procedure) (gavage) Sprague Dawley rats PMRA# 3305183	LD ₅₀ ♀ > 5000 mg/kg bw Piloerection and lethargy were noted. Low acute toxicity
Acute dermal toxicity Sprague Dawley (Crl:CD) rats PMRA# 3305185	LD ₅₀ ♂/♀ > 2000 mg/kg bw Clinical signs of toxicity included piloerection. Low acute toxicity
Acute dermal toxicity Wistar (albino) rats PMRA# 3305184	LD ₅₀ ♀ > 2000 mg/kg bw No clinical signs of toxicity. Low acute toxicity
Acute inhalation toxicity (nose-only) CRL:(WI) rats PMRA# 3305186	LC ₅₀ ♂/♀ > 4.6933 mg/L Clinical signs of toxicity included piloerection. Low acute toxicity
Acute inhalation toxicity (nose-only) Sprague Dawley (Crl:CD) rats PMRA# 3305187	LC ₅₀ ♂/♀ > 0.84 mg/L Clinical signs of toxicity included nasal congestion and piloerection. Slight acute toxicity
Primary eye irritation Albino rabbits PMRA# 3305188	MAS = 0.89/110 MIS = 4/110 at 1 hr Minimally irritating
Primary eye irritation Albino rabbits PMRA# 3305189	MAS = 0.667/110 MIS = 2/110 at 1 and 24 hrs Minimally irritating
Primary dermal irritation Albino rabbits PMRA# 3305190	MAS = 0/110 MIS = 0/110 Not a skin irritant

Study type / Animal / PMRA#	Study results
Primary dermal irritation Albino rabbits PMRA# 3305192	MAS = 0/110 MIS = 0/110 Not a skin irritant
Dermal sensitization (Buehler test) Guinea pigs PMRA# 3305193	Negative
Dermal sensitization (maximization test) Hartley guinea pigs PMRA# 3305194	Negative
Brevis 15 SG	
Acute oral toxicity (gavage) CRL:(WI) rats PMRA# 3306202	LC ₅₀ ♀ between 300 to 2000 mg/kg bw All animals died at 2000 mg/kg bw, none died at 300 mg/kg bw. Clinical signs of toxicity included hunched back, decreased activity, piloerection, and decreased general body tone. Estimated high acute toxicity
Acute oral toxicity (up and down procedure) Crl:WI(Han) rats PMRA# 3306203	LD ₅₀ ♀ = 1453 mg/kg bw Slight acute toxicity
Acute dermal toxicity CRL:(WI) rats PMRA# 3306204	LD ₅₀ ♂♀ > 2000 mg/kg bw Low acute toxicity
Acute inhalation toxicity (nose-only) CRL:(WI) rats PMRA# 3306205	LC ₅₀ ♂/♀ > 5.1 mg/L Clinical signs of toxicity included labored respiration, wet fur, and moderate weakness. Low acute toxicity
Primary eye irritation – in vitro 2012 ROSS 308 chicken eyes PMRA# 3306207	Neither classified as severe irritant, nor as non-irritant.
Primary eye irritation Albino rabbits PMRA# 3306206	MAS = 22.7/110 MIS = 42.3/110 at d 7 No reversibility Corrosive

Study type / Animal / PMRA#	Study results
Primary dermal irritation Albino rabbits PMRA# 3306208	MAS = 0/8 MIS = 0/8 Not a dermal irritant
Dermal sensitization (LLNA) CBA/CaOlaHsd mice PMRA# 3306209	Negative

Table 6 Comparison of mean percent recovery of metamitron absorbed through skin after eight hours of exposure (measured 24 hours post-exposure)

Formulation used	AG-M4-150 SG (Brevis 15 SG)				AG-M4-700 OF1 (suspension concentrate similar to Brevis 150 SC)					
	In vitro				In vivo		In vitro			
Dose group/ Skin type	High human	Low human	High rat	Low rat	High rat	Low rat	High human	Low human	High rat	Low rat
Concentration	150 g/kg	0.2 g/L	150 g/kg	0.2 g/L	700 g/L	2.0 g/L	700 g/L	2.0 g/L	700 g/L	2.0 g/L
Applied dose ($\mu\text{g}/\text{cm}^2$)	800	2	800	2	7000	20	6800	21	6800	21
Absorbed	2.16	52.59	9.58	56.08	0.2	15.8	1.92	14.56	4.52	37.30
Tape strips (all)	1.19	0.96	12.25	3.97	0.22	6.03	15.33	0.47	27.25	3.19
Potentially absorbed dose (including all tape strips)	3.35	53.55	21.83	60.05	0.43	21.82	17.26	15.03	31.76	40.49

Table 7 Mean percent recovery of applied metamitron in the rat in vivo study (eight hours exposure) at various time points post-exposure

Dose group	Concentrate (Group A)			Field dilution (Group B)		
	T1 24 Hrs	T2 72 Hrs	T3 144 Hrs	T1 24 Hrs	T2 72 Hrs	T3 144 Hrs
Applied dose ($\mu\text{g}/\text{cm}^2$)	6819	6838	6870	19.9	19.9	20.1
Urine (total)	0.07	0.09	0.14	8.21	7.47	9.16
Feces (total)	0.04	0.06	0.09	5.79	6.22	7.23
Cage wash	< 0.01	< 0.01	0.01	0.21	0.09	0.04

Dose group	Concentrate (Group A)			Field dilution (Group B)		
	T1 24 Hrs	T2 72 Hrs	T3 144 Hrs	T1 24 Hrs	T2 72 Hrs	T3 144 Hrs
Blood	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01
Control skin	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01
GIT	< 0.02	< 0.01	< 0.01	0.90	0.04	0.03
Residual carcass	0.06	0.08	0.13	0.35	0.16	0.20
Stripped skin	0.01	< 0.01	0.02	0.33	0.09	0.12
Absorbed (no tape strips)¹	0.20	0.25	0.40	15.80	14.07	16.77
Tape strips 1+2	0.14	0.12	0.28	3.89	3.48	4.21
Tape strips 3 to 20	0.08	0.11	0.15	2.14	2.01	2.40
Potentially absorbed²	0.43	0.48	0.83	21.82	19.56	23.38
Skin washes	96.13	97.70	96.77	73.59	77.35	73.27
O-ring/cover/tape	0.76	0.87	1.33	0.68	0.35	0.56
Total recovery	97.31	99.04	98.93	96.10	97.26	97.22

Values below LOQ were considered as equal to LOQ for the calculations. Values rounded as 0.00 are presented as

< 0.01. Each value is the mean of four (4) rats.

¹ Absorbed dose is defined as the percentage of radioactivity in urine, feces, cage wash, blood, control skin, GIT, residual carcass, and stripped skin.

² Potentially absorbed dose is defined as the absorbed dose including all tape strips.

Table 8.1 AHETF unit exposure estimates for mixer/loaders and applicators handling Brevis 150 SC (µg/kg a.i. handled)

Exposure scenario and PPE		Dermal	Dermal absorbed ¹	Inhalation ²	Total unit exposure ³
PPE: Single layer and chemical-resistant gloves plus hat					
Mixer/loader AHETF estimates					
A	Open mix/load liquid	58.5	9.945	0.63	10.575
Applicator AHETF estimates					
B	Airblast applicator	414.93	70.538	9.08	79.618
Mixer/loader + applicator AHETF estimates					

Exposure scenario and PPE		Dermal	Dermal absorbed ¹	Inhalation ²	Total unit exposure ³
A+B	Mixer/loader/applicator	473.43	80.48	9.71	90.19

¹ Adjusted with dermal absorption factor 17%

² Light inhalation rate

³ Total unit exposure = Dermal exposure + Inhalation exposure

Table 8.2 AHETF unit exposure estimates for mixer/loaders and applicators handling Brevis 15 SG (µg/kg a.i. handled)

Exposure scenario and PPE		Dermal	Dermal absorbed ¹	Inhalation ²	Total unit exposure ³
PPE: Single layer and chemical-resistant gloves plus hat					
Mixer/loader AHETF estimates					
A	Open mix/load dry flowable	84.14	3.3656	21.8	25.1656
Applicator AHETF estimates					
B	Airblast applicator	414.93	224.0622	9.08	233.1422
Mixer/loader + applicator AHETF estimates					
A+B	Mixer/loader/applicator	499.07	227.428	30.88	258.308

¹ Adjusted with dermal absorption factor 4% for mixer/loaders, 54% for all other exposure scenarios

² Light inhalation rate

³ Total unit exposure = Dermal exposure + Inhalation exposure

Table 9 Open mixer/loader and open airblast applicator risk assessment

Exposure scenario	Unit exposure (µg/kg a.i. handled) ¹	ATPD (ha/day) ²	Rate (kg a.i./ha)	Daily exposure (mg/kg bw/day) ³	MOE ⁴
PPE: Single layer and chemical-resistant gloves plus hat					
Brevis 150 SC	90.19	20	0.504	0.0114	994
Brevis 15 SG	258.308	20	0.504	0.0325	347

¹ Total unit exposures for mixer/loader/applicator based on AHETF from Tables 8.1 and 8.2

² Default Area Treated per Day (ATPD) table (2017-09-20)

³ Exposure = (Unit exposure × ATPD × Rate) / (80 kg bw × 1000 µg/mg)

⁴ Based on NOAEL = 11.3 mg/kg bw/day; Target MOE = 300

Table 10 Dislodgeable foliar residue (DFR) analysis for metamitron on apples

Model	Equation	R-Squared	Peak DFR ($\mu\text{g}/\text{cm}^2$)	Dissipation (%/day)	Tool recommendation
New York site DFR analysis					
LnDFR	$\text{Ln}(y) = -0.1792x + -0.7378$	0.96	0.478	16.5%	All models have poor fits and/or patterns in the residuals. Discretion is required to determine if a model, study data, or a combination of model and study data can be used.
Exponential	$y = 0.979E-0.454x$	-	0.979	36.5%	
Biphasic	$y = 0.895E-0.539x + 0.093E-0.081x$	-	0.988	-	
Study	-	-	0.938	-	
Ontario site DFR analysis					
LnDFR	$\text{Ln}(y) = -0.2196x + -0.8401$	0.92	0.432	19.8%	The Exponential and Biphasic model have good fits and residuals. The LnDFR model has poor fits and/or patterns in the residuals. The simpler Exponential model is recommended.
Exponential	$y = 0.875E-0.341x$	-	0.875	28.9%	
Biphasic	$y = 0.875E-0.341x + 0E-0.081x$	-	0.875	-	
Study	-	-	0.816	-	
Washington site DFR analysis					
LnDFR	$\text{Ln}(y) = -0.0851x + 0.205$	0.99	1.225	8.2%	ALL models have good fits and residuals. The simpler LnDFR model is recommended.
Exponential	$y = 1.292E-0.095x$	-	1.292	9.1%	
Biphasic	$y = 1.208E-0.086x + 0.143E-0.955x$	-	1.351	-	
Study	-	-	1.348	-	

Table 11 Postapplication worker exposure and risk estimates for Brevis 150 SC on day 0 after the last application

Postapplication activity	Peak DFR ($\mu\text{g}/\text{cm}^2$) ¹	TC (cm^2/hour) ²	Dermal exposure ($\text{mg}/\text{kg bw}/\text{day}$) ³	Dermal MOE ⁴	REI ⁵
High rate (0.504 kg a.i./ha)					
Hand thinning	1.21	3000	56.5	200	5 d (Dermal MOE = 303)
Hand harvesting	1.21	1400	26.4	428	12 hrs

Postapplication activity	Peak DFR ($\mu\text{g}/\text{cm}^2$) ¹	TC (cm^2/hour) ²	Dermal exposure ($\text{mg}/\text{kg bw}/\text{day}$) ³	Dermal MOE ⁴	REI ⁵
Hand pruning, scouting, training	1.21	580	10.9	1030	12 hrs
Transplanting	1.21	230	4.34	2610	12 hrs
Maintenance, Propping, Hand Weeding	1.21	100	1.88	5990	12 hrs
Low rate (0.336 kg a.i./ha)					
Hand thinning	0.81	3000	37.7	300	12 hrs
Hand harvesting	0.81	1400	17.6	642	12 hrs
Hand pruning, scouting, training	0.81	580	7.29	1550	12 hrs
Transplanting	0.81	230	2.89	3910	12 hrs
Maintenance, propping, hand weeding	0.81	100	1.26	8990	12 hrs

¹ Calculated using the DFR values 22% dislodgeable on the day of application and 8% dissipation per day (Washington Site of DFR study).

² TCs obtained from the PMRA Agricultural TC table PMRA-10.29.2024

³ Exposure = (Peak DFR [$\mu\text{g}/\text{cm}^2$] \times TC [cm^2/hr] \times 8 hrs \times 17% dermal absorption) / (80 kg bw \times 1000 $\mu\text{g}/\text{mg}$)

⁴ Based on a NOAEL of 11.3 mg/kg bw/day, Target MOE = 300

⁵ Minimum REI is 12 hrs to allow residues to dry, suspended particles to settle, and vapours to dissipate.

Table 12 Postapplication worker exposure and risk estimates for Brevis 15 SG on day 0 after the last application

Postapplication activity	Peak DFR ($\mu\text{g}/\text{cm}^2$) ¹	TC (cm^2/hour) ²	Dermal exposure ($\text{mg}/\text{kg bw}/\text{day}$) ³	Dermal MOE ⁴	REI ⁵
High rate (0.504 kg a.i./ha)					
Hand thinning	1.21	3000	180	63	19 d (Dermal MOE = 307)
Hand harvesting	1.21	1400	83.8	135	11 d (Dermal MOE = 310)
Hand pruning, scouting, training	1.21	580	34.7	325	12 hrs
Transplanting	1.21	230	13.8	821	12 hrs
Maintenance, propping, hand weeding	1.21	100	5.99	1890	12 hrs
Low rate (0.336 kg a.i./ha)					
Hand thinning	0.81	3000	120	94	14 d (Dermal MOE = 303)

Postapplication activity	Peak DFR ($\mu\text{g}/\text{cm}^2$) ¹	TC (cm^2/hour) ²	Dermal exposure ($\text{mg}/\text{kg bw}/\text{day}$) ³	Dermal MOE ⁴	REI ⁵
Hand harvesting	0.81	1400	55.9	202	5 d (Dermal MOE= 307)
Hand pruning, scouting, training	0.81	580	23.2	488	12 hrs
Transplanting	0.81	230	9.18	1230	12 hrs
Maintenance, propping, hand weeding	0.81	100	3.99	2830	12 hrs

¹ Calculated using the DFR values 22% dislodgeable on the day of application and 8% dissipation per day (Washington Site of DFR study).

² TCs obtained from the PMRA Agricultural TC table PMRA-10.29.2024

³ Exposure = (Peak DFR [$\mu\text{g}/\text{cm}^2$] \times TC [cm^2/hr] \times 8 hrs \times 54% dermal absorption) / (80 kg bw \times 1000 $\mu\text{g}/\text{mg}$)

⁴ Based on a NOAEL of 11.3 mg/kg bw/day, Target MOE = 300

⁵ Minimum REI is 12 hrs to allow residues to dry, suspended particles to settle, and vapours to dissipate.

Table 13 Major fate inputs for the modelling

Fate parameter	Drinking water	Ecological water***
K_{oc}	62 L/kg – 20 th percentile of 4 values for desamino-metamitron	67 L/kg – 20 th percentile of 23 values for metamitron
Water half-life*	320 d – 80 th percentile of 6 experiments from 3 studies	26 d – 80 th percentile of 6 experiments from 3 studies
Sediment half-life**	Stable – 4 experiments on only 2 systems	5.3 d – 80 th percentile of 4 experiments on only 2 systems
Photolysis half-life	Stable – no appreciable transformation of desamino-metamitron at pH 7	0.06 d – longer of 2 pH 7 values
Hydrolysis	710 d – single experiment at pH 7, 20°C	710 d – single experiment at pH 7, 20 °C
Soil half-life	120 d – 90% confidence bound on the mean of 7 values from 5 studies	46 d – 90% confidence bound on the mean of 7 values from 5 studies

* Aquatic whole system

** Anaerobic aquatic whole system

*** The ecological residue definition was parent compound only; however, no ecological modelling was required because the screening level RQs for aquatic organisms did not exceed the LOC.

Table 14 Level 1 estimated environmental concentrations of combined residue of metamitron, desamino-metamitron, M1, and M2 in potential sources of drinking water as the parent equivalent

Use pattern	Groundwater (µg a.i./L)		Surface water (µg a.i./L)		
	Acute ¹	Chronic ²	Daily ³	Yearly ⁴	Overall ⁵
Two (2) applications of 504 g a.i./ha at a 5-d interval	85	74	49	8.2	3.6

¹ Peak concentration

² Post-breakthrough average concentrations

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

⁴ 90th percentile of yearly average concentrations

⁵ Average of all yearly average concentrations

Table 15 Integrated food residue chemistry summary

Nature of the residue in apples		PMRA# 3303029, 3303030 and 3303031
Radiolabel position	[phenyl-U- ¹⁴ C]metamitron (specific activity: 0.999 MBq/mg) and [triazine-5,6- ¹⁴ C]metamitron (specific activity: 1.043–1.075 MBq/mg)	
Treatment		
Test site	Grown in pots or lysimeters containing 2–3 apple trees placed in an outdoor area, entirely covered by a plastic tent during application and moved under a roof for protection against rain, frost or hail.	
Treatment	For each radiolabel, there were 2 different treatments and both consisted of two foliar applications to apple trees using a hand-held pump sprayer at BBCH 70–72 with a 7-d retreatment interval.	
Total rate	<p>[phenyl-U-¹⁴C]metamitron-label: Treatment 1: 0.240–0.250 kg a.i./ha + 0.259–0.516 kg a.i./ha; Total rate of 0.498–0.516 kg a.i./ha Treatment 2: 0.108–0.277 kg a.i./ha + 0.301–0.320 kg a.i./ha; Total rate of 0.428–0.578 kg a.i./ha</p> <p>[¹⁴C- triazine-5,6-¹⁴C]metamitron-label: Treatment 1: 0.333–0.342 kg a.i./ha + 0.340–0.356 kg a.i./ha; Total rate of 0.675–0.695 kg a.i./ha Treatment 2: 0.443–0.505 kg a.i./ha + 0.468–0.505 kg a.i./ha; Total rate of 0.948–0.973 kg a.i./ha</p>	
Formulation	Soluble granule (SG) formulation of metamitron.	
Harvest	Apples were harvested at PHIs of 1, 29/30, 60, and 90 d (at maturity).	

Extraction solvents	<p>[phenyl-U-¹⁴C]metamitron-label: Subsamples of rinsed apple from each tree were extracted three times with acetonitrile (ACN):water (80:20, v/v) by homogenization, and the extracts were combined. An aliquot of the extract was concentrated to remove ACN, and the aqueous remainder was partitioned three times with dichloromethane. The non-extractable residues (NERs) were subjected to accelerated solvent extraction with ACN:water (80:20, v/v) for 15 minutes at 100°C.</p> <p>[¹⁴C- triazine-5,6-¹⁴C]metamitron-label: Samples of rinsed apple from each treatment and all PHIs were extracted three times with ACN:water (80:20, v/v) by homogenization. Each extract was isolated by centrifugation and filtered. The residual solids were extracted with ACN:water (20:80, v/v), and then mixed with diatomaceous earth. They were then subjected to two cycles of accelerated solvent extraction with ACN:water (80:20, v/v) for 15 minutes at 100 °C.</p>				
	Matrices	PHI (days)	[phenyl-U- ¹⁴ C]metamitron		[triazine-5,6- ¹⁴ C]metamitron
TRR (ppm)			TRR (ppm)		
		Treatment 1	Treatment 2	Treatment 1	Treatment 2
Apples	1	4.71	6.82	4.91	7.95
	29/30	2.04	2.93	1.10	3.96
	60	1.90	2.48	0.489	1.51
	90	1.25	2.10	0.434	0.978
Summary of major identified metabolites in plant matrices					
Radiolabel position		[phenyl-U- ¹⁴ C]metamitron		[triazine-5,6- ¹⁴ C]metamitron	
Metabolites identified		Major metabolites			
Apples		Metamitron; desamino-metamitron		Metamitron; desamino-metamitron; MTM-203-DAHM (90-d PHI) MTM-237-3C3O (30, 60, 90-d PHI)	

	desamino-metamitron-N-glycoside								
Strawberries	Metamitron and desamino-metamitron	0, 3, 6, and 12 months	-18	12.1					
Sugar beet leaves	Metamitron and desamino-metamitron	0, 1, 3, 6, 12, 18, and 24 months	-20	24					
Sugar beet roots	Metamitron and desamino-metamitron	0, 1, 3, 6, 12, 18, and 24 months	-20						
Crop field trials and residue decline on apples and pears			PMRA# 3305206						
Crop field trials were conducted in 2017 in Canada and the United States. Trials were conducted in North American growing regions 1 (3 trials), 2 (1 trial), 5 (5 trials), 9 (1 trial), 10 (1 trial), and 11 (4 trials) for a total of 15 trials on apples. Trials were conducted in North American growing regions 1 (1 trial), 5 (3 trials), 10 (2 trials), and 11 (3 trials) for a total of 9 trials on pears. ADA 46343 (15% w/w metamitron, equivalent to 150 g a.i./kg, formulated as SG) was applied twice as foliar broadcast sprays at a rate of 551–581 g a.i./ha/application at growth stage BBCH 71–72 for a seasonal application rate of 1.11–1.15 kg a.i./ha. The applications were made at 5- to 7-d intervals with the last application ranging from 86 to 136 d for apples and 73 to 117 d for pears (normal crop maturity).									
Crop	Total application rate (kg a.i./ha)	PHI (days)	Analyte	Residue levels (ppm)					
				n	LAFT ¹	HAFT ¹	Median ¹	Mean ¹	SDEV ¹
Apples	1.11–1.15	86-136	Metamitron	15	< 0.010	< 0.010	< 0.010	< 0.010	0.010
Pears	1.11–1.14	73-117	Metamitron	9	< 0.010	< 0.010	< 0.010	< 0.010	0.010
n = number of independent trials, LAFT = Lowest Average Field Trial, HAFT = Highest Average Field Trial, SDEV = Standard Deviation									
¹ Based on per-trial averages; For computation, values < LOQ are assumed to be at the LOQ.									
Processed food and feed - Apples			PMRA# 3305206						
A processing study was conducted using ADA 46343 or AG-M4-150 SG2 (SG formulation of metamitron [guarantee: 15%, equivalent to 150 g a.i./kg]) with 2 applications of 1.13–1.14 kg a.i./ha for a total rate of 2.28 kg a.i./ha (2.3× the proposed Good Agricultural Practice [GAP] for the area West of the Canadian Rockies and 3.4× the proposed GAP for the area East of the Canadian Rockies). The maximum theoretical concentration factor of 5× was not used due to phytotoxicity. Adequate storage stability data are available on diverse crop types to support the storage intervals of the apple processed fractions. Samples were analyzed using a validated analytical method.									

RAC	Processed fractions	HAFT _[RAC] (ppm)	Median processing factor of metamitron	Anticipated residues of metamitron (ppm)
Apples	Apple juice	0.01	NC	-
	Apple wet pomace		NC	-
	Apple dry pomace		> 2.3×	0.023
	Applesauce		NC	-

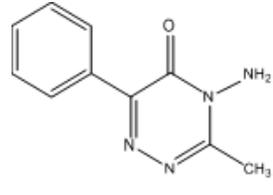
NC = not calculated (residues were below the LOQ in the RAC and processed fraction), RAC = raw agricultural commodity

Table 16 Food residue chemistry overview of metabolism studies and risk assessment

Plant studies			
Residue definition for enforcement		Metamitron	
Primary crops (apples, pears)			
Residue definition for risk assessment		Metamitron + desamino-metamitron (expressed as parent equivalents)	
Primary crops (apples, pears)			
Metabolic profile in diverse crops		The profile in diverse crops cannot be determined, because only pome fruit (apples) was investigated.	
Dietary risk from food and drinking water			
Basic acute dietary exposure analysis, 95th percentile ARfD = 0.1 mg/kg bw Estimated acute drinking water concentration = 0.085 ppm	Population	Estimated risk % of ARfD	
		Food alone	Food and drinking water
	All infants <1 year	0.32	15.58
	Children 1–2 years	0.47	6.61
	Children 3–5 years	0.29	5.24
	Children 6–12 years	0.12	4.08
	Youth 13–19 years	0.05	3.81
	Adults 20–49 years	0.04	4.44
	Adults 50+ years	0.03	3.86
	Females 13-49 years	0.04	4.48
Total population	0.08	4.55	
Basic chronic dietary exposure analysis ADI = 0.04 mg/kg	Population	Estimated risk % of ADI	
		Food alone	Food and drinking water
	All infants <1 year	0.2	14.1

bw/day Estimated chronic drinking water concentration = 0.074 ppm	Children 1–2 years	0.3	5.5
	Children 3–5 years	0.2	4.4
	Children 6–12 years	0.1	3.2
	Youth 13–19 years	0.0	2.7
	Adults 20–49 years	0.0	3.7
	Adults 50+ years	0.0	3.6
	Females 13-49 years	0.0	3.7
	Total population	0.0	3.8

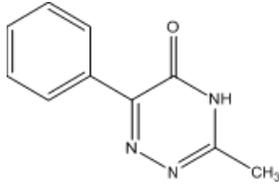
Table 17 Transformation products of metamitron in the environment

Record of transformation products				
Parent compound – Metamitron IUPAC: 4-Amino-4,5-dihydro-3-methyl-6-phenyl-1,2,4-triazin-5-one CAS: 4-Amino-3-methyl-6-phenyl-1,2,4-triazin-5(4H)-one CAS No.: 41394-05-2 Formula: C ₁₀ H ₁₀ N ₄ O MW: 202.22 g/mol SMILES: c1ccccc1C2=NN=C(C)N(N)C2(=O)				
<p>Metamitron degrades rapidly via aqueous photolysis (half-life = 0.037 d, adjusted to summer light and 40°N) and more slowly via soil photolysis (half-life = 40 d). Metamitron also degrades rapidly under anaerobic aquatic conditions with DT₅₀ values of 3.7–6.1 and 4.2–4.7 d for sandy and loam sediments. Metamitron is considered hydrolytically persistent at pH 7 (half-life = 158 d at 20°C) but hydrolyzes rapidly under alkaline conditions, pH 9 (half-life = 5.7 d at 20°C). Metamitron is a highly water-soluble chemical (up to 1680 mg/L). Metamitron is classified as mobile with a K_{oc} of 53 L/kg. Unextracted residues (URs) formed up to ~50% in various environmental fate studies. The environmental fate studies used solvents with a wide range of dielectric constants to conclude that the URs are strongly bound to soil and sediment. The major metabolite, desamino-metamitron, degrades slowly in aerobic soil conditions (half-life = 43 d).</p> <p>Based on fate information and the screening level ecological risk assessment, the ecological residue definition included the parent compound, metamitron, only. However, no refinements were required for the aquatic risk assessment such as drift or ecological modelling because the screening level RQs for aquatic organisms did not exceed the LOC for parent compound or transformation products (TPs).</p>				
Study type	PMRA# and MRID	Study condition	Maximum %AR (day)	Final %AR (study length)
Aerobic soil metabolism	3304620 51173777	100-d study	91.7% (d 0)	9.3% (d 100)
	3304602	120-d study	93% (d 0)	15.8% (d 120)
	3304625 51173784	120-d study	BI soil 89.2% (d 0) 2.1 soil 92.5% (d 0) 2.2 soil	BI soil 15.3% (d 120) 2.1 soil 0% (d 120) 2.2 soil

			93.8% (d 0) 6S soil 91.7% (d 0)	1.3% (d 120) 6S soil 1.4% (d 120)
Anaerobic soil metabolism	3304627 51173786	120-d study (with aerobic conditions for 14 d first and then anaerobic phase for 120 d) TZ- and BE-labels	LUFA 2.2 Anaerobic phase total system (TZ-label): 66.7% (d 3) LUFA 2.2 Anaerobic phase total system (BE-label): 23.8% (d 3)	LUFA 2.2 Anaerobic phase total system (TZ-label): 1.6% (d 120) LUFA 2.2 Anaerobic phase total system (BE-label): 2.4% (d 120)
	3304628 51173787	120-d anaerobic after initial 29-d aerobic BE-label	California total system 49.6% (d 50) Illinois total system 81.9% (d 32) North Dakota total system 64.3% (d 32)	California total system 24.3% (d 149) Illinois total system 58.1% (d 149) North Dakota total system 40.7% (d 149)
	3304629 51173788	120-d anaerobic after initial 29-d aerobic TZ-label	California total system 24% (d 44) Illinois total system 66.2% (d 31) North Dakota total system 72.7% (d 32)	California total system 6.3% (d 150) Illinois total system 34.3% (d 150) North Dakota total system 51.4% (d 150)
Soil phototransformation	3304613 51173789	21-d study	96.8 % (d 0)	75.7% (d 21)
	3304614 51173790	14.9-d study Moist and dry conditions, LUFA 2.3 soil BE-label	Irradiated and dry 98.5% (d 0) Irradiated and moist 97.2% (d 0)	Irradiated and dry 78.2% (d 14.9) Irradiated and moist 2.3% (d 14.9)
	3304615 51173811	2-d study	Irradiated 100.8% (d 0)	Irradiated Not detected (d 2)
Aqueous	3304616	pH 5, 7, 9, or pure	100% (pH 5, d 0)	0% (pH 5, 40 minutes)

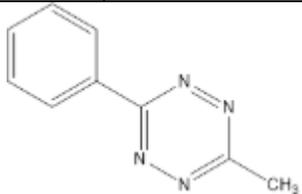
photolysis	51173812	water up to 18 hrs	100% (pH 7, d 0) 100% (pH 9, d 0) 100% (pure water, d 0)	0% (pH 7, 18 hrs) 0% (pH 9, 9 hrs) 0% (pure water, 60 minutes)
	3304617 51173813	Buffered water at pH 7 or natural pond water 354-hr study	Buffer water 100% (hr 0) Pond water 100% (hr 0)	Buffer water < LOD (hr 354) Pond water < LOD (hr 354)
Aerobic aquatic metabolism	3304631 51173818	100-d study	Waldwinkel total system 108% (d 0) Ruchkhaltebecken total system 110% (d 0)	Waldwinkel total system < 2% (d 100) Ruchkhaltebecken total system < 2% (d 100)
	3304632 51173819	100-d study	1WS Pfalz total system 93.9% (d 0) 2WS Humsterbach total system 99.8% (d 0)	1WS Pfalz total system 3.3% (d 100) 2WS Humsterbach total system 0% (d 100)
	3304634 51173823	100-d study	Fürwigge (non-sterile) total system 102.4% (d 0) Schwarzes Wasser (non- sterile) total system 101.8 % (d 0)	Fürwigge (non-sterile) total system 9.5% (d 100) Schwarzes Wasser (non-sterile) total system 21.4% (d 100)
	3304630 51173817	61-d study Water only	9.8 µg/L TZ-label 92.6% (d 0) 99 µg/L TZ-label 94.8% (d 0) 9.8 µg/L BE-label 100.1% (d 0) 99 µg/L BE-label 93.4% (d 0)	9.8 µg/L TZ-label 9.1% (d 61) 99 µg/L TZ-label 4.2% (d 61) 9.8 µg/L BE-label 20.8% (d 61) 99 µg/L BE-label 5.8% (d 61)

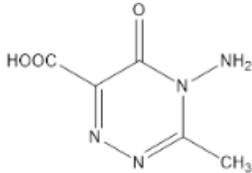
Anaerobic aquatic metabolism	3304636 51173820	100-d study	Lake location total system 95.8% (d 0) River location total system 98.2% (d 0)	Lake location total system < LOD (d 100) River location total system < LOD (d 100)
	3304637 51173821	100-d study	Lake location total system 93.4% (d 0) River location total system 96.5% (d 0)	Lake location total system < LOD (d 0) River location total system < LOD (d 100)
Hydrolysis	3304609 51173807	pH 4, 7, and 9 (20, 25, and 50 °C), only 20 °C and 25 °C reported.	20 °C 103% (pH 4, d 0) 103% (pH 7, d 0) 101% (pH 9, d 0) 25 °C 103% (pH 4, d 0) 103% (pH 7, d 0) 101% (pH 9, d 0)	20 °C 92.8% (pH 4, d 30) 92.2% (pH 7, d 30) < LOD (pH 9, d 30) 25 °C 90.7% (pH 4, d 30) 85% (pH 7, d 30) < LOD (pH 9, d 30)
	3304612 51173810	30-d study (results listed up to 10 d)	25 °C 99% (pH 9, d 0)	25 °C 40% (pH 9, d 30)
Field studies	3304650	365-d study in Washington and New York	Washington 100% (0 d after second application) New York 100% (0 d after second application)	Washington 0% (180 d after second application) New York 0.4% (365 d after second application)
Koc	PMRA# 3304645; MRID 51173803 [phenyl-UL- ¹⁴ C]metamitron K _F and K _{FOC} were 0.258 and 143.1, respectively. PMRA# 3304639; MRID 51173796 [phenyl-UL- ¹⁴ C]metamitron K _F and K _{FOC} ranged from 0.932 to 1.745 and from 55.99 to 86.25, respectively. PMRA# 3304640; MRID 51173797			

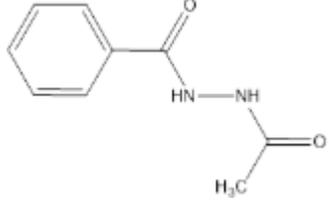
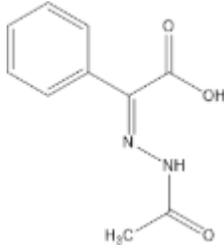
<p>[phenyl-UL-¹⁴C]metamitron K_F and K_{FOC} ranged from 0.364 to 5.943 and from 117 to 396, respectively. PMRA# 3304643 [phenyl-UL-¹⁴C]metamitron K_F and K_{FOC} ranged from 0.53 to 2.45 and from 31.52 to 109, respectively. PMRA# 3304644 (acceptable with limitations); MRID 51173802 [phenyl-UL-¹⁴C]metamitron K_F and K_{FOC} ranged from 0.657 to 2.294 and from 75.84 to 199.5, respectively.</p>					
<p>MAJOR (> 10%) TP – Desamino-metamitron (MH 1) IUPAC: 3-Methyl-6-phenyl-1,2,4-triazin-5(4H)-one CAS No.: 36993-94-9 Formula: C₁₀H₉N₃O MW: 187.2 g/mol SMILES: O=C1NC(C)=NN=C1C2=CC=CC=C2 Other names: DA-metamitron, DRW 1314</p>					
Study type	PMRA# and MRID	Study condition	Maximum %AR (day)	Final %AR (study length)	PMRA comment
Aerobic soil metabolism	3304601 51173779	Loamy sand	7.6% (28 d)	7.6% (56 d)	Formed as a major TP. Relevant system for run off and leaching. High levels of TPs occurring at study termination in many soils.
		Silt loam	9.2% (7 d)	9.2% (7 d)	
	3304602 51173780	Silt	17.1% (30 d)	15.4% (120 d)	Notes: Aerobic soil
	3304604 51173782	Sandy loam	11.3% (14 d)	4.8% (120 d)	PMRA# 3304623 – Limitations, no degradation pathway could be determined.
	3304625 51173784	Silt loam	10.3% (59 d)	10.3% (120 d)	PMRA# 3304624 – Study with TP resulted in complete mineralization to CO ₂ .
	3304620 51173777	Loamy sand	11.2% (30 d)	7.1% (100 d)	PMRA# 3304626 – Open literature review to identify degradation route in an isotope soil microcosm study. Not used

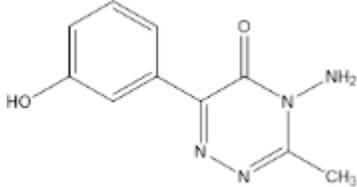
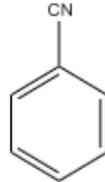
					for record of transformation table.
Anaerobic soil metabolism	3304627 51173786	Loamy sand Anaerobic phase	13.3% (120 d)	13.3% (120 d)	Formed as a major TP in multiple soils, and increasing at study termination.
	3304628 (BE-label) 51173787	Sandy loam Total system	26.2% (32 d)	19% (149 d)	
		Silt loam Total system	5.8% (30 d)	4.4% (149 d)	
		Sandy loam Total system	10.3% (150 d)	10.3% (150 d)	
	3304629 (TZ-label) 51173788	Loamy sand Total system	21.8% (150 d)	21.8% (150 d)	
		Silt loam Total system	50.8% (88 d)	25% (150 d)	
		Sandy loam Total system	10.4% (44 d)	7.2% (150 d)	
Soil phototransformation	3304613 51173789	Irradiated and dry	9.8% (14.9 d)	9.8% (14.9 d)	Formed as a major TP. Relevant system for run off and leaching.
		Non-irradiated and dry	4.7% (21 d)	4.7% (21 d)	
	3304614 51173790	Irradiated and moist	56.4% (14.9 d)	56.4% (14.9 d)	
Aqueous photolysis	3304615 (aqueous photolysis) 51173811	Irradiated	92.3% (2 d)	92.3% (2 d)	Formed as a major TP. Relevant system. Relevant for Surface Water.
	3304617 51173813	Sterile, pH 7	93.2% (0.05 d)	40.4% (14.75 d)	Formed as a major TP. Relevant system. Relevant for Surface Water.
		Natural pond water	81.5% (0.13 d)	8.1% (14.75 d)	

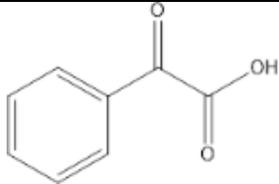
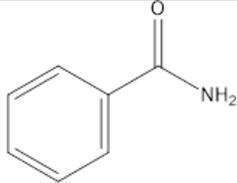
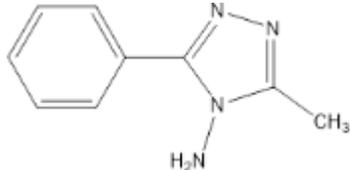
	3304616 51173812	pH 7	94.4% (6 hrs)	86.6% (18 hrs)	
		Pure water	87.2% (60 minutes)	87.2% (60 minutes)	
Aerobic aquatic metabolism	3304630 51173817	Surface water 100 µg/L, TZ- label	12.1% (61 d)	12.1% (61 d)	Formed as a major TP. Maximum formation at study termination in some systems. Relevant system for run off and leaching.
	3304631 51173818	Water:sediment (pH 7.04)	76.0% (58 d)	68% (100 d)	
		Water:sediment (pH 7.7)	79.0% (58 d)	72.0% (100 d)	
	3304632 51173819	Pond water: sandy clay loam	58.8% (59 d)	33% (100 d)	
		Creek water: silt loam	71.2% (30 d)	45.4% (100 d)	
	3304634 51173823	Water:sediment (pH 6.0)	15.7% (100 d)	15.7% (100 d)	
		Water:sediment (pH 6.1)	37.9% (100 d)	37.9% (100 d)	
Anaerobic aquatic metabolism	3304636 51173820	Lake water total system:loamy sand	81.3% (60 d)	75.2% (100 d)	Formed as a major TP. Maximum formation at study termination in some systems. Anaerobic system not as relevant.
		River water total system: loam	79.4% (100 d)	79.4% (100 d)	
	3304637 51173821	Lake water: loamy sand	72.6% (22 d)	71.6% (100 d)	
		River water:silt loam	77.5% (61 d)	70.5% (61 d)	

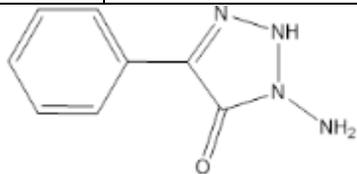
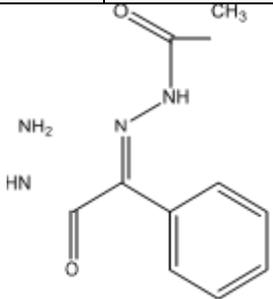
Hydrolysis	3304609 51173807	pH 4, 20°C	3.2% (14 d)	3.2% (14 d)	Not formed as a major TP.
		pH 4, 25°C	3.2% (14 d)	3.2% (14 d)	
		pH 4, 50°C	2.9% (14 d)	2.9% (14 d)	
		pH 7, 20°C	2.4% (14 d)	1.1% (30 d)	
		pH 7, 25°C	2.6% (14 d)	1.5% (30 d)	
		pH 7, 50°C	2.0% (0.25 d)	ND (30 d)	
		pH 9, 20°C	1.6% (1 d)	ND (30 d)	
		pH 9, 25°C	1.4% (0.083 d)	0.5% (30 d)	
		pH 9, 50°C	1.3% (0.083 d)	ND (30 d)	
Aerobic soil metabolism	3304601 51173779	Loamy sand	7.6% (56 d)	5.9% (100 d)	Not formed as a major TP.
		Silt loam	9.2% (7 d)	3.1% (100 d)	
Field studies	3304650	Formed in field studies, but less than 10%.			
Koc	3304646	[phenyl-UL- ¹⁴ C]desamino-metamitron K _F and K _{FOC} ranged from 0.802 to 2.974 and from 71.94 to 136, respectively.		Mobile	
MAJOR (> 10%) TP – MH5; MTM- 172-MPT IUPAC: 3-Methyl-6-phenyl-1,2,4,5-tetrazine CAS No.: 38634-12-7 Formula: C ₉ H ₈ N ₄ MW: 172.2 g/mol SMILES: CC(N=N1)=NN=C1C2=CC=CC=C2					

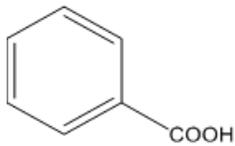
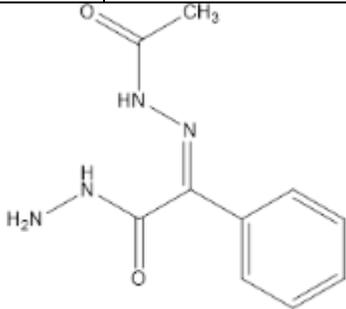
Study type	PMRA# and MRID	Study condition	Maximum %AR (day)	Final %AR (study length)	PMRA comment
Aerobic aquatic metabolism	3304630 51173817	Surface water (10 µg/L)	1.6% (7 d)	ND (61 d)	Formed as a major TP at higher application rate. Considered relevant. Although there is no sediment, based on the solubility of the parent compound and depth of water in many water bodies, it is plausible to have formation of 3-methyl-6-phenyl-1,2,4,5-tetrazine in the environment.
		Surface water (100 µg/L)	13.6% (61 d)	13.6% (61 d)	
Anaerobic aquatic metabolism	3304636 51173820	Lake water: loamy sand	9.9% (2 d)	1.0% (100 d)	Not formed as a major TP and declined by study termination. Not considered relevant system.
	3304637 51173821	River water: loam	5.8% (22 d)	< LOD (100 d)	
Hydrolysis	3304609 51173807	pH 7, 20°C	2.5% (30 d)	2.5% (30 d)	Only formed at high levels at very high temperatures; therefore, not considered relevant in the environment.
		pH 7, 25°C	5.7% (30 d)	5.7% (30 d)	
		pH 7, 50°C	19.9% (7 d)	5.1% (30 d)	
		pH 9, 20°C	5.0% (30 d)	5.0% (30 d)	
		pH 9, 25°C	6.1% (14 d)	5.9% (30 d)	
		pH 9, 50°C	9.9% (2 d)	< LOD (30 d)	
MAJOR (> 10%) TP – 4-Amino-3-methyl-5-oxo-4,5-dihydro-1,2,4-triazine-6-carboxylic acid IUPAC: 4-Amino-3-methyl-5-oxo-4,5-dihydro-1,2,4-triazine- 6-carboxylic acid CAS No.: 2168393-43-7 Formula: C ₅ H ₆ N ₄ O ₃ MW: 170.13 g/mol SMILES: O=C1N(N)C(C)=NN=C1C(O)=O					

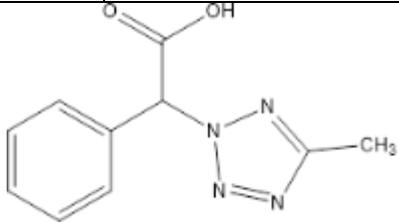
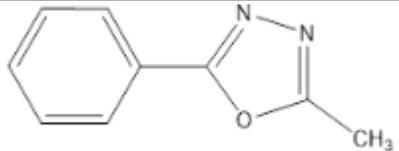
Study type	PMRA# and MRID	Study condition	Maximum %AR (day)	Final %AR (study length)	PMRA comment
Anaerobic soil metabolism	3304629 51173788	Loamy sand	10.8% (3 d)	ND (150 d)	Not formed as a major TP and declined by study termination. Not considered relevant system.
MAJOR (> 10%) TP – MTM-178-HD (M4) IUPAC: N-acetylbenzohydrazide CAS No.: 14331-27-2 Formula: C ₉ H ₁₀ N ₂ O ₂ MW: 178.2 g/mol SMILES: O=C(NNC(C)=O)C1=CC=CC=C1					
Study type	PMRA# and MRID	Study condition	Maximum %AR (day)	Final %AR (study length)	PMRA comment
Aqueous photolysis	3304617 51173813	Sterile water, pH 7	2.6% (0.05 d)	1.9% (14.75 d)	Major TP and declining by study termination.
		Natural pond water	10.0% (0.25 d)	4.2% (14.75 d)	
MAJOR (> 10%) TP – M2 IUPAC: 2-(Acetylhydrazineylidene)-2-phenylacetic acid CAS No.: 80238-38-6 Formula: C ₁₀ H ₁₀ N ₂ O ₃ MW: 206.2 g/mol SMILES: OC(/C(C1=CC=CC=C1)=N\NC(C)=O)=O NOTE: USEPA using EPI Suite* to determine K _{oc} *EPI (Estimation Programs Interface) Suite is a suite of physical/chemical property and environmental fate estimation programs.					
Study type	PMRA# and MRID	Study condition	Maximum %AR (day)	Final %AR (study length)	PMRA comment
Aerobic aquatic metabolism	3304630 51173817	Surface water (10 µg/L)	18.8% (61 d)	18.8% (61 d)	Formed as a major TP at higher application rate. Considered relevant. Although there is no sediment, based on the solubility

		Surface water (100 µg/L)	24.3% (61 d)	24.3% (61 d)	of the parent compound and depth of water in many water bodies, it is plausible to have formation of M2 in the environment.
MAJOR (> 10%) TP – M3 IUPAC: 4-Amino-6-(3-hydroxyphenyl)-3-methyl-1,2,4-triazin-5(4H)-one Formula: C ₁₀ H ₁₀ N ₄ O ₂ MW: 218.2 g/mol SMILES: O=C1N(N)C(C)=NN=C1C2=CC(O)=CC=C2					
Study type	PMRA# and MRID	Study condition	Maximum %AR (day)	Final %AR (study length)	PMRA comment
Aerobic Aquatic Metabolism	3304630 51173817	Surface water (10 µg/L)	20.3% (30 d)	19.6% (61 d)	Formed as a major TP at higher application rate. Considered relevant. Although there is no sediment, based on the solubility of the parent compound and depth of water in many water bodies, it is plausible to have formation of M3 in the environment.
		Surface water (100 µg/L)	16.9% (61 d)	16.9% (61 d)	
MAJOR (> 10%) TP – Benzonitrile IUPAC: Benzonitrile CAS No.: 100-47-0 Formula: C ₇ H ₅ N MW: 103.1 g/mol SMILES: N#CC1=CC=CC=C1					
Study type	PMRA# and MRID	Study condition	Maximum %AR (day)	Final %AR (study length)	PMRA comment
Hydrolysis	3304609 51173807	pH 7, 50°C	28.1% (30 d)	28.1% (30 d)	Formed as major TPs under high temperatures and/or high pH. Not considered as relevant in the environment.
		pH 9, 20°C	27.9% (30 d)	27.9% (30 d)	
		pH 9, 25°C	28.4% (30 d)	28.4% (30 d)	
		pH 9, 50°C	32.9% (14 d)	30.2% (30 d)	

MAJOR (> 10%) TP – Phenylglyoxylic acid (MH6) IUPAC: 2-Oxo-2-phenylacetic acid CAS No.: 611-73-4 Formula: C ₈ H ₆ O ₃ MW: 150.1 g/mol SMILES: O=C(C(O)=O)C1=CC=CC=C1					
Study type	PMRA# and MRID	Study condition	Maximum %AR (day)	Final %AR (study length)	PMRA comment
Hydrolysis	3304609 51173807	pH 4, 50°C	24.0% (30 d)	24.0% (30 d)	Formed as major TPs under high temperatures and/or high pH. Not considered as relevant in the environment.
		pH 9, 20°C	26.9% (14 d)	13.9% (30 d)	
		pH 9, 25°C	28.5% (7 d)	6.8% (30 d)	
		pH 9, 50°C	25.7% (1 d)	ND (30 d)	
MAJOR (> 10%) TP – MH7a IUPAC: Benzamide CAS No.: 55-21-0 Formula: C ₇ H ₇ NO MW: 121.1 g/mol SMILES: NC(C1=CC=CC=C1)=O					
Study type	PMRA# and MRID	Study condition	Maximum %AR (day)	Final %AR (study length)	PMRA comment
Hydrolysis	3304609 51173807	pH 4, 50°C	15% (21 d)	15% (21 d)	Formed as major TPs under high temperatures and/or high pH. Not considered as relevant in the environment.
		pH 7, 20°C	0.9% (14 d)	ND (30 d)	
MAJOR (> 10%) TP – MH7b (MTM-174-AM) CAS No.: 38345-25-4 IUPAC: 3-Methyl-5-phenyl-4H-1,2,4-triazol-4-amine Formula: C ₉ H ₁₀ N ₄ MW: 174.2 g/mol SMILES: CC1=NN=C(N1N)C2=CC=CC=C2					

Study type	PMRA# and MRID	Study condition	Maximum %AR (day)	Final %AR (study length)	PMRA comment
Hydrolysis	3304609 51173807	pH 7, 50°C	32.5% (30 d)	32.5% (30 d)	Formed as major TPs under high temperatures and/or high pH. Not considered as relevant in the environment
		pH 9, 20°C	3.7% (30 d)	3.7% (30 d)	
MAJOR (> 10%) TP – MH7c IUPAC: 3-Amino-5-phenyl-2,3- dihydro-4H-1,2,3-triazol-4-one Formula: C ₈ H ₈ N ₄ O MW: 176.2 g/mol SMILES: NN1C(C(C2=CC=CC=C2)=NN1)=O					
Study type	PMRA# and MRID	Study condition	Maximum %AR (day)	Final %AR (study length)	PMRA comment
Hydrolysis	3304609 51173807	pH 9, 25°C	3.8% (2 d)	3.6% (30 d)	Formed as major TPs under high temperatures and/or high pH. Not considered as relevant in the environment
		pH 9, 50°C	14.2% (30 d)	14.2% (30 d)	
MAJOR (> 10%) TP – MH11 (MTM-220E-HH) (E isomer of MH2) IUPAC: (2E)-(2-acetylhydrazineylidene)-2-phenylacetohydrazide CAS No.: 56735-29-6 Formula: C ₁₀ H ₁₂ N ₄ O ₂ MW: 220.2 g/mol SMILES: O=C(NN)/C(C1=CC=CC=C1)=N/N C(C)=O E isomer					
Study type	PMRA# and MRID	Study condition	Maximum %AR (day)	Final %AR (study length)	PMRA comment
Hydrolysis	3304609 51173807	pH 4, 50°C	17.5% (30 d)	17.5% (30 d)	Formed as major TPs under high temperatures and/or high pH. Not considered as relevant in the environment.
		pH 7, 25°C	2.0% (30 d)	2.0% (30 d)	
		pH 7, 50°C	4.1% (21 d)	ND (30 d)	

MAJOR (> 10%) TP – Benzoic acid (MH12) IUPAC: Benzoic acid CAS No.: 65-85-0 Formula: C ₇ H ₆ O ₂ MW: 122.1 g/mol SMILES: O=C(O)c1ccccc1					
Study type	PMRA# and MRID	Study condition	Maximum %AR (day)	Final %AR (study length)	PMRA comment
Hydrolysis	3304609 51173807	pH 7, 50°C	21.9% (30 d)	21.9% (30 d)	Formed as major TPs under high temperatures and/or high pH. Not considered as relevant in the environment.
		pH 9, 20 °C	48.5% (30 d)	48.5% (30 d)	
		pH 9, 25°C	53.6% (30 d)	53.6% (30 d)	
		pH 9, 50°C	50.8% (30 d)	50.8% (30 d)	
Aqueous Photolysis	3304617 51173813	Sterile water, pH 7	10.8% (14.75 d)	10.8% (14.75 d)	Major TP formed at study termination.
		Natural pond water	49.4% (14.75 d)	49.4% (14.75 d)	
MINOR (< 10%) TP – MTM-220Z-HH (MH2) (Z-isomer of MH11) IUPAC: (2Z)-(2-acetylhydra zineylidene)-2- phenylacetohydrazide CAS No.: 62191-12-2 Formula: C ₁₀ H ₁₂ N ₄ O ₂ MW: 220.2 g/mol SMILES: O=C(NN)/C(C1=CC=CC=C1)=N\N C(C)=O Z isomer					
Study type	PMRA# and MRID	Study condition	Maximum %AR (day)	Final %AR (study length)	PMRA comment
Hydrolysis	3304609 51173807	pH 7, 20°C	7.0% (21 d)	6.0% (30 d)	Not a major TP under extreme temperatures.
		pH 7, 25°C	6.8% (21 d)	5.3% (30 d)	
		pH 7, 50°C	7.2% (2 d)	ND (30 d)	

		pH 9, 20°C	6.7% (21 d)	2.6% (30 d)	
		pH 9, 25°C	5.2% (1 d)	2.1% (30 d)	
		pH 9, 50°C	3.7% (1 d)	ND (30 d)	
MINOR (< 10%) TP – MTM-218-5MT (MH4) IUPAC: 2-(5-Methyl-2H-tetrazol- 2-yl)-2-phenylacetic acid Formula: C ₁₀ H ₁₀ N ₄ O ₂ MW: 218.2 g/mol SMILES: O=C(O)C(N1N=NC(C)=N1)C2=CC=CC=C2					
Study type	PMRA# and MRID	Study condition	Maximum %AR (day)	Final %AR (study length)	PMRA comment
Hydrolysis	3304609 51173807	pH 7, 20°C	1.0% (21 d)	ND (30 d)	Not a major TP under extreme temperatures.
		pH 7, 25°C	2.1% (30 d)	2.1% (30 d)	
		pH 7, 50°C	8.0% (30 d)	8.0% (30 d)	
		pH 9, 20°C	5.9% (30 d)	5.9% (30 d)	
		pH 9, 25°C	8.8% (30 d)	8.8% (30 d)	
		pH 9, 50°C	9.1% (14 d)	7.8% (30 d)	
MINOR (< 10%) TP – MTM-160-2MPO (MH10) IUPAC: 2-Methyl-5-phenyl-1,3,4-oxadiazole CAS No.: 4046-03-1 Formula: C ₉ H ₈ N ₂ O MW: 160.2 g/mol SMILES: CC1=NN=C(O1)C2=CC=CC=C2					
Study type	PMRA# and MRID	Study condition	Maximum %AR (day)	Final %AR (study length)	PMRA comment
Hydrolysis	3304609 51173807	pH 9, 25°C	2.7% (30 d)	2.7% (30 d)	Not a major TP under extreme temperatures.
		pH 9, 50°C	3.4% (1 d)	2.1% (30 d)	

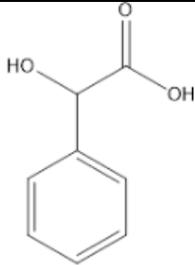
MINOR (< 10%) TP – Mandelic acid (MH14) IUPAC: 2-Hydroxy-2- phenylacetic acid CAS No.: 90-64-2 Formula: C ₈ H ₈ O ₃ MW: 152.2 g/mol SMILES: OC(C(O)=O)C1=CC=CC=C1					
Study type	PMRA# and MRID	Study condition	Maximum %AR (day)	Final %AR (study length)	PMRA comment
Hydrolysis	3304609 51173807	pH 9, 50°C	2.4% (0.25 d)	ND (30 d)	Not a major TP under extreme temperatures.

Table 18 Summary of abiotic transformation

Test substance and study details	Half-lives/DT ₅₀ (days), calculated by the PMRA, unless otherwise stated	Persistence	TP formation (% formation) and non-extractables	PMRA# of study, acceptability, and notes
Hydrolysis				
Unlabelled and labelled metamitron Unlabelled test: 32 mg/L pH 4 at 40°C pH 7 at 40°C pH 9 at 30°C Labelled test: 38.4 mg/L pH 4 at 60°C pH 7 at 60°C pH 9 at 40°C 675 hrs	pH 4: 20°C: 254.9* 25°C: 158.3* 40°C: 47.3 pH 7: 20°C: 450.7* 25°C: 236.9* 40°C: 39.4 pH 9: 20°C: 8.6* 25°C: 4.9* 40°C: 1.0 *estimated	NA	Unidentified substance 6 (17.7% at pH 4) 3-methyl-6-phenyl-1,2,4,5-tetrazine (17.3% at pH 7) 2-methyl-5-phenyl-1,3,4-oxadiazole (18.6% at pH 9) Benzonitrile (25.2% at pH 9) Unidentified substance 4 (18.6% at pH 9)	PMRA# 3304608 Acceptable with limitations Three major TPs were identified, while two additional TPs were not fully identified. A more valuable analysis of TPs has been undertaken (Bloß 2019, PMRA# 3304609).

Test substance and study details	Half-lives/DT ₅₀ (days), calculated by the PMRA, unless otherwise stated	Persistence	TP formation (% formation) and non-extractables	PMRA# of study, acceptability, and notes
Unlabelled metamitron 24.14 mg/L pH 5, 7, and 9 (20–22°C) 61 d	Study author-calculated pH 5: 52.9 pH 7: 41.8 pH 9: 2.1	NA	Not included in study design	PMRA# 3304610 Unacceptable Description of the laboratory methodology was almost non-existent. The test was only performed at one temperature that was poorly controlled, other significant test conditions are poorly controlled or unknown.
Unlabelled metamitron pH 4: 50, 60, 70, and 80°C pH 7: 50, 60, and 70°C pH 9: 30 and 50°C 140 hrs	pH 4: 25°C: 64.3* 50°C: 8.2 60°C: 4.1 70°C: 2.0 80°C: 1.0 pH 7: 25°C: 70.6* 50°C: 4.0, 4.1 60°C: 1.4 70°C: 0.5 pH 9: 25°C: 5.3* 30°C: 2.9 50°C: 0.4, 0.3 *estimated	NA	Not included in study design	PMRA# 3304611 Acceptable for the parent compound Radiolabelling was not part of the study, hence no mass balance can be determined. TPs were not considered. Fate of parent compound can be determined. Based on the solubility and vapour pressure provided in the data evaluation report, losses through volatilization or adsorption to test vessels are expected to be minimal. A more valuable analysis of TPs has been undertaken (Bloß 2019, PMRA# 3304609).
Unlabelled metamitron at 6–7 mg a.i./L, combined with radiolabelled metamitron at 1–1.3 mg	pH 5 (25°C): 140 pH 7 (25°C): 133 pH 9 (25°C): 13.4, 16.6	NA	pH 9: 2H-tetrazole-2-acetic acid (α -phenyl)-5-methyl) (32%) Benzoic acid (11%)	PMRA# 3304612 Acceptable for the purpose of the study, which was to identify TPs at pH 9.

Test substance and study details	Half-lives/DT ₅₀ (days), calculated by the PMRA, unless otherwise stated	Persistence	TP formation (% formation) and non-extractables	PMRA# of study, acceptability, and notes
a.i./L pH 5, 7, and 9 at 25°C 30 d			Benzonitrile (11%)	
Labelled metamitron at 1.0 mg/L pH 4, 7, and 9, at 20, 25, and 50°C 30 d	pH 4: 20°C: 224.3 25°C: 136.7 50°C: 15.2 pH 7: 20°C: 157.6 25°C: 95 50°C: 5.5 pH 9: 20°C: 5.7 25°C: 3.3 50°C: 0.2	NA	pH 4: none pH 7: none pH 9 (25°C): MH3 (benzonitrile) (27.2%) MH6 (phenylglyoxylic acid) (28.5%) MH12 (benzoic acid) (53.6%)	PMRA# 3304609 Acceptable Used for water modelling for Drinking Water and ecological modelling because the experiments included 20°C and pH 7.
Photolysis – Soil				
Radiolabelled metamitron pH 6.24, 0.7% TOC 3.3 kg a.i./ha soil for 357 hrs at 20 ± 2°C in both dry and moist soils (75% moisture) 14.9 d	Dry soil irradiated: 51.2 Half-life equivalent under natural sunlight: 305 (dark control corrected) Moist soil irradiated: 3.98 Half-life equivalent under natural sunlight: 10 (dark control corrected)	Phototransformation on soil is not expected to be a route of transformation	Dry soil Major TPs: No major TPs (desamino-metamitron formed up to 8.6% by study termination) UR: 6.4% at study termination in irradiated samples Moist soil Major TPs: Desamino-metamitron	PMRA# 3304614 Acceptable with limitations Some of the main limitations include the lack of information for the dry soil (in other words, if the soil was very dry prior to adding water, the water may have been drawn into pore spaces and not available on soil surface to be exposed to incoming ultraviolet light), and the decrease in irradiance over the course of the

Test substance and study details	Half-lives/DT ₅₀ (days), calculated by the PMRA, unless otherwise stated	Persistence	TP formation (% formation) and non-extractables	PMRA# of study, acceptability, and notes
			(56.7%) UR: 12.8% in dark 22.6% in irradiated	study. There are also issues with the dark controls and it is unknown if the soil was kept moist. Overall, however, metamitron is stable and these study limitations are not expected to impact the overall study conclusions.
Radiolabelled and non-labelled metamitron pH 5.6, 2.3% TOC 3.5 kg/ha Maximum water holding capacity: 500 g/kg dry mass 21 d	Irradiated: 21.92 Half-life equivalent under natural sunlight: 90.6	Not assessed due to unacceptability of study.	Major TPs: None (desamino-metamitron reached 4.7% at 21 d) UR: 8.4% in dark 14.9% in irradiated	PMRA# 3304613 Unacceptable This study is classified as unacceptable due to several inconsistencies with reported study data and method. As well, in the study report, it appears that the parent compound, TP, and dark control recoveries are reported as a percent of the methanol extraction.
Photolysis – Water				
Radiolabelled and non-labelled metamitron 8.34 µg a.i./mL Natural pond water 25 ± 1°C, pH 7.02 2 d	1.44 hrs Half-life equivalent under natural sunlight: 1.86 hrs	Phototransformation is expected to be an important route of transformation in water for the parent compound.	Major TPs: Desamino-metamitron (92.4% at 2 d)	PMRA# 3304615 Acceptable

Test substance and study details	Half-lives/DT ₅₀ (days), calculated by the PMRA, unless otherwise stated	Persistence	TP formation (% formation) and non-extractables	PMRA# of study, acceptability, and notes
<p>Radiolabelled metamitron and unlabelled desamino-metamitron</p> <p>Three tests conducted using approximately 5 mg/L in pure water with metamitron, and for desamino-metamitron in sterilized water, at pH 5, 7, and 9 and also assessment of indirect photodegradation with humic substance (potassium salt)</p> <p>2 d</p>	<p>Metamitron Pure water (direct): 10.6 minutes pH 5* pH 7* pH 9* *Half-life equivalent under natural sunlight cannot be calculated because irradiance was not measured.</p> <p>Desamino-metamitron Pure water (direct): 435 hrs pH 5: 397 hrs pH 7: 198 hrs pH 9: 48 hrs</p> <p>Desamino-metamitron with humic substance: 23 hrs</p>	<p>Phototransformation is expected to be an important route of transformation in water for the parent compound and slower dissipation for desamino-metamitron. Humic material is expected to enhance transformation</p>	<p>Major TPs from metamitron experiment: Desamino-metamitron (pH 5: 94.8% at 0.5 hrs; pH 7: 91.7% at 12.5 hrs; pH 9: 94.5% at 2.7 hrs)</p>	<p>PMRA# 3304616 Acceptable</p>
<p>Radiolabelled metamitron</p> <p>3.78 mg/L in buffered water at pH 7 and 4.08 mg/L in natural pond water (pH 7)</p> <p>25 °C</p> <p>14 d</p>	<p>Pure water pH 7: 0.142 hrs Half-life equivalent under natural sunlight: 0.142 hrs Natural pond water: 0.487 hrs Half-life equivalent under natural sunlight (pond water): 0.487 hrs</p>	<p>Phototransformation is expected to be an important route of transformation in water for the parent compound.</p>	<p>Pure buffered water Desamino-metamitron (92.8%) Benzoic acid (M6) (10.1%) M8 (14.7%) Natural pond water Desamino-metamitron (80.6%) Benzoic acid (M6)</p>	<p>PMRA# 3304617 Acceptable</p>

Test substance and study details	Half-lives/DT ₅₀ (days), calculated by the PMRA, unless otherwise stated	Persistence	TP formation (% formation) and non-extractables	PMRA# of study, acceptability, and notes
			(42.1%) M4 (MTM-178-HD) (10%) M8 (11.7%)	
Unlabelled metatritron 67 µmol/L pH 5 15 minutes	12.7 minutes (0.209 hrs) Half-life equivalent under natural sunlight: 20.4 minutes (0.340 hrs)	Phototransformation is expected to be an important route of transformation in water for the parent compound.	Desamino-metatritron (up to 50% in 15 minutes)	PMRA# 3304618 Acceptable with limitations This study is considered as supplemental to other available studies on the photodegradation of metatritron, especially PMRA# 3304616, which is cited as a reference in the study. Some of the limitations include the calculation methods and results are no longer considered best practice; there was no LOD or LOQ reported although the described analytical method seems to be sufficient using HPLC-UV method, and some changes in temperature over the course of the study.

Table 19 Summary of biotic transformation

Test substance and study details	Half-lives/DT ₅₀ (days), calculated by the PMRA, unless otherwise stated	Persistence	TP formation (% formation) and non-extractables	PMRA# of study, acceptability, and notes
Terrestrial environments				
Soil biotransformation				
NA	NA	NA	NA	PMRA# 3304622 Results of studies on soil metabolism of metamitron indicated that the metabolite, M3, occurs only in studies where acetone was used as a means of extraction procedure. The purpose of this study was to verify this assumption, and to identify M3 (formed up to 6%) in PMRA# 3304620.
Unlabelled desamino-metamitron Lufa Speyer 2.1 (sand, pH 6.0 ± 0.2, % TOC 0.59 ± 0.04), Lufa Speyer 2.2 (loamy sand, pH 6.1 ± 0.2, % TOC 2.27 ± 0.28), Lufa Speyer 2.3 (sandy loam, pH 6.6 ± 0.1, % TOC 1.24 ± 0.14) 120 d 1 mg/kg soil	<u>DT₅₀</u> : Lufa Speyer 2.1: 53 Lufa Speyer 2.2: 35 Lufa Speyer 2.3: 18.7 Representative half-life: Lufa Speyer 2.1: 53 (SFO) Lufa Speyer 2.2: 35 (SFO)	Slightly persistent	Could not be determined from the experiment.	PMRA# 3304623, supplemental to PMRA# 3304624 Details of the experimental design and conditions, including soil sampling procedure, the apparatus, method of application of the test substance, the control, and maintenance of the experimental conditions, is not provided in this report. Volatiles, CO ₂ , and NERs were not tracked. As such, the

Test substance and study details	Half-lives/DT ₅₀ (days), calculated by the PMRA, unless otherwise stated	Persistence	TP formation (% formation) and non-extractables	PMRA# of study, acceptability, and notes
	Lufa Speyer 2.3: 30 (DFOP)			reviewer was not able to verify the mass balance and validity of results. In general, the study is classified as supplemental/informative and will be considered with PMRA# 3304623. Half-lives were similar.
Radiolabelled phenyl desamino-metamitron German soil, Laacher Hof AXXa (sandy loam, pH 6, 1.32% TOC) 140 d Aerobic conditions in the dark at 20°C and 40% of the maximum water holding capacity 1.85 mg/kg soil	DT ₅₀ : 43 Representative half-life: 43 (SFO)	Slightly persistent	Major TPs: None. CO ₂ : 42.9% at 140 d UR: 40% at 120 d	PMRA# 3304624 Acceptable

Test substance and study details	Half-lives/DT ₅₀ (days), calculated by the PMRA, unless otherwise stated	Persistence	TP formation (% formation) and non-extractables	PMRA# of study, acceptability, and notes
<p>Radiolabelled phenyl-UL metamitron</p> <p>German soil, Laacher Hof AXXa (sandy loam, pH 6.3, 1.02% TOC)</p> <p>120 d</p> <p>Aerobic conditions in the dark at 20°C and 40% of the maximum water holding capacity</p> <p>312 µg a.i./100g soil</p>	<p>DT₅₀: 13</p> <p>Representative half-life: 90 (DFOP): 24.97 (IORE)</p>	<p>Non-persistent</p>	<p>Major TPs:</p> <p>Desamino-metamitron: maximum of 11.3% AR at 14 d</p> <p>CO₂: 44.6% at 120 d</p> <p>UR: 37.3% at 120 d</p>	<p>PMRA# 3304604</p> <p>Acceptable</p>
<p>Radiolabelled metamitron (triazine)</p> <p>Soil BI (silt loam, pH 5.28, 4.28% TOC)</p> <p>Soil 2.1 (sandy loam, pH 6.34, 0.72% TOC)</p> <p>Soil 2.2 (loamy sand, pH 5.98, 1.54% TOC)</p> <p>Soil 6S (clay, pH 7.19, 1.65% TOC)</p> <p>120 d</p> <p>Dark at 20°C and 50% moisture content</p> <p>6.88 mg test item/kg soil</p>	<p>DT₅₀:</p> <p>BI soil: 42</p> <p>Soil 2.1: 9.3</p> <p>Soil 2.2: 21.8</p> <p>Soil 6S: 10.5</p> <p>Representative half-life:</p> <p>BI soil: 51.5 (IORE)</p> <p>Soil 2.1: 9.3 (SFO)</p> <p>Soil 2.2: 21.8 (SFO)</p> <p>Soil 6S : 10.5 (SFO)</p>	<p>Persistence ranges from non-persistent to slightly persistent, depending on soil type.</p>	<p>BI soil:</p> <p>Desamino-metamitron: 9.8% at 120 d</p> <p>CO₂: 33% at 120 d</p> <p>UR: 36.4% at 120 d</p> <p>Soil 2.1:</p> <p>CO₂: 65.4% at 120 d</p> <p>UR: 51.8% at 30 d</p> <p>Soil 2.2:</p> <p>CO₂: 58.7% at 120 d</p> <p>UR: 39.6% at 59 d</p> <p>Soil 6S:</p> <p>CO₂: 56.7% at 120 d</p> <p>UR: 47.2% at 30 d</p>	<p>PMRA# 3304625</p> <p>Acceptable with limitations</p> <p>Given that this study does not describe the fate of the entire molecule, this study must be considered in conjunction with other studies, including those using metamitron radiolabelled at triazinone ring, to characterize the transformation pathway of the molecule.</p>

Test substance and study details	Half-lives/DT ₅₀ (days), calculated by the PMRA, unless otherwise stated	Persistence	TP formation (% formation) and non-extractables	PMRA# of study, acceptability, and notes
<p>Radiolabelled met amitron (phenyl)</p> <p>BBA 2.2 (loamy sand, pH 6.2, 2.58% TOC)</p> <p>Laacher Hof AII (silt loam, pH 7.3, 0.9% TOC)</p> <p>100 d</p> <p>Dark at 20°C and 40% of the maximum water holding capacity</p> <p>5.6 mg a.i./kg soil</p>	<p>DT₅₀:</p> <p>BBA 2.2: 21</p> <p>Laacher Hof AII: 3.4</p> <p>Representative half-life:</p> <p>BBA 2.2: 21 (SFO)</p> <p>Laacher Hof AII: 3.4 (SFO)</p>	<p>Persistence ranges from non-persistent to slightly persistent, depending on soil type.</p>	<p>BBA 2.2:</p> <p>CO₂: 48.9% at 100 d</p> <p>UR: 39.7% at 56 d</p> <p>Laacher Hof AII:</p> <p>CO₂: 57.4% at 100 d</p> <p>UR: 41.7% at 7 d</p>	<p>PMRA# 3304601</p> <p>Acceptable with limitations</p> <p>There was overheating at study termination up to 300 which may have overheated organic material resulting in radioactivity losses during drying. As such, the NER calculation at this time point is not reliable. The earlier sampling of residues can be used to characterize the fate.</p>
<p>Radiolabelled met amitron (phenyl)</p> <p>Hoefchen (silt, pH 6.7, 2.11% TOC)</p> <p>120 d</p> <p>Dark at 20°C and 40% of the maximum water holding capacity</p> <p>0.467 mg a.i./100 g soil</p>	<p>DT₅₀: 26.7</p> <p>Representative half-life: 77.8 (IORE)</p>	<p>Slightly persistent</p>	<p>Hoefchen:</p> <p>Desamino-met amitron: 17.1% at 30 d</p> <p>CO₂: 23.3% at 120 d</p> <p>UR: 43.5% at 90 d</p>	<p>PMRA# 3304602 (in combination with PMRA# 3304603 for identification of NERs)</p> <p>Acceptable with limitations</p> <p>There are no duplicate soil samples. However, the fate and kinetics of met amitron can be assessed with the available data in combination with other studies. The half life is comparable to other studies.</p>
<p>Radiolabelled met amitron (phenyl)</p> <p>German soil 2.2 (loamy sand, pH 6.2, 2.58% TOC)</p>	<p>DT₅₀: 35</p> <p>Representative half-life: 35 (SFO)</p>	<p>Slightly persistent</p>	<p>Desamino-met amitron: 11.2% at 30 d</p> <p>CO₂: 48% at 120 d</p>	<p>PMRA# 3304620</p> <p>Acceptable</p>

Test substance and study details	Half-lives/DT ₅₀ (days), calculated by the PMRA, unless otherwise stated	Persistence	TP formation (% formation) and non-extractables	PMRA# of study, acceptability, and notes
100 d in the dark at 20°C and 40% of the maximum water holding capacity 3.5 mg a.i./kg soil			UR: 34% at 64 d and 30% at 100 d	
Anaerobic soil (flooded soil)				
Radiolabelled metamitron (triazine and benzene) LUFA 2.2 soil (loamy sand, pH 5.8, 1.8% TOC) 120 d under anaerobic (flooded) conditions in the dark at 20 ± 2°C, after 14 d of aerobic incubation at 44.2% of the maximum water holding capacity	Total system: DT ₅₀ : TZ-label Total system: 28 BE-label Total system: 48 Representative half-life: TZ-label Total system: 28 (SFO) BE-label Total system: 48 (SFO)	Metamitron ranges from slightly persistent to moderately persistent in total system	Total system: TZ-label UR: 25.1% at the end of aerobic incubation, increasing after flooding, reaching 42.3% by 120 d Desamino-metamitron: 3% in aerobic phase, and after flooding, 13.2% at 58 d, and declining to 8.7% at 120 d M2a: 15.2% CO ₂ : 40% at 120 d BE-label UR: 38.8% at the end of aerobic incubation, and then decreasing slightly after flooding, reaching 31.1% Desamino-metamitron: 5.5% in	PMRA# 3304627 Acceptable

Test substance and study details	Half-lives/DT ₅₀ (days), calculated by the PMRA, unless otherwise stated	Persistence	TP formation (% formation) and non-extractables	PMRA# of study, acceptability, and notes
			aerobic phase, and after flooding, 7.2% AR at 1 d, and increasing to 13.3% at 120 d M2a: 11.6% CO ₂ : 51.9% at 120 d	
<p>Radiolabelled metamitron (benzene) California (sandy loam, pH 6.8, 0.27% TOC) Illinois (silt loam, pH 6.4, 2.5% TOC) North Dakota (sandy loam, pH 7.4, 1.35% TOC) 120 d under anaerobic (flooded) conditions in the dark at 20 ± 2°C, after 29 d of aerobic incubation at 46.1% average water holding capacity 758.2 µg a.i./100 g dw soil</p>	<p>Total system: DT₅₀: California: 196.2 Illinois: 272.2 North Dakota: 192.5 Representative half-life: California: 196.2 (SFO) Illinois: 272.2 (SFO) North Dakota: 192.5 (SFO)</p>	<p>Metamitron is persistent in total system</p>	<p>California UR: 24.2% Desamino-metamitron: 18.2% in aerobic phase, and reaching 26.2% in anaerobic phase at 3 d (mostly formed in water aerobic phase) CO₂: 24.9% Illinois UR: 24.4% CO₂: 10.3% North Dakota UR: 24% Desamino-metamitron: 7.5% aerobic phase, and reaching 10.3% at 120 d (mostly formed mostly in soil) CO₂: 19.9%</p>	<p>PMRA# 3304628 Acceptable</p>

Test substance and study details	Half-lives/DT ₅₀ (days), calculated by the PMRA, unless otherwise stated	Persistence	TP formation (% formation) and non-extractables	PMRA# of study, acceptability, and notes
<p>Radiolabelled metamitron (triazine) California (loamy sand, pH 6.89, 0.25% TOC) Illinois (silt loam, pH 4.99, 2.35% TOC) North Dakota (sandy loam, pH 7.08, 1.88% TOC) 120 d under anaerobic (flooded) conditions in the dark at 20 ± 2°C, after 30 d of aerobic incubation at 46% average water holding capacity 680.73 µg a.i./100 g dw soil</p>	<p>Total system: DT₅₀: California: 190 Illinois: 72.3 North Dakota: 279.3 Representative half-life: California: 190 (SFO) Illinois: 44 (IORE) North Dakota: 279.3 (SFO)</p>	<p>Metamitron ranges from moderately persistent to persistent in total system.</p>	<p>California UR: 23.4% at 120 d Desamino-metamitron: 13.2% in the aerobic phase and 21.8% in the anaerobic phase at 120 d Illinois UR: 22.1% at 120 d Desamino-metamitron: 24% in the aerobic phase and 50.8% in the anaerobic phase at 58 d North Dakota UR: 19.8% at 120 d Desamino-metamitron: 6.9% in the aerobic phase and 10.4% in the anaerobic phase at 14 d</p>	<p>PMRA# 3304629 Acceptable</p>
<p>Wayne New York (sand soil, pH 6.3) Grant Washington (loamy fine sand, pH 7.9)</p>	<p>Wayne New York Metamitron: DT₅₀: 7.44 Representative half-life:</p>	<p>Metamitron and desamino-metamitron not expected</p>	<p>Wayne New York Desamino-metamitron: 9.4% 3 d after 2nd application</p>	<p>PMRA# 3304650 Acceptable Note: TP values were converted to parent equivalents and were</p>

Test substance and study details	Half-lives/DT ₅₀ (days), calculated by the PMRA, unless otherwise stated	Persistence	TP formation (% formation) and non-extractables	PMRA# of study, acceptability, and notes
	11.9 (IORE) Desamino-metamitron: DT ₅₀ : 11.8 Representative half-life: 127 (DFOP) Grant Washington Metamitron: DT ₅₀ : 12.8 Representative half-life: 12.8 (SFO) Desamino-metamitron: DT ₅₀ : 21.1 Representative half-life: 24.1 (SFO)	to carry over to next growing season.	Grant Washington Desamino-metamitron: 6.72% 3 d after 2 nd application Metamitron and desamino-metamitron were non-detectable by 180 and 365 d in the Washington and New York sites, respectively. As such, no carry over is expected.	based on the target application rate.
Aquatic environments				
Aerobic aquatic				
Radiolabelled [triazine-5,6- ¹⁴ C]metamitron was applied at rates of 9.8 and 99 µg a.i./L while [benzene ring-U- ¹⁴ C]metamitron was applied at rates of 10.2 and 102.6 µg a.i./L Surface water (no sediment) (water pH 8.1, DOC 9.6 mg/L) 61 d in the dark at 20–25°C	TZ-label DT ₅₀ : 9.8 µg a.i./L: 21 99 µg a.i./L: 15.4 Representative half-life: 9.8 µg a.i./L: 21 (SFO) 99 µg a.i./L: 15.4 (SFO) BE-label DT ₅₀ : 10.2 µg a.i./L: 24.6 106.2 µg a.i./L: 18.6	Metamitron is slightly persistent in total system.	TZ-label CO ₂ : 40% in the low concentration and 27.3% in the high concentration 6-Methyl-3-phenyl-1,2,4,5-tetrazine (M1_TZ): 12.1% (high concentration) at 61 DAT 2-	PMRA# 3304630 Acceptable

Test substance and study details	Half-lives/DT ₅₀ (days), calculated by the PMRA, unless otherwise stated	Persistence	TP formation (% formation) and non-extractables	PMRA# of study, acceptability, and notes
	Representative half-life: 10.2 µg a.i./L: 24 (SFO) 106.2 µg a.i./L: 18.6 (SFO)		(Acetylhydrazinylidene)-2-(phenyl) acetic acid (M2_TZ): 18.9% (low test concentration) after 61 d and 11.4% (high test concentration) after 61 d of incubation BE-label CO ₂ : 26.6% in the low concentration and 35.5% in the high concentration 3-methyl-6-phenyl-1,2,4-triazin-5(4H)-one: 11.7% (low concentration) at 61 DAT 2-(Acetylhydrazinylidene)-2-(phenyl) acetic acid (M2_BE): 24.3% (high concentration) after 61 d of incubation M3_BE: 20.3% (low concentration) after 30 DAT	

Test substance and study details	Half-lives/DT ₅₀ (days), calculated by the PMRA, unless otherwise stated	Persistence	TP formation (% formation) and non-extractables	PMRA# of study, acceptability, and notes
Radiolabelled metamitron (phenyl) Water/sediment Waldwinken (pH 7.04, 6.1% TOC) Rückhaltebecken (pH 7.7, 1.7% TOC) 20°C in the dark 1.17 mg a.i./L	Total system DT ₅₀ : Waldwinken: 10.8 Rückhaltebecken: 11.4 Representative half-life: Waldwinken: 10.8 (SFO) Rückhaltebecken: 11.4 (SFO)	Metamitron is non-persistent in total system.	Waldwinkel UR: 26% Desamino-metamitron: 48% at 58 d in water and 27.5% on sediment Rückhaltebecken UR: 29% Desamino-metamitron: 54% at 58 d in water and 23.5% on sediment	PMRA# 3304631 Acceptable with limitations
Radiolabelled metamitron (triazine) Water/sediment system 1 WS Pfalz (pH 8 in water, 0.3% TOC) 2WS humsterbach (pH 7.5 in water, 3.4% TOC) 20°C in the dark 64.2 µg/L	Total system DT ₅₀ : 1 WS Pfalz: 22.2 2WS humsterbach: 8.9 Representative half-life: 1 WS Pfalz: 22.2 (SFO) 2WS humsterbach: 8.9 (SFO)	Metamitron ranges from non-persistent to slightly persistent in total system.	1 WS Pfalz UR: 40.5% Desamino-metamitron: 38.3% in water phase and 20.5% in sediment phase at 59 d 2WS humsterbach UR: 35.3% Desamino-metamitron: 29.7% in water phase and 42% in sediment phase at 59 d	PMRA# 3304632 Acceptable

Test substance and study details	Half-lives/DT ₅₀ (days), calculated by the PMRA, unless otherwise stated	Persistence	TP formation (% formation) and non-extractables	PMRA# of study, acceptability, and notes
<p>Metamitron Water/sediment Fürwigge-sediment (pH 5, 7.36% TOC) Schwarzes Wasser (pH 5.5, 3.2% TOC) 100 d in the dark at 20°C 3500 g a.i./ha 256.7 µg per test vessel</p>	<p>Total system DT₅₀: Fürwigge: 26.1 Schwarzes Wasser: 50.1 Representative half-life: Fürwigge: 28.1 (IORE) Schwarzes Wasser: 50.1 (SFO)</p>	<p>Metamitron ranges from slightly to moderately persistent in total system. Note: pH of this system may not be relevant under environmental conditions. However, the study may offer degradation information under pH with less hydrolysis.</p>	<p>Fürwigge UR: 49.4% at 100 d (sterile samples in the experiment resulted in 28.9% at 100 d) Desamino-metamitron: 14.7% at 60 d in the total system (majority in sediment) Schwarzes Wasser UR: 25.9% at 100 d (sterile samples in the experiment resulted in 33.7% at d 100) Desamino-metamitron: 37.2% at 100 d in the total system (majority in sediment)</p>	<p>PMRA# 3304634 Acceptable with limitation Only methanol was used in the extraction and high bound residues were found. The amounts of NERs in the non-sterile systems were higher than that in the sterile systems, which suggests that a fraction of NERs may have consisted of TPs in the non-sterile system. Other studies included more rigorous extraction methods. It is noted that most studies have high URs.</p>
Anaerobic water/sediment				
<p>Radiolabelled metamitron (benzene) Golden Lake water: pH 8.17, 16% TOC; sediment: loamy sand, pH 7.88, 1.4% TOC</p>	<p>Total system DT₅₀: Golden Lake: 3.8 Goose River: 4.2 Representative half-life: Golden Lake: 3.8 (SFO)</p>	<p>Metamitron is non-persistent in total system.</p>	<p>Golden Lake UR: 16.1% at 100 d Desamino-metamitron: 53% in water phase (30 d) and 30.2% in</p>	<p>PMRA# 3304636 Acceptable Results can be considered with flooded soil (conducted at lower pHs).</p>

Test substance and study details	Half-lives/DT ₅₀ (days), calculated by the PMRA, unless otherwise stated	Persistence	TP formation (% formation) and non-extractables	PMRA# of study, acceptability, and notes
Goose River water: pH 8.26, 16% TOC; sediment: loam, pH 7.74, 2.7% TOC 100 d in the dark at 20±2°C 174 µg a.i./L	Goose River: 4.2 (SFO)		sediment phase (60 d) Goose River UR: 21.4% at 30 d Desamino- metamitron: 41% in water phase (14 d) and 51.4% in sediment phase (100 d)	
Radiolabelled metamitron (triazine) Golden Lake water: pH 8.94, 13% TOC; sediment: loamy sand, pH 7.71, 1.6% TOC Goose River water: pH 8.98, 12% TOC; sediment: silt loam, pH 7.83, 3.5% TOC 100 d in the dark at 20±2°C 197 µg a.i./L	Total system DT ₅₀ : Golden Lake: 6.1 Goose River: 4.7 Representative half-life: Golden Lake: 6.1 (SFO) Goose River: 4.7 (SFO)	Metamitron is non- persistent in total system.	Golden Lake UR: 14% at 100 d Desamino- metamitron: 55.7% in water phase (30 d) and 18.4% in sediment phase (100 d) Goose River UR: 16.1% at 30 d Desamino- metamitron: 46.5% in water phase (14 d) and 39.9% in sediment phase (100 d)	PMRA# 3304637 Acceptable Results can be considered with flooded soil (conducted at lower pHs).

Persistence in soils characterized according to Goring *et al.* 1975

Persistence in natural waters characterized according to McEwan and Stephenson, 1979

Table 20 Summary of mobility

Mobility ^a				
<p>Batch equilibrium study with [phenyl-UL-¹⁴C]metamitron US sediment (California 9WS) Adsorption for 48 hrs and desorption for 24 hrs pH: 6.7 CEC (meq/100g): 15.8 TOC: 0.18% Note: Metamitron stable under test conditions with good recovery.</p>	<p>K_d: 0.277 K_{OC}: 154.1 K_{F-DES}: 0.30 1/n: 0.945 (linear)</p>	Moderately mobile	NA	<p>PMRA# 3304645 Acceptable The desorption values were similar to, but slightly higher than those obtained for adsorption.</p>
<p>Batch equilibrium study with [phenyl-UL-¹⁴C]metamitron Adsorption for 48 hrs and desorption for 24 hrs pH: 5.1–7.1 CEC (meq/100g): 11–19.5 TOC: 1.08–2.60% Note: Metamitron stable under test conditions with good recovery.</p>	<p>K_F: 0.932–1.745 K_{FOC}: 56–86.25 $K_{FOC-DES}$: 94.2–208.5 1/n: 0.788–0.827 (non-linear)</p>	High mobility	NA	<p>PMRA# 3304639 Acceptable Desorption K_F and K_{FOC} values were greater than the corresponding adsorption values, indicating that adsorption may not be completely reversible.</p>
<p>Batch equilibrium study with [phenyl-UL-¹⁴C]metamitron Adsorption for 48 hrs and desorption for 24 hrs pH: 5.5–7.4 CEC (meq/100g): Not measured TOC: 0.4–1.5% Note: Metamitron stable under test conditions with good recovery.</p>	<p>K_F: 0.364–5.94 K_{FOC}: 117–396 $K_{FOC-DES}$: 265–513 1/n: 0.671–0.844 (non-linear)</p>	Moderate to high mobility	NA	<p>PMRA# 3304640 Acceptable Desorption K_F and K_{FOC} values were greater than the corresponding adsorption values indicating that adsorption was only partially reversible.</p>

Mobility^a				
Batch equilibrium study with non-radiolabelled metamitron pH: 5–7.5 CEC (meq/100g): 5.47–14.9 TOC: 0.84–2.25% Note: Metamitron stable under test conditions with good recovery.	K_F : 0.53–2.45 K_{FOC} : 31.52–109 1/n: 0.645–0.779 (non-linear) Desorption was not performed.	Very highly mobile to highly mobile	NA	PMRA# 3304643 Acceptable Desorption was not performed.
Batch equilibrium study with [phenyl-UL- ¹⁴ C]metamitron pH: 6.3–7 CEC (meq/100g): not measured TOC: 0.65–1.35% Note: Metamitron stable under test conditions with good recovery.	K_F : 0.657–2.294 K_{FOC} : 75.84–199.5 $K_{FOC-DES}$: 150–446 1/n: 0.79–0.92 (most soils non-linear)	Moderately mobile to highly mobile	NA	PMRA# 3304644 Acceptable with limitations Desorption K_F and K_{FOC} values were greater than the corresponding adsorption values indicating that adsorption was only partially reversible.
Batch equilibrium study with [phenyl-UL- ¹⁴ C]desamino-metamitron pH: 5.8–7.2 CEC (meq/100g): Not measured TOC: 0.59–2.62% Note: Metamitron stable under test conditions with good recovery.	K_F : 0.802–2.974 K_{FOC} : 71.94–136 $K_{FOC-DES}$: 142–350 1/n: 0.79–0.92 (most soils non-linear)	Highly mobile	NA	PMRA# 3304646 Acceptable Desorption K_F and K_{FOC} values were greater than the corresponding adsorption values indicating that adsorption was only partially reversible.

^a Persistence classification for mobility in accordance with McCall et al. 1981

* Note: Metamitron stable under test conditions with good recovery, converted from Arrhenius equation, using equation: $\ln k = 22.6 - 8383.1 (1/T^{**})$ for pH 4, $\ln k = 32.0 - 11320.2 (1/T^{**})$ for pH 7, and $\ln k = 30.9 - 9845.5 (1/T^{**})$ for pH 9

** Temperature, in kelvin

Table 21 Comparison of the properties of compound with the leaching criteria of Cohen et al. (1984)

Property	Criteria of Cohen et al. (1984) indicating a potential for leaching	Compound	Meets criterion for leaching
Metamitron			
Solubility in water	> 30 mg/L	pH 7: 1760 mg/L	Yes
K _d	< 5 and usually < 1 or 2	K _F /K _d : 0.277–5.94 mL/g	Yes, for the majority of soils
K _{OC}	< 300	K _{FOC} /K _{OC} : 31.5–396 mL/g	Yes, for the majority of soils
Henry's law constant	< 10 ⁻² atm m ³ /mol	HLC = 2.44 × 10 ⁻⁶ Pa·m ³ mol ⁻¹	No
pK _a	Negatively charged (either fully or partially) at ambient pH	pK _a = 2.97 (20°C) (expected to be largely neutral under environmental conditions)	No
Hydrolysis half-life	> 20 wks (>140 d)	pH 7 (20/25°C): 70.6–450.7 d	Meets criteria depending on study
Soil phototransformation half-life	> 1 wk (> 7 d)	10–90.6 d	Yes
Half-life in soil	> 2–3 wks (> 14–21 d)	3.4–42 d	Meets criteria depending on soil type
Desamino-metamitron			
Solubility in water	> 30 mg/L	399.9 mg/L+	Yes
K _d	< 5 and usually < 1 or 2	K _F : 0.802–2.974	Yes
K _{OC}	< 300	K _{FOC} : 71.94–136	Yes
Henry's law constant	< 10 ⁻² atm m ³ /mol	1.4E-9 atm m ³ /mol (estimated from EPI Suite**)	No
pK _a	Negatively charged	No data	Unknown

	(either fully or partially) at ambient pH		
Hydrolysis half-life	> 20 wks (> 140 d)	Not a major TP from hydrolysis, potentially stable or similar decline to parent compound (formed up to 17% by study termination [d 8])	Potentially meets criteria
Soil phototransformation half-life	> 1 wk (> 7 d)	Formed as a major TP (with little decline observed in study period; formed up to 57% by study termination [15 d])	Potentially meets criteria
Half-life in soil	> 2–3 wks (> 14–21 d)	18.7–53 d	Yes

* From European Union regulatory and evaluation data as published by European Commission (EC), European Food Safety Agency (EFSA; Renewal Assessment Report [RAR], Draft Assessment Report [DAR], and Conclusion dossiers), European Medicines Agency (EMA; for example, European Union Annex III Prior Informed Consent [PIC] Decision Guidance Document [DGD]).

** EPI (Estimation Programs Interface) Suite is a suite of physical/chemical property and environmental fate estimation programs. Note: M1 and M2 are not formed as major TPs in soil. As such, they are not part of the leaching assessment and are not included in the table. However, their vapour pressure and Henry's law constants (HLCs) are considered for evaluating the potential for dissipation into air, and therefore, the values are reported in this footnote. The estimated vapour pressure for M1 and M2 are 0.00248 Pa and 1.87E-5 Pa, respectively. The estimated HLC for M1 and M2 are 4.1E-8 atm⁻³/mol and 3.58E-13 atm⁻³/mol, respectively. The vapour pressure and HLC indicate low volatility.

Table 22 Estimated environmental concentration (EEC) for metamitron and desamino-metamitron in the environment (excluding birds and mammals)

Substance	EEC	Method of calculation	Notes
Soil: Screening level risk assessment			
Metamitron and desamino-metamitron	The resulting soil EEC for the parent, metamitron, was 0.432 mg a.i./kg (972 g a.i./ha). The resulting soil	Screening level soil EECs were calculated for direct over-spray application at the maximum rate, assuming soil bulk density of 1.5 g/cm ³ and soil depth of 15 cm. The maximum cumulative rate was used in the calculation of the EEC, and based on two applications of 504 g a.i./ha with a 5-d interval. The EEC was calculated for both the parent compound and desamino-	EECs in g a.i./ha were used to evaluate risks to non-target terrestrial plants (seedling emergence). EECs in mg/kg dw soil were used to evaluate risks

Substance	EEC	Method of calculation	Notes
	EEC for the major TP, desamino-metamitron, was 0.415 mg a.i./kg.	metamitron. The 90 th confidence bound on the mean was calculated to be 46 d based on PMRA# 3304620, 3304625, 3304603, and 3304604. Desamino-metamitron was calculated using the molar ratio of the parent compound and TP. Soil EECs are used in the screening level risk assessment for vascular plants (based on seedling emergence), earthworms, and soil-dwelling beneficial arthropods.	to earthworms and soil-dwelling beneficial arthropods.
Soil: Refined risk assessment – Spray drift terrestrial plants			
Metamitron applied as end-use product	Off-field (airblast 59%): 573 g a.i./ha	The refined EECs and risk assessment considered 59% spray drift at one-metre downwind resulting from early-season airblast application using a fine spray.	EECs were used to evaluate risks to plants from seedling emergence studies.
Water: Screening level risk assessment			
The resulting EECs in water for the parent, metamitron, were 0.65 and 0.12 mg a.i./L for 15 cm and 80 cm depth, respectively. The resulting EECs in water for the major TP, desamino-metamitron, were 0.62 and 0.12 mg a.i./L for 15 cm and 80 cm depth, respectively.	Screening level water EECs were calculated for direct over-spray for surface waters for seasonal water body (15 cm used by amphibians) and permanent water body (80 cm). The longest of three available aerobic aquatic studies (water/sediment systems) was considered in the calculation (PMRA# 3304634, total system half-life: 50.1 d [SFO]). The maximum cumulative rate was used in the calculation of the EEC, and based on two applications of 504 g a.i./ha with a 5-d interval. Desamino-metamitron was calculated using the molar ratio of the parent compound and TP.	The EECs in surface water at 15 cm depth were used to determine risk to amphibians while the 80 cm depth EECs were used to evaluate risks to all other aquatic organisms.	
Water: Refined risk assessment – Spray drift and runoff to freshwater and estuarine/marine environments			
NR			

Substance	EEC	Method of calculation	Notes
Plant surfaces and leaf dwelling beneficial arthropods: Screening level and refined risk assessments			
Metamitron applied as end-use product	In-field: 860 g a.i./ha Off-field (airblast 59%): 507 g a.i./ha		Used to evaluate on- and off-field risks to beneficial arthropods and non-target terrestrial plants (vegetative vigour).
Bees matrices			
Metamitron	14.4 µg a.i./bee (adult)	Oral exposure estimates for bees = maximum single application rate (0.504 kg a.i./ha) × adjustment factor. The consumption rate is 0.292 g/bee/d for adult bees and 0.124 g/bee/d for larvae. Oral exposure estimate 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 × consumption rate*	Used to evaluate risks to pollinators (bees).
	6.1 µg a.i./bee (larvae)	Note: Where the toxicity endpoint is in concentration (mg a.i./kg), the level of exposure should also be estimated as the concentration in the same units. Empirical residue data can be used to refine the risk assessment, ideally as residues measured from plant pollen and nectar.	
	1.2 µg a.i./bee (adult, contact)	Estimated contact exposure (µg a.i./bee) = 2.4 µg a.i./bee/kg a.i./ha × 0.504 kg a.i./ha	

Table 23 Toxicity to terrestrial organisms

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity ^a	PMRA#
Invertebrates					
Earthworm <i>Eisenia fetida</i>	14-d acute	Metamitron (technical grade active ingredient)	LC ₅₀ : > 1000 mg a.i./kg soil NOEC: ≥ 1000 mg/kg soil	NA	3304656 Acceptable
					3304657 Acceptable
Earthworm <i>Eisenia andrei</i>	28-d chronic	Metamitron 700 SC (end-use product – 58% w/w technical grade active ingredient)	NOEC: 104 mg a.i./kg soil (reproduction) LOEC: 188 mg a.i./kg soil (reproduction)	NA	3304654 Acceptable
Earthworm <i>Eisenia fetida</i>	28-d chronic	Desamino- metamitron (TP)	NOEC: 5.5 mg TP/kg soil LOEC: > 5.5 mg TP/kg soil (reproduction)	NA	3304655 Acceptable
Collembola <i>Folsomia candida</i>	28-d chronic	Desamino- metamitron (TP)	NOEC: 100 mg TP/kg soil LOEC: 1000 mg TP/kg soil (reproduction and adult mortality)	NA	3304667 Acceptable
Honey bee <i>Apis mellifera</i>	48-hr adult acute oral	Metamitron (technical grade active ingredient)	LD ₅₀ : > 97.2 µg a.i./bee	Practically non-toxic	3304658 Acceptable
	48-hr adult acute contact		LD ₅₀ : > 100 µg a.i./bee		
	10-d adult chronic oral	Metamitron (technical grade active ingredient)	Mortality NOEC: 410 mg a.i./kg diet NOEDD: 7.3 µg a.i./bee/d LOEC: 1100 mg a.i./kg diet LOEDD: 14 µg a.i./bee/d Body weight reduction NOEC: 160 mg a.i./kg diet NOEDD: 2.9 µg a.i./bee/d	NA	3304661 Acceptable

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity ^a	PMRA#
			LOEC: 410 mg a.i./kg diet LOEDD: 7.3 µg a.i./bee/d		
	7-d acute single dose brood (fed for 4 d and observed for 3 d)	Metamitron (technical grade active ingredient)	LD ₅₀ : 78 µg a.i./larva (2300 µg a.i./g diet)	NA	3304659 Acceptable
	22-d repeated feeding with brood	Metamitron (technical grade active ingredient)	NOED: 13 µg a.i./larva NOEC: 77 µg a.i./g diet LOED: 44 µg a.i./g diet Effects to 8-d larval survival, 22-d adult emergence and adult weight	NA	3304660 Acceptable
Parasitic wasp <i>Aphidius rhopalosiphi</i>	48-hr glass plate Tier I screening study	Metamitron 150 SG (end-use product – 150 g/kg technical grade active ingredient)	LR ₅₀ : > 5400 g end-use product/ha (> 810 g a.i./ha) NOER: > 5400 g end-use product/ha (> 810 g a.i./ha)	NA	3304666 Acceptable
	11-d extended lab test for reproduction (including 48-hr mortality test)	Metamitron 150 SG (end-use product – 150 g/kg technical grade active ingredient)	LR ₅₀ : >5400 g end-use product/ha (> 810 g a.i./ha) NOER: >5400 g end-use product/ha (> 810 g a.i./ha)		3304665 Acceptable
Predatory Mite <i>Typhlodromus pyri</i>	7-d glass plate Tier I screening study	Metamitron 150 SG (end-use product – 150 g/kg technical grade active ingredient)	LR ₅₀ : >5400 g end-use product/ha (> 810 g a.i./ha) NOER: >5400 g end-use product/ha (> 810 g a.i./ha)	NA	3304664 Acceptable
	14-d extended lab test for reproduction	Metamitron 700 SC (end-use product – 58% w/w)	LR ₅₀ : > 13800 mL end-use product/ha (>9660 g a.i./ha) NOER: 9200 mL end-use product/ha		3304665 Acceptable

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity ^a	PMRA#
	(including 7-d mortality test and 7-d reproduction test)	technical grade active ingredient)	(6440 g a.i./ha) based on reduction in egg production		
	14-d extended lab test for reproduction (including 7-d mortality test and 7-d reproduction test)	Metamitron 150 SG (end-use product – 150 g/kg technical grade active ingredient)	LR ₅₀ : >5400 g end-use product/ha (> 810 g a.i./ha) NOER: >5400 g end-use product/ha (> 810 g a.i./ha)	NA	3304663 Acceptable
Birds					
Japanese quail <i>Coturnix coturnix japonica</i>	14-d acute (oral gavage with observation period)	Metamitron (technical grade active ingredient)	LD ₅₀ : 1326 mg a.i./kg bw NOEL (sublethal effects including dyspnoea, lethargy, and ataxia): 340 mg a.i./kg bw	Slightly toxic	3304563 and 3304564 (amendment clarifying test item) Acceptable
			LD ₅₀ : 2000 mg a.i./kg bw NOEL (sublethal effects including diarrhea and lethargy in all test groups for 4–7 d and then subsiding): 1000 mg a.i./kg bw		3304565 Acceptable with limitations (no control, but considered low dose effects and in conjunction with other study results)

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity ^a	PMRA#
			LD ₅₀ : 1534 mg a.i./kg bw NOEL (sublethal effects, including unsteadiness, and subdued behaviour): 500 mg a.i./kg bw		3304566 Acceptable
Canary <i>Serinus canaria</i>	8-d dietary (5 d with feed and 3 d with untreated food)	Metamitron (technical grade active ingredient)	LC ₅₀ : > 7710 mg a.i./kg feed LD ₅₀ : > 663 mg a.i./kg bw/d (30% mortality in highest test group) NOEL (Abnormal behaviours were observed in the 2280, 4370, and 7710 mg a.i./kg feed treatment groups, and generally increased in frequency and intensity with increasing dietary concentration. Observations from post-mortem examination of mortalities commonly included pale organs in the circulatory, respiratory, and gastrointestinal systems and black material in the gastrointestinal tract. Body weight loss occurred among birds in the 2280, 4370, and 7710 mg a.i./kg feed treatment groups during the exposure period): 196 mg a.i./kg bw/d	Practically non-toxic	3304571 Acceptable
Bobwhite quail <i>Colinus virginianus</i>	11-d dietary (5 d with feed and 6 d with untreated food)		LC ₅₀ : > 5000 mg a.i./kg feed LD ₅₀ : > 904 mg a.i./kg bw/d (no mortality or sublethal effects)		3304569 Acceptable
Mallard duck <i>Anas platyrhynchos</i>	17-d dietary (5 d with feed and 12 d with untreated)		LC ₅₀ : > 5000 mg a.i./kg feed LD ₅₀ : > 1586 mg a.i./kg bw/d (no mortality or sublethal effects)		3304570 Acceptable

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity ^a	PMRA#
	food)				
Bobwhite quail <i>Colinus virginianus</i>	23-wk reproduction		NOAEC: 100 mg a.i./kg feed NOAEL: 81.5 mg/kg bw/d (reduction in # of eggs laid and eggshell thickness)	NA	3304572 Acceptable
Mallard duck <i>Anas platyrhynchos</i>	20-wk reproduction		NOEAC: 454 mg a.i./kg feed NOAEL: 39.2 mg/kg bw/d LOAEC: 971 mg a.i./kg feed LOAEL: 85.7 mg/kg bw/d (hatchling weight and survivor weight)	NA	3304573 Acceptable
Mammals					
Rat	Acute	Metamitron (technical grade active ingredient)	LD ₅₀ ♂: 1183 mg/kg bw	Slightly toxic	3303527
	90-d oral toxicity		NOEL: 34.4/7.9 or 42.9 mg/kg bw ♂/♀ LOEL: 3182.7/42.9 or 201.8 mg/kg bw ♂/♀	NA	3303555 and 3303556
	Two-generation reproduction	Metamitron (technical grade active ingredient)	Parental Toxicity LOAEL not determined (effects at lowest dose < 7.3/12.0 mg/kg bw/d ♂/♀) LOAEL: 7.3/12.0 mg/kg bw/d ♂/♀ Effects observed at various doses ≥ 7.3/12.0 mg/kg bw/d ♂/♀ F0: ↓ bw, bwg during pre-mating, gestation and lactation (♀) F1: ↓ bw during pre-mating (♂/♀); ↓ FC during pre-mating (♂) ≥ 36.4/59.3 mg/kg bw/d ♂/♀ F0: ↓ bwg during pre-mating (♂)	NA	3304702 and 3304704

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity ^a	PMRA#
			<p>F1: ↓ bwg during pre-mating, ↓ FC during pre-mating, gestation and lactation (♀)</p> <p>239.1/354.3 mg/kg bw/d ♂/♀</p> <p>F0: ↓ bw during pre-mating (♂)</p> <p>F1: ↑ incidence of urinary incontinence (2/2, 6/5, 5/16, 21/20) (♂/♀); ↓ bw during pre-mating (♂); ↓ bwg during gestation, ↓ bw, bwg during lactation (♀)</p> <p>Reproductive Toxicity</p> <p>NOAEL: 36.4/59.3 mg/kg bw/d ♂/♀</p> <p>LOAEL = 239.1/354.3 mg/kg bw/d ♂/♀</p> <p>239.1/354.3 mg/kg bw/d ♂/♀</p> <p>↓ mean # of corpora lutea and mean # of implantations in F0 and F1, ↓ # of live birth and litter size in F1</p> <p>Offspring Toxicity</p> <p>NOAEL: 11.3 mg/kg bw/d</p> <p>LOAEL: 53.8 mg/kg bw/d</p> <p>≥ 41/53.8 mg/kg/bw/d</p> <p>↓ d-21 survival index in F1 pups, ↓ bw in F2 pups, ↑ incidence of missing/cannibalised pups in F1 (5, 12, 21, 30) and F2 (14, 14, 27, 51) pups</p> <p>263.3/306.9 mg/kg bw/d</p> <p>↓ bw in F1 pups, ↓ litter size (d 1, 14 and 21) in F2 pups</p> <p>No sensitivity of the young</p>		

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity ^a	PMRA#
Mouse	Acute oral gavage	Metamitron (technical grade active ingredient)	LD ₅₀ ♀: 644 mg/kg bw	Slightly toxic	3303530
	90-d oral toxicity		NOAEL: 54.8/93.0 mg/kg bw	NA	3303558 and 3303559
Vascular plants					
Vascular plant	21-d seedling emergence	AG-M4-150 SG (end-use product – 15% technical grade active ingredient)	ER ₂₅ : 69.4 g a.i./ha (lettuce)	NA	3304586 Acceptable
	21-d vegetative vigour		ER ₂₅ : 86.4 g a.i./ha (lettuce)	NA	3304587 Acceptable

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

Table 24 Toxicity to aquatic organisms

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity ^a	PMRA#
Freshwater species					
<i>Daphnia magna</i>	48-hr acute Static conditions	Metamitron (technical grade active ingredient)	EC ₅₀ : 6.7 mg a.i./L	Moderately toxic	3304668 Acceptable
			EC ₅₀ : 5.7 mg a.i./L		3304669 Acceptable
		Desamino-metamitron (TP)	EC ₅₀ : > 560 mg TP/L	Practically non-toxic	3304670 Acceptable
		Desamino-metamitron (TP)	EC ₅₀ : 745 mg TP/L	Practically non-toxic	3304671 Acceptable
	21-d chronic Static renewal	Metamitron (technical grade active ingredient)	NOEC: 10 mg a.i./L LOEC (reproduction and growth): 18 mg a.i./L	NA	3304673 Acceptable

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity ^a	PMRA#
Rainbow trout <i>Oncorhynchus mykiss</i>	96-hr acute Static	Metamitron (technical grade active ingredient)	LC ₅₀ : 222 mg a.i./L NOEC (sublethal effects and mortality): 100 mg a.i./L	Practically non-toxic	3304679 Acceptable
Bluegill sunfish <i>Lepomis macrochirus</i>	96-hr acute Semi-static (24 hr renewal)	Metamitron (technical grade active ingredient)	LC ₅₀ : > 96 mg a.i./L NOEC (sublethal effects and mortality): 96 mg a.i./L	Practically non-toxic up to the highest concentration tested	3304556 Acceptable
Common carp <i>Cyprinus carpio</i>	96-hr acute Static	Metamitron (technical grade active ingredient)	LC ₅₀ : 194 mg a.i./L NOEC (sublethal effects and mortality): 46.5 mg a.i./L	Practically non-toxic	3304557 Acceptable
Golden orfe <i>Leuciscus idus</i>	96-hr acute Semi-static (24 hr renewal)	Metamitron (technical grade active ingredient)	LC ₅₀ : 300 mg a.i./L NOEC (sublethal effects and mortality): 100 mg a.i./L	Practically non-toxic	3304558 Acceptable
Fathead minnow <i>Pimephales promelas</i>	33-d exposure (from egg stage) chronic Flow through	Metamitron (technical grade active ingredient)	NOEC: 10.3 mg a.i./L LOEC (highest concentration, no effects): > 10.3 mg a.i./L	NA	3304560 Acceptable
Freshwater algae <i>Selenastrum capricornutum</i>	72-hr acute Static	Metamitron (technical grade active ingredient)	EC ₅₀ (area under growth curve): 0.46 mg a.i./L	Highly toxic	3304574 Acceptable with limitations, supplemental to other studies Control growth of algae exceeded guidance

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity ^a	PMRA#
Freshwater algae <i>Desmodesmus subspicatus</i>			EC ₅₀ (yield): 0.31 mg a.i./L EC ₅₀ (growth rate): 0.83 mg a.i./L	Highly toxic	3304575 Acceptable
Freshwater algae <i>Rhaphidocelis subcapitata</i>			EC ₅₀ (yield): 0.49 mg a.i./L EC ₅₀ (growth rate): 0.96 mg a.i./L	Highly toxic	3304576 Acceptable
Freshwater algae <i>Chlorella vulgaris</i>			EC ₅₀ (growth rate): 2.41 mg a.i./L EC ₅₀ (yield): 1.45 mg a.i./L	Moderately toxic	3304577 Acceptable
Freshwater algae <i>Anabaena flos-aquae</i>	96-hr acute Static		EC ₅₀ (biomass): 0.66 mg a.i./L EC ₅₀ (growth rate): 6.26 mg a.i./L	Moderately toxic to highly toxic	3304580 Unacceptable (control contamination)
			EC ₅₀ (biomass): 0.65 mg a.i./L EC ₅₀ (growth rate): 1.24 mg a.i./L	Moderately toxic to highly toxic	3304581 Acceptable with limitations (validity criteria not met for control biomass [too low] and growth [too high])
Freshwater diatom <i>Navicula pelliculosa</i>	72-hr acute Static		EC ₅₀ (yield): 0.28 mg a.i./L EC ₅₀ (growth rate): 0.50 mg a.i./L	Highly toxic	3304582 Acceptable

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity ^a	PMRA#
Cyanobacteria <i>Synechococcus leopoliensis</i>			EC ₅₀ (yield): 1.04 mg a.i./L EC ₅₀ (growth rate): 3.38 mg a.i./L	Moderately toxic	3304583 Acceptable
Freshwater diatom <i>Navicula pelliculosa</i>	72-hr Static	Desamino- Metamitron (TP)	EC ₅₀ (yield): 33.83 mg a.i./L EC ₅₀ (growth rate): 52.22 mg a.i./L	Slightly toxic	3304584 Acceptable
Freshwater diatom <i>Raphidocelis subcapitata</i>			EC ₅₀ (yield): 26 mg a.i./L EC ₅₀ (growth rate): 72.5 mg a.i./L EC ₅₀ (biomass): 26 mg a.i./L	Slightly toxic	3304578 Acceptable
Freshwater algae <i>Desmodesmus subspicatus</i>			EC ₅₀ (yield): 98 mg a.i./L EC ₅₀ (growth rate): > 100 mg a.i./L	Slightly toxic to practically non-toxic	3304579 Acceptable
Vascular plant Duckweed <i>Lemna gibba</i>			7-d Static renewal	Metamitron (technical grade active ingredient)	EC ₅₀ (frond yield): 0.451 mg a.i./L EC ₅₀ (frond growth rate): 0.981 mg a.i./L EC ₅₀ (biomass yield): 0.282 mg a.i./L EC ₅₀ (biomass growth rate): 0.586 mg a.i./L
	EC ₅₀ (frond yield): 0.43 mg a.i./L EC ₅₀ (frond growth rate): 1.4 mg a.i./L EC ₅₀ (biomass yield): 0.33 mg a.i./L EC ₅₀ (biomass growth rate): 1.4 mg a.i./L	Moderately toxic to highly toxic			3304589 Acceptable
	Desamino- metamitron (TP)	EC ₅₀ (frond yield): 33.6 mg a.i./L EC ₅₀ (frond growth rate): 126.8 mg		Practically non-toxic to slightly toxic	3304590 Acceptable

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity ^a	PMRA#
			a.i./L EC ₅₀ (biomass yield): 37.3 mg a.i./L EC ₅₀ (biomass growth rate): 122.9 mg a.i./L		
Marine Species					
Sheepshead minnow <i>Cyprinodon variegatus</i>	96-hr acute Static renewal	Metamitron (technical grade active ingredient)	LC ₅₀ : 94 mg a.i./L	Slightly toxic	3304559 Acceptable
Marine algae <i>Skeletonema marinoi</i>	96-hr acute Static		EC ₅₀ (growth rate): 647 mg a.i./L EC ₅₀ (yield): 349.4 mg a.i./L EC ₅₀ (area under growth curve, biomass): 345 mg a.i./L	Practically non-toxic	3304585 and 3527921 Acceptable

^a USEPA classification, where applicable.

Table 25 Effect metrics and uncertainty factors

Organism	Exposure and PMRA# of study	Test substance	Endpoint	Value	Uncertainty factor applied	Effect metric	LOC
Terrestrial species							
Earthworm <i>Eisenia fetida</i>	14-d acute 3304656	Metamitron (technical grade active ingredient)	LC ₅₀	> 1000 mg a.i./kg soil	2	> 500 mg a.i./kg soil	1
Earthworm <i>Eisenia andrei</i>	28-d chronic 3304654	Metamitron 700 SC (end-use product -58% w/w technical grade active ingredient)	NOEC (reproduction)	104 mg a.i./kg soil	1	104 mg a.i./kg soil	1

Organism	Exposure and PMRA# of study	Test substance	Endpoint	Value	Uncertainty factor applied	Effect metric	LOC
Earthworm <i>Eisenia fetida</i>	28-d chronic 3304655	Desamino- metamitron (TP)	NOEC	5.5 mg TP/kg soil (no effects)	1	5.5 mg TP/kg soil	1
Collembola <i>Folsomia candida</i>	28-d chronic 3304667	Desamino- metamitron (TP)	NOEC (reproduction and adult mortality)	100 mg TP/kg soil	1	100 mg TP/kg soil	1
Honey bee <i>Apis mellifera</i>	48-hr adult acute oral 3304658	Metamitron (technical grade active ingredient)	LD ₅₀	> 97.2 µg a.i./bee	1	> 97.2 µg a.i./bee	0.4
	48-hr adult acute contact 3304658		LD ₅₀	> 100 µg a.i./bee		> 100 µg a.i./bee	0.4
	10-d adult chronic oral 3304661	Metamitron (technical grade active ingredient)	NOEDD (mortality)	2.9 µg a.i./bee/d	1	2.9 µg a.i./bee/d	1
	7-d acute single dose 3304659	Metamitron (technical grade active ingredient)	LD ₅₀	78 µg a.i./larva (2300 µg a.i./g diet)	1	78 µg a.i./larva (2300 µg a.i./g diet)	1
	22-d repeated feeding with brood 3304660	Metamitron (technical grade active ingredient)	NOED (NOEC) Effects to 8-d larval survival, 22-d adult emergence and adult weight	13 µg a.i./larva (77 µg a.i./g diet)	1	13 µg a.i./larva (77 µg a.i./g diet)	1
Parasitic wasp <i>Aphidius</i>	48-hr glass plate 3304665	Metamitron 150 SG (end-use product – 150 g/kg technical	LR ₅₀	> 810 g a.i./ha	1	> 810 g a.i./ha	2

Organism	Exposure and PMRA# of study	Test substance	Endpoint	Value	Uncertainty factor applied	Effect metric	LOC
<i>rhopalosiphi</i>		grade active ingredient)					
	11-d extended lab test for reproduction 3304666	Metamitron 150 SG (end-use product – 150 g/kg technical grade active ingredient)	NOER	> 810 g a.i./ha	1	> 810 g a.i./ha	1
Predatory mite <i>Typhlodromus pyri</i>	48-hr glass plate 3304663	Metamitron 150 SG (end-use product – 150 g/kg technical grade active ingredient)	LR ₅₀	> 810 g a.i./ha	1	> 810 g a.i./ha	2
	48-hr glass plate and 11-d extended lab test for reproduction 3304664 and 3304665	Metamitron 150 SG (end-use product – 150 g/kg technical grade active ingredient)	NOER	> 810 g a.i./ha	1	> 810 g a.i./ha	1
Japanese quail <i>Coturnix coturnix japonica</i>	14-d acute 3304563 and 3304564	Metamitron (technical grade active ingredient)	LD ₅₀ NOEL (sublethal effects)	1326 mg a.i./kg bw 340 mg a.i./kg bw	10	132.6 mg a.i./kg bw	1
Canary <i>Serinus canaria</i>	8-d dietary 3304571	Metamitron (technical grade active ingredient)	LD ₅₀ NOEL	> 663 mg a.i./kg bw/d (30% mortality at highest dose) 196 mg a.i./kg	10	> 66.3 mg a.i./kg bw/d	1

Organism	Exposure and PMRA# of study	Test substance	Endpoint	Value	Uncertainty factor applied	Effect metric	LOC
			(sublethal effects)	bw/d			
Mallard duck <i>Anas platyrhynchos</i>	20-wk reproduction 3304573		NOAEL	39.2 mg a.i./kg bw/d	1	39.2 mg/kg bw/d	1
			LOAEL (hatchling weight and survivor weight)	85.7 mg a.i./kg bw/d		85.7 mg/kg bw/d	
Rat	Acute oral gavage 3303527	Metamitron (technical grade active ingredient)	LD ₅₀ ♂	1183 mg a.i./kg bw	10	118.3 mg/kg bw	1
	Two-generation reproduction toxicity 3304702 and 3304704	Metamitron (technical grade active ingredient)	Parental toxicity LOAEL not determined (effects at lowest dose < 7.3/12.0 mg/kg bw/d ♂/♀) LOAEL: 7.3/12.0 mg/kg bw/d ♂/♀ Effects observed at various doses ≥ 7.3/12.0 mg/kg bw/d ♂/♀ F0: ↓ bw, bwg during pre-mating, gestation and lactation (♀) F1: ↓ bw during pre-mating (♂/♀); ↓ FC during pre-mating (♂) ≥ 36.4/59.3 mg/kg bw/d ♂/♀ F0: ↓ bwg during pre-mating (♂) F1: ↓ bwg during pre-mating, ↓ FC during pre-mating, gestation, and lactation (♀) 239.1/354.3 mg/kg bw/d ♂/♀ F0: ↓ bw during pre-mating (♂)		1	7.3 mg/kg bw/d	1

Organism	Exposure and PMRA# of study	Test substance	Endpoint	Value	Uncertainty factor applied	Effect metric	LOC
			F1: ↑ incidence of urinary incontinence (2/2, 6/5, 5/16, 21/20) (♂/♀); ↓ bw during pre-mating (♂); ↓ bwg during gestation, ↓ bw, bwg during lactation (♀).				
Mouse	Acute oral gavage 3303530	Metamitron (technical grade active ingredient)	LD ₅₀ ♀	644 mg/kg bw	10	64.4 mg/kg bw	1
Vascular plant	21-d seedling emergence 3304586	AG-M4-150 SG (end-use product – 15% technical grade active ingredient)	ER ₂₅ (lettuce)*	69.4 g a.i./ha	1	69.4 g a.i./ha	1
	21-d vegetative vigour 3304587		ER ₂₅ (lettuce)*	86.4 g a.i./ha	1	86.4 g a.i./ha	1
Aquatic species							
Freshwater invertebrates Daphnid	48-hr acute 3304668	Metamitron (technical grade active ingredient)	EC ₅₀	5.7 mg a.i./L	2	2.9 mg a.i./L	1
	21-d chronic 3304673		NOEC (reproduction and growth)	10 mg a.i./L	1	10 mg a.i./L	1
	48-hr acute 3304671	Desamino-metamitron (TP)	EC ₅₀	745 mg TP/L	2	375.5 mg TP/L	1
Freshwater fish Bluegill sunfish	96-hr acute 3304556	Metamitron (technical grade active ingredient)	LC ₅₀	> 96 mg a.i./L	10	> 9.6 mg a.i./L	1
Freshwater fish Common carp	96-hr acute 3304557	Metamitron (technical grade active ingredient)	LC ₅₀	194 mg a.i./L	10	19.4 mg a.i./L	1

Organism	Exposure and PMRA# of study	Test substance	Endpoint	Value	Uncertainty factor applied	Effect metric	LOC
Freshwater fish Golden orfe	96-hr acute 3304558	Metamitron (technical grade active ingredient)	LC ₅₀	300 mg a.i./L	10	30 mg a.i./L	1
Freshwater fish Rainbow trout	96-hr acute 3304679	Metamitron (technical grade active ingredient)	LC ₅₀	222 mg a.i./L	10	22.2 mg a.i./L	1
Freshwater fish Fathead minnow	33-d chronic 3304560	Metamitron (technical grade active ingredient)	NOEC	10.3 mg a.i./L (no effects at highest concentration)	1	10.3 mg a.i./L	1
Amphibians Fish as a surrogate (bluegill sunfish)	96-hr acute 3304556	Metamitron (technical grade active ingredient)	LC ₅₀	> 96 mg a.i./L	10	> 9.6 mg a.i./L	1
Amphibians Fish as a surrogate (common carp)	96-hr acute 3304556	Metamitron (technical grade active ingredient)	LC ₅₀	194 mg a.i./L	10	19.4 mg a.i./L	1
Amphibians Fish as a surrogate (fathead minnow)	33-d chronic 3304560	Metamitron (technical grade active ingredient)	NOEC	10.3 mg a.i./L (no effects at highest concentration)	1	10.3 mg a.i./L	1
Freshwater algae <i>Desmodesmus subspicatus</i>	72-hr acute 3304575	Metamitron (technical grade active ingredient)	EC ₅₀ (yield)	0.31 mg a.i./L	2	0.155 mg a.i./L	1
Freshwater diatom <i>Navicula pelliculosa</i>	72-hr acute 3304582	Metamitron (technical grade active ingredient)	EC ₅₀ (yield)	0.28 mg a.i./L	2	0.14 mg a.i./L	1

Organism	Exposure and PMRA# of study	Test substance	Endpoint	Value	Uncertainty factor applied	Effect metric	LOC
Freshwater diatom <i>Raphidocelis subcapitata</i>	72-hr acute 3304578	Desamino-metamitron (TP)	EC ₅₀ (yield and biomass)	26 mg TP/L	2	13 mg TP/L	1
Aquatic vascular plants	7-d 3304588 and 3446767	Metamitron (technical grade active ingredient)	EC ₅₀ (yield)	0.282 mg a.i./L	2	0.141 mg a.i./L	1
Duckweed	7-d 3304590	Desamino-Metamitron (TP)	EC ₅₀ (yield)	33.6 mg TP/L	2	16.8 mg a.i./L	1
Saltwater fish Sheepshead minnow	96-hr acute 3304559	Metamitron (technical grade active ingredient)	LC ₅₀	94 mg a.i./L	10	9.4 mg a.i./L	1
Saltwater algae <i>Skeletonema marinoi</i>	96-hr acute 3304585 and 3527921	Metamitron (technical grade active ingredient)	EC ₅₀ (biomass)	345 mg a.i./L	2	172.5 mg a.i./L	1

* SSD/ HC₅ was not calculated for terrestrial plants because most of the endpoints were non-definitive.

Note: For birds, sublethal effects are also considered in the risk assessment discussion.

Table 26 Screening risk to terrestrial organisms other than birds and mammals

Organism	Test substance	Endpoint	Effect metric	EEC	RQ	Risk? (RQ > LOC)
Earthworm	Metamitron (technical grade active ingredient)	14-d acute LC ₅₀	> 500 mg a.i./kg	0.432 mg a.i./kg*	< 0.01	No
	Metamitron 700SC	28-d chronic NOEC	104 mg a.i./kg (no effects at highest test concentration)	0.432 mg a.i./kg*	< 0.01	No

Organism	Test substance	Endpoint	Effect metric	EEC	RQ	Risk? (RQ > LOC)
	Desamino-metamitron (TP)	28-d chronic NOEC	5.5 mg a.i./kg (no effects at highest test concentration)	0.415 mg a.i./kg**	0.08	No
Collembola	Desamino-metamitron (TP)	28-d chronic NOEC	100 mg a.i./kg (no effects to reproduction)	0.415 mg a.i./kg**	0.01	No
Honey bee	Metamitron (technical grade active ingredient)	48-hr acute oral adult LD ₅₀	> 97.2 µg a.i./bee Note: 30% mortality in the highest test group	14.4 µg a.i./bee	< 0.15	No
	Metamitron (technical grade active ingredient)	48-hr acute contact adult LD ₅₀	> 100 µg a.i./bee	1.2 µg a.i./bee	< 0.012	No
	Metamitron (technical grade active ingredient)	10-d chronic adult NOEC	2.9 µg a.i./bee	14.4 µg a.i./bee	5	No Note: post-bloom applications only as it is a fruit thinning product
	Metamitron (technical grade active ingredient)	7-d single dose larvae LD ₅₀	78 µg a.i./bee	6.1 µg a.i./bee	0.078	No
	Metamitron (technical grade active ingredient)	22-d repeated feeding with larvae NOEC	13 µg a.i./bee (8-d survival and 22-d adult weight emergence and 22-d emergence)	6.1 µg a.i./bee	0.47	No
Parasitic wasp <i>Aphidius rhopalosiphi</i>	Metamitron (technical grade active ingredient)	48-hr glass plate Tier I LR ₅₀	> 810 g a.i./ha (0% mortality in highest test)	In-field: 860 g a.i./ha Off-field (airblast	In field: < 1.1 Off-field	No

Organism	Test substance	Endpoint	Effect metric	EEC	RQ	Risk? (RQ > LOC)
			concentration)	59%): 507 g a.i./ha	(airblast 59%): < 0.62	
Predatory mite <i>Typhlodromus pyri</i>	Metamitron (technical grade active ingredient)	7-d glass plate Tier I LR ₅₀	> 810 g a.i./ha (> 3% mortality in highest test concentration)	In-field: 860 g a.i./ha Off-field (airblast 59%): 507 g a.i./ha	In field: < 1.1 Off-field (airblast 59%): < 0.62	No
Vascular plant	AG-M4-150 SG	ER ₂₅	69.4 g a.i./ha (lettuce) Seedling emergence	In-field: 972 g a.i./ha Off-field (airblast 59%): 573 g a.i./ha	In- field: 14 Off-field (airblast 59%): 8.3	Yes
	AG-M4-150 SG	ER ₂₅	86.4 g a.i./ha (lettuce) Vegetative vigour	In-field: 860 g a.i./ha Off-field (airblast 59%): 573 g a.i./ha	In-field: 9.9 Off-field (airblast 59%): 6.6	Yes

* Based on the 90th percentile of PMRA# 3304623, 3304624, 3304625, 3304601 and 3304602.

**Based on molar ratio between metamitron and desamino-metamitron (0.93), based on molar mass of 202.2 g/mol for metamitron and 187.2 g/mol for desamino-metamitron.

LOC of 1, except for acute bee studies (LOC of 0.4) and LOC of 2 for predators and parasites for screening assessment.

For predators and parasites, the on-field EEC is the cumulative application rate with 10-day foliar half-life and the off-field EEC is the cumulative rate with dissipation and drift factor (59% for airblast during apple and pear thinning).

Table 27 Screening risk to birds based on cumulative application rate (504 g a.i./ha x 2 with 5-day interval and 10-day half-life) and maximum nomogram

Exposure and endpoint	Effect metric (mg a.i./kg bw/day)	Food guild (food item)	On-field	
			EDE (mg a.i./kg bw)	RQ
Small bird (0.02 kg)				
Acute LD ₅₀ /10	132.6	Insectivore	70.03	0.5
Reproduction NOAEL	39.2	Insectivore	70.03	1.8
Medium bird (0.1 kg)				
Acute LD ₅₀ /10	132.6	Insectivore	54.65	0.4
Reproduction NOAEL	39.2	Insectivore	54.65	1.4
Large bird (1 kg)				
Acute LD ₅₀ /10	132.6	Herbivore (short grass)	35.30	0.3
Reproduction NOAEL	39.2	Herbivore (short grass)	35.30	0.9

Bolded text exceed the level of concern (LOC = 1).

Table 28 Further characterization of risk to birds based on cumulative application rate (504 g a.i./ha x 2 with 5-day interval and 10-day half-life) for maximum and mean nomogram residues from on- and off-field exposure

Endpoint and feeding guild			Maximum nomogram residues				Mean nomogram residues			
			On-field		Off-field (59%)		On-field		Off-field (59%)	
Endpoint	Toxicity (mg a.i./kg bw/day)	Food guild (food item)	EDE (mg a.i./kg bw)	RQ	EDE (mg a.i./kg bw)	RQ	EDE (mg a.i./kg bw)	RQ	EDE (mg a.i./kg bw)	RQ
Small-sized bird (0.02 kg)										
Reproduction	39.20	Insectivore	70.03	1.8	41.32	1.1	48.36	1.23	28.53	0.73
Medium-sized bird (0.1 kg)										
Reproduction	39.20	Insectivore	54.65	1.4	32.25	0.8	37.74	0.96	22.26	0.57

Bolded text exceed the level of concern (LOC = 1).

Table 29 Risk to birds based on cumulative application rate (504 g a.i./ha x 2 with 5 day interval and 10 day half-life) and maximum nomogram residues on- and off-field considering a LOAEL

Exposure	LOAEL* (mg a.i./kg bw/d)	Food guild (food item)	On-field		Off-field (59%)	
			EDE (mg a.i./kg bw)	RQ	EDE (mg a.i./kg bw)	RQ
Small bird (0.02 kg)						
Reproduction	85.7	Insectivore	70.03	0.82	41.32	0.48

*< 10% from control reduction in weight of hatchling and 14-d old chicks.

Table 30 Percent of diet required to reach RQ for birds

Bird size and guild	RQ for reproductive NOAEL and maximum residues	% diet required to reach effect metrics (1/RQ x 100)	RQ for reproductive NOAEL and mean residues	% diet required to reach effect metrics (1/RQ x 100)	Effect metric for reproductive LOAEL and maximum residues	% diet required to reach effect metrics (1/RQ x 100)
On-field						
Small insectivore	1.8	56%	1.23	81%	RQ < LOC	> 100%
Medium insectivore	1.4	72%	RQ < LOC	> 100%	RQ < LOC	> 100%
Off-field						
Small insectivore	1.23	81%	RQ < LOC	> 100%	RQ < LOC	> 100%

Bolded text exceed the level of concern (LOC = 1).

Table 31 Screening risk to mammals based on cumulative application rate (504 g a.i./ha x 2 with 5-day interval and 10-day half-life) and maximum nomogram on field

Feeding guild	Toxicity (mg a.i./kg bw/day)	Feeding guild (food item)	EDE (mg a.i./kg bw)	RQ
Small-sized mammal (0.015 kg)				
Acute	64.40	Insectivore	40.28	0.63
Reproduction (NOAEL)	< 7.30	Insectivore	40.28	> 5.52
Medium-sized mammal (0.035 kg)				
Acute	64.40	Herbivore (short grass)	78.12	1.21

Feeding guild	Toxicity (mg a.i./kg bw/day)	Feeding guild (food item)	EDE (mg a.i./kg bw)	RQ
Reproduction (NOAEL)	< 7.30	Herbivore (short grass)	78.12	> 10.70
Large-sized mammal (1 kg)				
Acute	64.40	Herbivore (short grass)	41.74	0.65
Reproduction (NOAEL)	< 7.30	Herbivore (short grass)	41.74	> 5.72

Bolded text exceed the level of concern (LOC = 1).

Table 32 Further characterization of risk to mammals based on cumulative application rate (504 g a.i./ha x 2 with a 5-day interval and 10-day half-life) for maximum and mean nomogram residues from on- and off-field exposure

Endpoint and feeding guild			Maximum nomogram residues				Mean nomogram residues			
			On-field		Off-field (59%)		On-field		Off-field (59%)	
Endpoint	Toxicity (mg ai/kg bw/day)	Food guild (food item)	EDE (mg a.i./kg bw)	RQ	EDE (mg a.i./kg bw)	RQ	EDE (mg a.i./kg bw)	RQ	EDE (mg a.i./kg bw)	RQ
Small-sized mammal (0.015 kg)										
Reproduction NOAEL	< 7.30	Insectivore	40.28	> 5.52	23.8	> 3.26	27.8	> 3.81	16.4	> 2.25
	< 7.30	Frugivore (fruit)	12.47	> 1.71	7.4	> 1.01	5.9	> 0.815	3.5	> 0.48
Medium-sized mammal (0.035 kg)										
Acute oral	64.40	Herbivore (short grass)	78.12	1.21	46.1	0.72	27.7	0.431	16.4	0.25
	64.40	Herbivore (forage crops)	72.28	1.12	42.6	0.66	23.9	0.371	14.1	0.22

Endpoint and feeding guild			Maximum nomogram residues				Mean nomogram residues			
			On-field		Off-field (59%)		On-field		Off-field (59%)	
Endpoint	Toxicity (mg ai/kg bw/day)	Food guild (food item)	EDE (mg a.i./kg bw)	RQ	EDE (mg a.i./kg bw)	RQ	EDE (mg a.i./kg bw)	RQ	EDE (mg a.i./kg bw)	RQ
Reproduction NOAEL	< 7.30	Insectivore	35.31	> 4.84	20.8	> 2.85	24.4	> 3.34	14.4	> 1.97
	< 7.30	Frugivore (fruit)	10.93	> 1.50	6.4	> 0.88	5.2	> 0.714	3.1	> 0.42
	< 7.30	Herbivore (short grass)	78.12	> 10.7	46.1	> 6.31	27.7	> 3.80	16.4	> 2.24
	< 7.30	Herbivore (long grass)	47.70	> 6.53	28.1	> 3.86	15.6	> 2.13	9.2	> 1.26
	< 7.30	Herbivore (forage crops)	72.28	> 9.90	42.6	> 5.84	23.9	> 3.27	14.1	> 1.93
Large-sized mammal (1 kg)										
Reproduction NOAEL	< 7.30	Insectivore	18.87	> 2.58	11.1	> 1.52	13.0	> 1.79	7.7	> 1.05
	< 7.30	Herbivore (short grass)	41.74	> 5.72	24.6	> 3.37	14.8	> 2.03	8.7	> 1.20
	< 7.30	Herbivore (long grass)	25.49	> 3.49	15.0	> 2.06	8.3	> 1.14	4.9	> 0.67
	< 7.30	Herbivore (forage crops)	38.62	> 5.29	22.8	> 3.12	12.8	> 1.75	7.5	> 1.03

Bolded text exceed the level of concern (LOC = 1).

Table 33 Percent diet required to reach RQ of 1 for mammals

Effect metric (mg a.i./kg bw/d)	Mammal size and guild	Maximum residues				Mean residues			
		On-field RQ and maximum residues	% diet required to reach effect metrics (1/RQ x 100)	Off-field RQ and maximum residues	% diet required to reach effect metrics (1/RQ x 100)	On-field RQ and mean residues	% diet required to reach effect metrics (1/RQ x 100)	Off-field RQ and mean residues	% diet required to reach effect metrics (1/RQ x 100)
Small mammals									
Reproduction LOAEL (non- definitive NOAEL)	Small insectivore	5.52	18	3.26	31	3.81	26	2.25	44
	Small frugivore (fruit)	1.71	58	1.01	99	1	100	1	100
Medium mammals									
Acute LD ₅₀ /10	Medium herbivore (short grass)	1.21	83	0.89	> 100	< 1	> 100	< 1	> 100
	Medium herbivore (forage crops)	1.12	89	0.83	> 100	< 1	> 100	< 1	> 100
Reproduction LOAEL (non- definitive NOAEL)	Medium insectivore	4.84	21	2.85	35	3.34	30	1.97	51
	Medium frugivore (fruit)	1.50	67	1	100	1	100	1	100
	Medium herbivore (short grass)	10.7	9	6.31	16	3.8	26	2.24	45
	Medium herbivore (long grass)	6.53	15	3.86	26	2.13	47	1.26	79

Effect metric (mg a.i./kg bw/d)	Mammal size and guild	Maximum residues				Mean residues			
		On-field RQ and maximum residues	% diet required to reach effect metrics (1/RQ x 100)	Off-field RQ and maximum residues	% diet required to reach effect metrics (1/RQ x 100)	On-field RQ and mean residues	% diet required to reach effect metrics (1/RQ x 100)	Off-field RQ and mean residues	% diet required to reach effect metrics (1/RQ x 100)
	Medium herbivore (broadleaf plants)	9.90	10	5.84	17	3.27	31	1.93	52
Large mammals									
Reproduction LOAEL (non- definitive NOAEL)	Large insectivore	2.58	39	1.52	66	1.79	56	1.05	95
	Large herbivore (short grass)	5.72	17	3.37	30	2.03	49	1.20	83
	Large herbivore (long grass)	3.49	29	2.06	49	1.14	88	1	100
	Large herbivore (broadleaf plants)	5.29	19	3.12	32	1.75	57	1.03	97

Bolded text exceed the level of concern (LOC = 1).

Table 34 Screening-level risk assessment for aquatic organisms

Organism	Test substance	Endpoint	Effect metric	EEC (mg/L)	RQ	Risk? (RQ > LOC)
Freshwater organisms						
Freshwater invertebrates Daphnid	Metamitron (technical grade active ingredient)	EC ₅₀	2.9 mg a.i./L	0.12	0.04	No
		NOEC	10 mg a.i./L (reproduction and growth)	0.12	0.01	No
	Desamino-metamitron (TP)	EC ₅₀	375.5 mg TP/L	0.12	< 0.01	No
Freshwater fish Bluegill sunfish	Metamitron (technical grade active ingredient)	LC ₅₀	> 9.6 mg a.i./L	0.12	< 0.01	No
Freshwater fish Common carp	Metamitron (technical grade active ingredient)	LC ₅₀	19.4 mg a.i./L	0.12	< 0.01	No
Freshwater fish Rainbow trout	Metamitron (technical grade active ingredient)	LC ₅₀	22.2 mg a.i./L	0.12	< 0.01	No
Freshwater fish Golden orfe	Metamitron (technical grade active ingredient)	LC ₅₀	30 mg a.i./L	0.12	< 0.01	No
Freshwater fish Fathead minnow	Metamitron (technical grade active ingredient)	NOEC	10.3 mg a.i./L	0.12	0.01	No
Amphibians Fish as a surrogate (bluegill sunfish)	Metamitron (technical grade active ingredient)	LC ₅₀	> 9.6 mg a.i./L	0.65	< 0.07	No
Amphibians Fish as a surrogate (common carp)	Metamitron (technical grade active ingredient)	LC ₅₀	19.4 mg a.i./L	0.65	0.03	No
Amphibians Fish as a surrogate (fathead minnow)	Metamitron (technical grade active ingredient)	NOEC	10.3 mg a.i./L	0.65	0.06	No
Freshwater algae <i>Desmodesmus subspicatus</i>	Metamitron (technical grade active ingredient)	EC ₅₀ (yield)	0.155 mg a.i./L	0.12	0.87	No

Organism	Test substance	Endpoint	Effect metric	EEC (mg/L)	RQ	Risk? (RQ > LOC)
Freshwater diatom <i>Navicula pelliculosa</i>	Metamitron (technical grade active ingredient)	EC ₅₀ (yield)	0.14 mg a.i./L	0.12	0.79	No
Freshwater diatom <i>Raphidocelis subcapitata</i>	Desamino-metamitron (TP)	EC ₅₀ (yield and biomass)	13 mg TP/L	0.12	< 0.01	No
Aquatic vascular plants	Metamitron (technical grade active ingredient)	EC ₅₀ (yield)	0.141 mg a.i./L	0.12	0.86	No
Duckweed	Desamino-metamitron (TP)	EC ₅₀ (yield)	16.8 mg TP/L	0.12	< 0.01	No
Marine organisms						
Saltwater fish Sheepshead minnow	Metamitron (technical grade active ingredient)	LC ₅₀	9.4 mg a.i./L	0.12	0.01	No
Saltwater algae <i>Skeletonema marinoi</i>	Metamitron (technical grade active ingredient)	EC ₅₀ (biomass)	172.5 mg a.i./L	0.12	< 0.01	No

Table 35 List of supported uses

Items	Supported label claims for Brevis 150 SC and Brevis 15 SG	
Host crops	Apple and pear	
Application rate range (g a.i./ha)	Apple (west of Canadian Rockies): 168-504 Apple (east of Canadian Rockies): 168-336 Pear: 168-336	
	Rate used is dependent on the amount of fruit thinning required, the carbon status of the tree, cultivar sensitivity, tree age, degree of environmental stress, orchard cropping history, orchard management practices and the use of any other fruit thinning products.	
Product application rate range	Brevis 150 SC Apple (west of Canadian Rockies): Apple (east of Canadian Rockies): Pear: Brevis 15 SG Apple (west of Canadian Rockies): Apple (east of Canadian Rockies): Pear: 1.12-2.24	L/ha 1.12-3.36 1.12-2.24 1.12-2.24 Kg/ha 1.12-3.36 1.12-2.24 1.12-2.24
Adjuvant	Apples grown west of Canadian Rockies only: A non-ionic surfactant at 0.125% v/v may be used when conditions on the day of application favour fast droplet drying.	
Efficacy claims	Post-bloom fruitlet thinning when fruit set is higher than optimal in apple and pear.	
Application timing	Applied when fruit diameter is between 6 and 18 mm. For difficult to thin varieties that typically have high fruit set or in situations where the carbon status of the tree is high, a second treatment may be made 5–10 d after the first, provided that fruit diameter does not exceed 20 mm.	

Table 36 Toxic Substances Management Policy (TSMP) considerations-comparison to TSMP Track 1 criteria

TSMP Track 1 criteria	TSMP Track 1 criterion value		Active ingredient endpoints [metamitron]	TP endpoints [desamino-metamitron]	TP endpoints [M1]	TP endpoints [M2]
CEPA-toxic or CEPA-toxic equivalent ¹	Yes		Yes	Yes	Yes	Yes
Predominantly anthropogenic ²	Yes		Yes	Yes	Yes	Yes
Persistence ³	Soil	Half-life \geq 182 d	No Half lives: 3.4–42 d	No Half lives: 18.7–53 d	Not formed in soil	Not formed in soil
	Water	Half-life \geq 182 d	No Anaerobic water/sediment* half-life: 3.8–6.1 d Aerobic water/sediment half-life: 8.9–50 d	No studies conducted with only desamino-metamitron. Formed as a major TP from parent compound studies, and did not decline to below 50% by study termination. It is noted that desamino-metamitron dissipated within a couple of days in photolysis studies with metamitron.	No studies conducted with only M1. Formed in surface water from parent compound studies, and did not decline to below 50% by study termination.	No studies conducted with only M2. Formed in surface water from parent compound studies, and did not decline to below 50% by study termination.
	Sediment	Half-life \geq 365 d				
	Air	Half-life \geq 2 d, or evidence of atmospheric transport to	ND. The AOPWIN model is not suited for predicting the atmospheric half-life of metamitron	ND. The AOPWIN model is not suited for predicting the atmospheric half-life of desamino-	ND. The AOPWIN model is not suited for predicting the atmospheric half-life of M1 given the	ND. The AOPWIN model is not suited for predicting the atmospheric half-life of M2 given the

TSMP Track 1 criteria	TSMP Track 1 criterion value		Active ingredient endpoints [metamitron]	TP endpoints [desamino-metamitron]	TP endpoints [M1]	TP endpoints [M2]
		remote regions such as the Arctic	given the large fraction expected to be sorbed to airborne particles.	metamitron given the large fraction expected to be sorbed to airborne particles.	large fraction expected to be sorbed to airborne particles.	large fraction expected to be sorbed to airborne particles.
Bioaccumulation ⁴	Log $K_{ow} \geq 5$		No – 0.96	No – 2.46 (KOWWIN v1.68 predicted value)	No – 0.2 (KOWWIN v1.68 predicted value)	No – 0.8 (KOWWIN v1.68 predicted value)
	BCF ≥ 5000		NR	NR	NR	NR
	BAF ≥ 5000		Not available	Not available	Not available	Not available
Is the chemical a TSMP Track 1 substance (all four criteria must be met)?			No, does not meet TSMP Track 1 criteria.	No, does not meet TSMP Track 1 criteria.	No, does not meet TSMP Track 1 criteria.	No, does not meet 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 TP(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 BAF, the BCF, or the 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.

*Anaerobic water/sediment systems, not including anaerobic flooded soils.

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

Metamitron is an active ingredient that is being registered in Canada for use on apples and pears. The MRLs proposed for metamitron in Canada are the same as corresponding tolerances in the United States.

The American tolerances for metamitron are listed in the Electronic Code of Federal Regulations, 40 CFR Part 180, by pesticide.

Currently, there are no Codex MRLs¹⁰ listed for metamitron in or on any commodity on the Codex Alimentarius Pesticide Index website.

Table 1 compares the MRLs proposed for metamitron in Canada with corresponding American tolerances and Codex MRLs.

Table 1 Comparison of Proposed Canadian MRLs, American Tolerances and Codex MRLs

Food Commodity	Canadian MRL (ppm)	American Tolerance (ppm)	Codex MRL (ppm)
Apples; Pears	0.01	0.01	Not established

¹⁰ The Codex Alimentarius Commission is an international organization under the auspices of the United Nations that develops international food standards, including MRLs.

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A. List of studies/Information submitted by registrant

1.0 Chemistry

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3302997	2021, Metamitron: Evaluation of Dissociation Constant, DACO: 2.14.10
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2.0 Human and Animal Health

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3303529	1993, Metamitron Tech: Acute Oral Toxicity Study (Limit Test) in the Rat, DACO: 4.2.1
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3303537	1997, DRW 1139 Study on Acute Inhalation Toxicity in Rats According to OECD No. 403, DACO: 4.2.3
3303538	1993, Metamitron Tech: Acute Inhalation Toxicity Study Four-Hour Exposure (Nose Only) in the Rat, DACO: 4.2.3
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