Proposed Registration Decision PRD2026-13

Epyrifenacil, S-3100 0.46 EC Herbicide and V-10488 0.94 SE Herbicide

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Overview

Proposed Registration Decision for Epyrifenacil

Health Canada, pursuant to subsection 28(1) of the *Pest Control Products Act*, is proposing registration for the sale and use of S-3100 Technical (Rapidicil Technical), S-3100 0.46 EC Herbicide and V-10488 0.94 SE Herbicide, containing the active ingredient epyrifenacil. S-3100 0.46 EC Herbicide is to be applied pre-plant surface to canola, field corn, spring and winter wheat, and pre-plant surface and pre-emergence to soybean. V-10488 0.94 SE Herbicide is to be applied pre-plant surface to spring wheat and pre-emergence to soybean. Both products can also be used in fall burndown and fallow land programs, to maintain bare ground non-cropland, and for industrial vegetation management (IVM).

The co-active ingredient flumioxazin (in V-10488 0.94 SE Herbicide) is currently registered for the control of weeds in numerous crops and container-grown ornamentals. For details, see Evaluation Report ERC2010-05, *Flumioxazin*, Proposed Registration Decision PRD2013-20, *Flumioxazin*, and Registration Decision RD2014-11, *Flumioxazin*.

The co-active ingredient pyroxasulfone (in V-10488 0.94 SE Herbicide) is currently registered for the control of weeds in numerous crops. For details, see Proposed Registration Decision PRD2012-20, *Pyroxasulfone*, and Registration Decision RD2016-01, *Pyroxasulfone*.

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 epyrifenacil, S-3100 0.46 EC Herbicide and V-10488 0.94 SE Herbicide.

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 acceptable[1] if there is reasonable certainty that no harm to human health, future generations or the environment will result from use or exposure to the product under its proposed conditions of registration. The Act also requires that products have value[2] when used according to the label directions. Conditions of registration may include precautionary measures on the product label to further reduce risk.

To reach its decisions, Health Canada 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

[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."

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 regulates pesticides, the assessment process and risk-reduction programs, please visit the Pesticides and Pest Management portion of Canada.ca.

Before making a final registration decision on epyrifenacil, S-3100 0.46 EC Herbicide and V-10488 0.94 SE Herbicide, Health Canada 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 Decision[4] on epyrifenacil, S-3100 0.46 EC Herbicide and V-10488 0.94 SE Herbicide, 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 epyrifenacil?

Epyrifenacil is an inhibitor of protoporphyrinogen oxidase (PPO) in the chlorophyll biosynthetic pathway. Inhibiting PPO in plants leads to an accumulation of phototoxic chlorophyll precursors which, in the presence of light, produce activated oxygen species that disrupt cell membrane integrity and cause necrosis of plant tissues, leading to plant death. Epyrifenacil uses a novel binding mechanism and controls weed biotypes that are resistant to other chemical families classified as PPO inhibitor herbicides. Epyrifenacil is rapidly absorbed into foliage, and unlike other PPO inhibitor herbicides, it is translocated in the plant.

Health considerations

Can approved uses of epyrifenacil affect human health?

Products containing epyrifenacil are unlikely to affect your health when used according to proposed label directions.

Potential exposure to epyrifenacil may occur through the diet, or when handling and applying the end-use products. 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.

[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*.

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 technical grade active ingredient epyrifenacil was of low acute toxicity via the oral, dermal, and inhalation routes. It was minimally irritating to the eyes and skin. It did not cause an allergic skin reaction.

The acute toxicity of the end-use product S-3100 0.46 EC Herbicide, containing epyrifenacil, was low via the oral, dermal, and inhalation routes of exposure. S-3100 0.46 EC Herbicide was moderately irritating to the eyes and severely irritating to the skin. It caused an allergic skin reaction. Consequently, the signal word and hazard statements "DANGER – EYE AND SKIN IRRITANT" and "POTENTIAL SKIN SENSITIZER" are required on the label.

The acute toxicity of the end-use product V-10488 0.94 SE Herbicide, containing epyrifenacil, flumioxazin, and pyroxasulfone, was low via the oral, dermal, and inhalation routes of exposure. It did not cause an allergic skin reaction. V-10488 0.94 SE Herbicide was mildly irritating to the eyes and skin. Consequently, the signal word and hazard statement "CAUTION – EYE AND SKIN IRRITANT" is 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 epyrifenacil to cause neurotoxicity, immunotoxicity, chronic toxicity, cancer, reproductive and developmental toxicity, and various other health effects. The most sensitive endpoints for risk assessment were decreased anogenital distance and effects on the blood and the liver. There was no evidence to suggest that epyrifenacil damaged genetic material. Epyrifenacil did, however, cause liver tumours in male mice. There was no evidence of increased sensitivity of the young compared to adult animals. 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.

Occupational risks from handling S-3100 0.46 EC Herbicide and V-10488 0.94 SE Herbicide

Occupational risks are not of health concern when S-3100 0.46 EC Herbicide or V-10488 0.94 SE Herbicide is used according to the proposed label directions, which include protective measures.

Workers mixing, loading or applying S-3100 0.46 EC Herbicide or V-10488 0.94 SE Herbicide, and workers entering recently treated fields and non-cropland areas can be exposed to epyrifenacil residues through direct skin contact or through inhalation. Therefore, the product labels specify that anyone mixing, loading and applying the end-use products must wear the personal protective equipment specified in Appendix I, Tables 10 and 11. The labels also require that workers do not enter or be allowed into treated fields during the restricted-entry interval (REI) of 12 hours, except for non-crop areas where entry is permitted once sprays have dried. 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 from exposure to S-3100 0.46 EC Herbicide or V-10488 0.94 SE Herbicide are not of health concern when the end-use products are used according to the proposed label directions.

Health risks in residential and other non-occupational environments

Risks in residential and other non-occupational environments are not of health concern when S-3100 0.46 EC Herbicide or V-10488 0.94 SE Herbicide is used according to the proposed label directions, and restricted-entry intervals (REIs) are observed.

Residential exposure to S-3100 0.46 EC Herbicide or V-10488 0.94 SE Herbicide is not expected, as they are not proposed for use in residential areas or other non-occupational environments.

Health risks to bystanders

Bystander risks are not of health concern when S-3100 0.46 EC Herbicide or V-10488 0.94 SE Herbicide is 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 both product labels. Therefore, health risks to bystanders are not of concern when the end-use product is used according to the proposed label directions.

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 females 13–49 years old are exposed to less than 30% of the acute reference dose, 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 76% of the acceptable daily intake, and therefore are not of health concern.

On the strength of the overall information, it was determined that a threshold approach was appropriate for the cancer risk assessment based on the observed tumours. Overall, the endpoints selected for the chronic dietary risk assessment are considered protective of the findings, including potential cancer effects.

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 the *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 epyrifenacil is used according to the supported label directions, MRLs are being proposed as a result of this assessment (refer to PMRL2026-08, *Epyrifenacil*).

MRLs for epyrifenacil determined from the acceptable residue trials conducted throughout Canada and the United States, on soybeans, field corn, wheat, and canola can be found in the Science evaluation of this document.

One of these epyrifenacil end-use products, V-10488 0.94 SE Herbicide, is also formulated with the active ingredients flumioxazin and pyroxasulfone. These co-active ingredients are already registered for these uses in Canada, and residues in treated commodities will be covered under the existing MRLs for each active ingredient.

Environmental considerations

What happens when epyrifenacil is introduced into the environment?

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

Epyrifenacil would enter the environment when its end-use products, S-3100 0.46 EC Herbicide and V-10488 0.94 SE Herbicide, are used to control listed weeds in labelled crops and non-crop areas. Epyrifenacil is quickly broken down by sunlight in shallow water and by microorganisms in soil and water to form up to 18 major transformation products. The transformation products are less toxic than epyrifenacil, although some are more persistent in the environment. The transformation products of epyrifenacil may move through soil to reach groundwater. They may also move off the treatment area in spray drift or runoff. Epyrifenacil and its transformation products are not expected to move into air in significant quantities or to accumulate in the tissues of animals.

Without risk mitigation measures, the use of epyrifenacil at the proposed rates may cause adverse effects in aquatic organisms and non-target terrestrial plants. Risk mitigation measures to reduce risks to these organisms are described below. After a scientific review of the available information, Health Canada has concluded that environmental risks from the uses of epyrifenacil are acceptable when used according to the proposed label directions, which include the required risk mitigation measures.

Value considerations

What is the value of S-3100 0.46 EC Herbicide and V-10488 0.94 SE Herbicide?

S-3100 0.46 EC Herbicide provides burndown control of both grass and broadleaf weeds in canola, field corn, soybean, and wheat. V-10488 0.94 SE Herbicide provides burndown control of the weeds controlled by S-3100 0.46 EC Herbicide, and residual control of the weeds controlled by flumioxazin and pyroxasulfone in soybean and wheat. Both products can also be used in fall burndown and fallow land programs, to maintain bare ground non-cropland, and for industrial vegetation management (IVM).

S-3100 0.46 EC Herbicide, a formulation of epyrifenacil, is to be applied pre-plant surface to canola, field corn, and spring and winter wheat and pre-plant surface and pre-emergence to soybean. It can also be used in fall burndown and fallow land programs, to maintain bare ground non-cropland, and as well for IVM.

It provides burndown control of both grass and broadleaf weeds at a rate range of 182–363 mL/ha in canola and fall burndown and fallow land programs, 363–726 mL/ha in field corn, soybean, spring and winter wheat, and 726–1452 mL/ha to maintain bare ground non-cropland and for IVM.

V-10488 0.94 SE Herbicide, a co-formulation of epyrifenacil with registered active ingredients flumioxazin and pyroxasulfone, is to be applied pre-plant surface to spring wheat and pre-emergence to soybean. It can also be used in fall burndown and fallow land programs, to maintain bare ground non-cropland, and for IVM. It provides burndown control of the weeds controlled by S-3100 0.46 EC Herbicide and residual control of the weeds controlled by flumioxazin and pyroxasulfone at 1.75–2.0 L/ha in soybean and in fall burndown and fallow land programs, 1.75 L/ha in spring wheat, and 1.75–3.5 L/ha to maintain bare ground non-cropland and for IVM.

S-3100 0.46 EC Herbicide and V-10488 0.94 SE Herbicide provide contact and systemic control of a broad-spectrum of grass and broadleaf weeds, including many that are considered to be the most damaging problematic weeds in conservation crop tillage systems. Although epyrifenacil is classified as a Group 14 mode of action herbicide, it has a unique binding mechanism, which controls weed biotypes that are resistant to other chemical families within the same mode of action group. The application of these herbicides reduces early-season weed competition to the emerging crop, allowing the crop to benefit from additional moisture, nutrients, and light that would otherwise be captured by the weeds. Weed management at this time is critical as the crop does not compete well with weeds until crop canopy closure. Starting with a clean field is one of the most important steps in conservation crop tillage weed control and cover crop management to ensure maximum yield.

Measures to minimize risk

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

The key risk-reduction measures being proposed on the labels of S-3100 Technical, S-3100 0.46 EC Herbicide and V-10488 0.94 SE Herbicide 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 epyrifenacil through direct skin contact or inhalation of sprays, workers mixing, loading and applying S-3100 0.46 EC Herbicide or V-10488 0.94 SE Herbicide and performing cleaning and repair activities must wear the personal protective equipment presented in Appendix I, Tables 10 and 11. The labels also require that workers do not enter or be allowed entry into treated fields during the REI of 12 hours; and do not enter or allow others to enter treated non-cropland or industrial and vegetation areas until sprays have dried. Furthermore, a standard label statement to protect against drift during application is present on the labels.

Environment

The following mitigation measures are required on the labels of the end-use products, S-3100 0.46 EC Herbicide and V-10488 0.94 SE Herbicide:

- Precautionary statements indicating toxicity to aquatic organisms and terrestrial plants.
- Precautionary statements indicating the products contain aromatic petroleum distillates which are toxic to aquatic organisms.
- Mandatory spray buffer zones of up to 275 metres to minimize exposure of terrestrial and aquatic habitats from spray drift.
- Precautionary statements with best management practices to reduce runoff and leaching to groundwater.

Next steps

Before making a final registration decision on epyrifenacil, S-3100 0.46 EC Herbicide and V-10488 0.94 SE Herbicide, Health Canada 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 30 days from the date of publication (by the 20 September 2026) 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 Pesticides Regulatory Directorate Publications, through the Public Engagement Portal (Public Engagement Portal 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

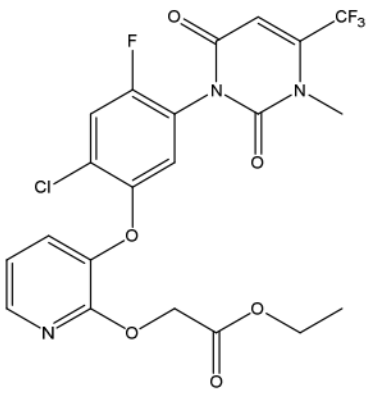
When Health Canada makes its registration decision, it will publish a Registration Decision on epyrifenacil, S-3100 0.46 EC Herbicide and V-10488 0.94 SE Herbicide (based on the Science evaluation of this consultation document). In addition, the test data referenced in this consultation document will be available for public inspection, upon application, in the Pesticides Regulatory Directorate’s Reading Room. For more information or if you have questions, please contact the Pesticides Information Service: pesticides-info@hc-sc.gc.ca

Science evaluation

Epyrifenacil, S-3100 0.46 EC Herbicide and V-10488 0.94 SE Herbicide

1.0 The active ingredient, its properties and uses

1.1 Identity of the active ingredient

Active substance	Epyrifenacil
Function	Herbicide
Chemical name	
1. International Union of Pure and Applied Chemistry (IUPAC)	ethyl [(3-{2-chloro-4-fluoro-5-[3-methyl-2,6-dioxo-4-(trifluoromethyl)-3,6-dihydropyrimidin-1(2*H*)-yl]phenoxy}-2-pyridyl)oxy]acetate
2. Chemical Abstracts Service (CAS)	ethyl 2-[[3-[2-chloro-5-[3,6-dihydro-3-methyl-2,6-dioxo-4-(trifluoromethyl)-1(2*H*)-pyrimidinyl]-4-fluorophenoxy]-2-pyridinyl]oxy]acetate
CAS number	353292-31-6
Molecular formula	$C_{21}H_{16}ClF_4N_3O_6$
Molecular weight	517.8 g/mol
Structural formula	
Purity of the active ingredient	98.0%

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

Technical Product - S-3100 Technical

Property	Result		
Colour and physical state	White solid		
Odour	No discernible odour		
Melting range	97.0 – 107.5°C		
Boiling point or range	Decomposes at ~ 212°C before boiling.		
Density	1.4 – 1.5 g/cm^3		
Vapour pressure at 20°C	1.3 × 10^{-13} Pa (= 1.3 × 10^{-10} mPa)		
Ultraviolet (UV)-visible spectrum	No dissociative activity observed between pH 1.2 and 13.2, degradation observed at pH 13.2		
	pH	λ_{max} (nm)	(ε) (L×mol^{-1}×cm^{-1})
	5.9	246	5410
	5.9	275	16500
	1.2	246	5480
	1.2	275	16700
	13.2	256	4570
	13.2	278	9220
Solubility in water at 20°C	pH	Solubility (mg/L)	
	5 – 6	3.69 – 4.12 ($\bar{x}$ = 3.91)	
Solubility in organic solvents at 20°C	Solvent	Solubility (g/L)	
	Methanol	46	
	Acetone	> 250	
	Toluene	> 250	
	Dichloromethane	> 250	
	Ethyl acetate	> 250	
	n-heptane	0.67	
	n-octanol	4.9	
n-Octanol-water partition coefficient (K_{ow})	log K_{ow} = 3.42		
Dissociation constant (pK_a)	The active ingredient is unionized in the pH range 1 to 13.		
Stability (temperature, metal)	The technical grade active ingredient is stable when stored at ambient (20 – 22°C) and elevated temperatures (54°C) for 14 days in the presence of metals (iron and aluminum) and metal ions (Iron (II) acetate and aluminum acetate, basic hydrate) The technical grade active ingredient is not corrosive to low-density polyethylene (LDPE) containers when stored for a year at 25°C and 50% relative humidity (RH).		

End-use product - S-3100 0.46 EC Herbicide

Property	Result
Colour	Light brown
Odour	Paint-like odour
Physical state	Liquid
Formulation type	Emulsifiable concentrate
Label concentration	Epyrifenacil at 55.1 g/L
Container material and description	The end-use product will be commercially available in fluorinated HDPE bottles/jugs and HDPE/EVOH totes.
Density	1.0 – 1.04 g/cm^3 at 20°C
pH of 1% dispersion in water	5.9
Oxidizing or reducing action	Does not contain potential oxidizing/reducing agents.
Storage stability	The active ingredient is stable in fluorinated HDPE for a year between 18.4 and 21.9°C.
Corrosion characteristics	Not corrosive to its fluorinated HDPE packaging.
Explodability	Product does not contains explosive ingredients.

End-use product — V-10488 0.94 SE Herbicide

Property	Result
Colour	White
Odour	Paint-like odour
Physical state	Opaque, viscous liquid
Formulation type	Emulsion
Label concentration	Epyrifenacil at 11.4 g/L Flumioxazin at 49.8 g/L Pyroxasulfone at 51.5 g/L
Container material and description	The end-use product will be commercially available in HDPE bottles.
Density	1.03 – 1.07 g/cm^3
pH of 1% dispersion in water	6.4 – 8.4
Oxidizing or reducing action	Does not contain potential oxidizing/reducing agents
Storage stability	The active ingredients are stable in HDPE for a year between 19.5 – 22.7°C.
Corrosion characteristics	Not corrosive to HDPE packaging.
Explodability	Product does not contain explosive ingredients.

1.3 Directions for use

1.3.1 S-3100 0.46 EC Herbicide

S-3100 0.46 EC Herbicide containing epyrifenacil at 55.1 g/L is a non-selective herbicide for burndown control of a broad-spectrum of broadleaf and grassy weeds in canola, field corn, soybean, spring and winter wheat, for use in fall burndown and fallow land programs, to maintain bare ground non-cropland, and for industrial vegetation management (IVM). In conservation tillage systems, it is to be applied in place of tillage to burndown emerged weeds and/or cover crops prior to planting or after planting but prior to the crop emergence.

- Canola: Apply up to 363 mL/ha at a minimum of seven days prior to planting. One application per year.
- Field corn and wheat (spring and winter): Apply up to 726 mL/ha at least one day prior to planting. A maximum of two applications per year with a minimum of 14-day interval is allowed and the maximum annual application rate is 726 mL/ha.
- Soybean: Apply up to 726 mL/ha prior to planting or up to 3-days after planting. A maximum of two applications per year with a minimum of 14-day interval is allowed and the maximum annual application rate is 726 mL/ha.
- For use in fall burndown and fallow land programs: Apply at 181–363 mL/ha in combination with labelled herbicides. A maximum of two applications per year with a minimum of 30-day interval is allowed and the maximum annual application rate is 726 mL/ha.
- To maintain bare ground non-cropland and for IVM: Apply up to 726 mL/ha in combination with labelled herbicides. A maximum of two applications per year with a minimum of 14-day interval is allowed and the maximum annual application rate is 1452 mL/ha.

S-3100 0.46 EC Herbicide may be applied using ground application equipment in a minimum of 100 L/ha of water. If weed populations are moderate to heavy and/or weeds are approaching maximum label growth stage and/or crop canopy is dense, use a minimum of 187 L/ha of water. S-3100 0.46 EC Herbicide may also be applied using aerial application equipment in a minimum of 70 L/ha of water.

S-3100 0.46 EC Herbicide must be applied in tank mix with one of the following adjuvants: 1% v/v crop oil concentrate (COC) or methylated seed oil (MSO) or 0.5% v/v Carrier. A spray grade nitrogen fertilizer, either 2.25 to 2.8 kg/ha or 28–32% nitrogen liquid fertilizer at 2.3–4.6 L/ha, may also be added to the spray tank to negate the effect of hard water.

For best results, apply S-3100 0.46 EC Herbicide to actively growing weeds up to 10 cm in height. S-3100 0.46 EC Herbicide may also be applied in tank mix with listed herbicides for increased burndown activity and as well for additional weed control.

Do not apply S-3100 0.46 EC Herbicide if rain is expected within one hour of application or efficacy may be reduced.

1.3.2 V-10488 0.94 SE Herbicide

V-10488 0.94 SE Herbicide is a coformulation of epyrifenacil at 11.4 g/L with the registered active ingredients flumioxazin at 49.8 g/L and pyroxasulfone at 51.5 g/L. The application of V-10488 0.94 SE Herbicide provides burndown control of weeds controlled by S-3100 0.46 EC Herbicide and residual control of weeds controlled by a precedent product containing flumioxazin and pyroxasulfone at the same active ingredient rates per hectare in soybean and spring wheat, for use in fall burndown and fallow land programs, to maintain bare ground non-cropland, and for IVM.

- Soybean: Apply pre-plant or within three days after planting at 1.75–2.0 L/ha. The higher rate of 2.0 L/ha is for use on medium-fine textured soils and for season-long residual weed control. Severe injury may occur if V-10488 0.94 SE Herbicide is applied when soybeans have begun to crack. Do not apply more than one application per year.
- Spring wheat (minimum and no-tillage only): Apply a minimum of 30 days prior to planting in no-till or minimum tillage fields at 1.75 L/ha. Do not apply more than one application per year.
- For use in fall burndown and fallow land programs: Apply at 1.75–2.0 L/ha in combination with labelled herbicides in the fall to provide burndown weed control in fields that will be planted the following spring. Application should be made in the fall, prior to freeze-up and when winter annual and perennial weeds are still growing to allow the optimum herbicide absorption and activity.
- To maintain bare ground non-crop areas and for IVM: Apply 1.75–3.5 L/ha prior to weed emergence for residual weed control or to weeds up to 10 cm in height for burndown weed control. V-10488 0.94 SE Herbicide may be applied twice per year with a minimum of 30-day interval. The maximum annual application rate is 3.5 L/ha.

    Use higher rates of V-10488 0.94 SE Herbicide in soils with high organic matter and/or high clay content and for season-long residual control.

    For optimal residual weed control, precipitation or sprinkler irrigation of at least 0.6 cm is required to bring the product into contact with germinating weed seeds. Otherwise, weed control may be improved by using a rotary hoe or similar equipment to incorporate the herbicide.

V-10488 0.94 SE Herbicide may be applied using ground application equipment only in a minimum of 100 L/ha of water. If weed populations are moderate to heavy and/or weeds are approaching maximum label growth stage and/or crop canopy is dense, use a minimum of 187 L/ha of water.

V-10488 0.94 SE Herbicide must be applied in tank mix with one of the following adjuvants: 1% v/v COC or MSO or 0.5% v/v Carrier. When an adjuvant is required by the tank mixture partner, use of 0.25% v/v non-ionic surfactant (NIS) is also allowed. When applying with a combination of COC and NIS, the burndown activity may be improved. A spray grade nitrogen fertilizer, either 2.25 to 2.8 kg/ha or 28-32% nitrogen liquid fertilizer at 2.3–4.6 L/ha, may also be added to the spray tank to negate the effect of hard water.

V-10488 0.94 SE Herbicide may be applied in tank mix with listed herbicides for increased burndown activity and/or for additional weed control.

Do not apply V-10488 0.94 SE Herbicide if rain is expected within one hour of application or efficacy may be reduced.

1.4 Mode of Action

Epyrifenacil is a phenyluracil herbicide which targets a specific enzyme, protoporphyrinogen oxidase (PPO), in the chlorophyll biosynthetic pathway. Inhibiting PPO in plants leads to an accumulation of phototoxic chlorophyll precursors which, in the presence of light, produce activated oxygen species that rapidly disrupt cell membrane integrity and cause necrosis of plant tissues. It uses a novel binding mechanism and controls weed biotypes that are resistant to other chemical families classified as PPO inhibitor herbicides. Epyrifenacil is rapidly absorbed into foliage, and unlike other PPO inhibitor herbicides, it is also translocated in both grass and broadleaf plants. Epyrifenacil also has minimal residual activity.

Foliar applied PPO inhibitor herbicides are recognized for quick burndown because of their rapid contact action and, as a result, possess minimal systemic properties. However, despite rapid contact action, epyrifenacil is also translocated in plants following absorption, which may account for superior control of grassy and broadleaf weeds compared to other PPO inhibitor herbicides. The downward translocation pattern of epyrifenacil ensures that a toxic level of herbicide accumulates at the base of young plants and kills the growing point.

Epyrifenacil is classified as a Group 14 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 methods provided for the analysis of the active ingredients in the formulations have been validated and assessed to be acceptable for use as enforcement analytical methods.

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. Acceptable recoveries (70–120%) were obtained in environmental media. Methods for residue analysis are summarized in Appendix I, Table 1a.

Plant and animal matrices: High performance liquid chromatography methods with tandem mass spectrometric detection (HPLC-MS/MS; Methods RM-52C-2b and RM-52C-1a in plant matrices and Methods RM-52T and RM-52AM-1 in animal matrices) were developed and proposed for data generation and enforcement purposes. These methods fulfilled the requirements with regards to specificity, accuracy and precision at the respective method limit of quantitation. Acceptable recoveries (70–120%) were obtained in plant and animal matrices. The proposed enforcement methods were successfully validated in plant and animal matrices by an independent laboratory. For crop matrices, adequate extraction efficiencies were demonstrated using radiolabelled samples analyzed with the enforcement method. For animal matrices, extraction solvents used in the method were similar to those used in the metabolism studies; thus, further demonstration of extraction efficiency with radiolabelled samples was not required for the enforcement method. Methods for residue analysis in plant and animal matrices are summarized in Appendix I, Table 1b.

3.0 Impact on human and animal health

3.1 Hazard assessment

3.1.1 Toxicology summary

Epyrifenacil (also known as S-3100) is a herbicide belonging to the pyrimidione class of chemicals. The primary pesticidal mode of action (MOA) of epyrifenacil is inhibition of protoporphyrinogen IX oxidase (PPO) in plants for non-selective burndown weed control. PPO inhibitors act by disrupting chlorophyll synthesis, with protoporphyrin IX accumulation leading to cell membrane and oxidative damage in plants. The same enzyme is also a component of a similar pathway in animals that is involved in heme biosynthesis. Deficiency of this enzyme is found in humans as an autosomal dominantly-inherited disease known as variegate porphyria.

A detailed review of the toxicology database for epyrifenacil was conducted. The database is complete, consisting of the full array of toxicity studies currently required for hazard assessment purposes. The applicant submitted several mechanistic studies to support a proposed MOA for tumour formation in the rat. Additionally, data were generated to explore the increased sensitivity in mice to PPO inhibition from exposure to epyrifenacil. The required studies were carried out in accordance with currently accepted international testing protocols and Good Laboratory Practices. Supplementary in vitro and in vivo studies were included for evaluation of metabolites.

In addition, quantitative structure-activity relationship (QSAR) analyses pertaining to genotoxicity and general toxicity of unchanged S-3100 and select metabolites of epyrifenacil were provided. The scientific quality of the data is acceptable and the database is considered adequate to characterize the majority of the toxic effects that may result from exposure to epyrifenacil.

The absorption, distribution, metabolism, and elimination profile of epyrifenacil was investigated alongside bile duct-cannulation experiments in rats using [phenyl-^{14}C]S-3100, [pyrimidinyl-4-^{14}C]S-3100, or [pyridyl-4(6)-^{14}C]S-3100 radiolabels. The toxicokinetic data demonstrated that orally administered epyrifenacil was rapidly and extensively absorbed from the gastrointestinal tract, distributed, and excreted. Absorption was estimated to be approximately 74% following administration of a low dose in both sexes as determined by the radioactivity detected in bile, urine and carcass. Peak concentrations in blood and plasma were reached within two to eight hours of dosing at the low dose level and within one to two hours of dosing at the high dose level. No significant dose-related change was observed in absorption and metabolism. No remarkable sex-related difference was observed in ^{14}C-concentrations in blood and plasma following a single dose; however, the half life ($T_{1/2}$) was longer and the area under curve (AUC) was larger (twofold) in females following repeat dosing. The tissue distribution of radioactivity was mainly located in the liver and kidneys. By 72 hours post-dosing, excretion was complete with no detectable radioactivity remaining in the carcass or tissues. No significant radiolabel- or sex-dependent differences were observed in distribution. The excretion of radioactivity was extensive and mostly via feces within 48 hours following administration. The major route of excretion was via the feces in both sexes, although a sex difference was noted with urinary excretion representing a greater portion of the administered dose (AD) in females. There were no significant changes in the excretion profiles by different doses or labels. ^{14}C-excretion with the pyrimidinyl label was higher via urine and expired air, and with the pyridyl label, excretion was higher via urine, compared to the phenyl label.

The metabolism of epyrifenacil was qualitatively similar between sexes regardless of dose level. The identification of select metabolites is presented in Appendix I, Table 2. Nine metabolites (S-3100-CA, S-3100-CA-UR, S-3100-CA-RD, 4"-OH-S-3100-CA, S-3100-CA-AM, S-3100-DA, S-3100-DP, S-3100-DA-UR, and (S)-TFP-Glu), as well as unchanged epyrifenacil, were identified in the rat. S-3100-CA was the predominant metabolite in bile, feces, and urine with all radiolabels (42.7-67.8% AD recovered in total in these matrices). The amount of S-3100-CA in urine of females was markedly high while it was barely detected in males. More unchanged epyrifenacil and less S-3100-CA (about 10% AD) were detected in feces at the high dose level. In plasma, liver, and kidney, unchanged epyrifenacil was not detected. The concentrations of major metabolites (S-3100-CA and 4"-OH- S-3100-CA) were noticeably higher in liver than in kidney and plasma.

The metabolic pathway of epyrifenacil was determined to include: 1) cleavage of the ester bond to form carboxylic acid derivatives; 2) hydroxylation of the 4”-position of the pyrimidine ring; 3) reduction of the double bond in the pyrimidine ring; 4) cleavage of the ether bond to form pyridone metabolites; 5) cleavage of the uracil ring followed by further elimination reaction to produce methyl urea derivatives; 6) further metabolism on the counterpart of the urea derivatives to produce the glucuronide of trifluoroisopropanol.

Technical epyrifenacil was of low acute toxicity via the oral, dermal, and inhalation routes in rats. It was minimally irritating to the rabbit eye and skin. Skin sensitization testing in guinea pigs using the Maximization method did not demonstrate a potential for sensitization.

Both end-use products, S-3100 0.46 EC Herbicide and V-10488 0.94 SE Herbicide, were of low acute toxicity via the oral, dermal, and inhalation routes in rats. S-3100 0.46 EC Herbicide was moderately irritating to the rabbit eye and was severely irritating when applied to the rabbit skin. V-10488 0.94 SE Herbicide was mildly irritating to the rabbit eye and skin. S-3100 0.46 EC Herbicide demonstrated dermal sensitization potential in the Buehler test in guinea pigs, whereas V-10488 0.94 SE Herbicide did not demonstrate a potential for sensitization in mice in the local lymph node assay (LLNA).

Repeat-dose toxicity studies with epyrifenacil were available in mice (diet), rats (diet, dermal, inhalation) and dogs (capsule). In these studies, the most sensitive species for toxicity was the mouse, followed by the rat and dog. In vitro PPO inhibition studies confirmed these results by providing evidence that rodents in general and mice especially were more sensitive than non-rodent species including humans. To an extent, male mice appear to be more sensitive than female mice.

The primary target of toxicity for all species was the heme biosynthesis pathway via PPO enzyme inhibition. Alterations in the erythropoietic system were consistently observed in all examined species, with red blood cell parameters being affected. These included decreases in erythrocyte counts, hemoglobin, hematocrit, mean cell volume, mean corpuscular hemoglobin, or mean corpuscular hemoglobin concentrations and increases in reticulocyte counts. These effects led to microcytic hypochromic anemia in experimental animals.

Other target organs affected by epyrifenacil were the liver (mouse, rat and dog), spleen and heart (rat), and bone marrow (rat and dog). The findings in the liver, spleen, and bone marrow indicative of extramedullary hematopoiesis suggest an adaptive response to reduced circulating red blood cells brought about by the MOA of epyrifenacil. Increases in liver enzymes and liver weight as well as pathology of the liver were observed in mice, rats, and dogs. Histopathology changes in the liver included increased incidence of pale liver, single cell degeneration/necrosis, hepatocellular hypertrophy, hepatocellular single cell necrosis/apoptosis, and liver mixed cell infiltrate in mice, liver bile duct hyperplasia and multifocal hepatocellular degeneration/necrosis in rats, and liver glycogen in dogs.

The exposure of rats to epyrifenacil via the dermal route for 28 days resulted in increased sternum and femur bone marrow erythropoiesis, spleen extramedullary hematopoiesis, and decreased red blood cell parameters as well as increased liver enzymes and liver weight. The exposure of rats to epyrifenacil via the inhalation route for 90 days resulted in increased incidences of degeneration and inflammatory cell infiltrate and/or squamous metaplasia of the olfactory epithelium in nasal turbinates as well as increased liver and/or kidney weights along with decreased α-1 globulin concentration at the high dose.

Epyrifenacil was negative in a battery of in vitro and in vivo genotoxicity assays.

Long-term dietary toxicity studies in mice and rats demonstrated systemic toxicity similar to the findings in shorter-term studies. Increases in liver enzymes, liver and spleen weight, and increased incidences of regenerative hepatocellular hyperplasia, vacuolation of periportal hepatocytes, mixed cell inflammation, chronic centrilobular inflammation, centrilobular fibrosis, and karyocytomegaly were observed in mice. Increased incidences of hepatocellular adenomas and/or carcinomas were observed in males of the higher dose groups in the mouse dietary carcinogenicity study. An MOA for the development of the liver tumours in mice was proposed by the applicant in conjunction with supplied mechanistic studies to support this proposed MOA. For the liver tumours in males, a porphyria-mediated cytotoxicity MOA was proposed. This MOA posits that administration of the test substance induces PPO inhibition resulting in accumulation of porphyrin in hepatocytes. Accumulation of protoporphyrin IX (PPIX) is followed by hepatocyte injury and subsequent regenerative proliferation. Eventually, this progresses to hepatocyte tumour formation. The provided mechanistic data included in vitro PPO inhibition measurements in multiple studies, studies on the effects of liver alteration, a PPIX distribution study by mass spectrometry imaging analysis, a PPIX measurement study, and studies examining cellular uptake and clearance of epyrifenacil, S-3100-CA, and downstream metabolites by hepatocytes sampled from multiple species including humans. These mechanistic data, in conjunction with the full toxicity database, were supportive of the proposed MOA. Other possible tumourigenic MOAs, including genotoxicity, PPARα activation, and constitutive androstane receptor (CAR), pregnane X receptor (PXR), or aryl hydrocarbon receptor (AhR) activation, were considered to be inconsistent with the available data. Although mice have been shown to be considerably more sensitive to the liver tumour precursor events than humans, this tumourigenic MOA has not been excluded from being relevant to humans. Overall, the weight of evidence supported the proposed MOA and a threshold approach for cancer risk assessment was considered appropriate for the liver tumours.

In the rat dietary carcinogenicity study, increases in liver weight as well as incidences of cystic degeneration, bile duct hyperplasia, hepatocellular pigment, liver single cell necrosis, liver sinusoidal pigment, and liver coagulative necrosis were observed. There was no evidence to indicate that epyrifenacil was tumourigenic in rats.

There was limited evidence of reproductive toxicity in the 2-generation reproductive dietary toxicity study in rats with increased ovarian primordial follicles observed in F1 females; a measure of growing follicles was not assessed. While there was no evidence of reproductive toxicity in the 1-generation range-finding dietary toxicity studies in rats, this study is limited in its ability to characterize hazard given its primary design to inform dose-selection for the main study. Parental toxicity in the main 2-generation toxicity study was consistent with the hematotoxicity and hepatotoxicity observed throughout the database. Increases in liver and spleen weights and incidences of bile duct hyperplasia, Kupffer cell pigment, and hepatocellular necrosis, as well as decreases in red blood cell parameters were observed in parental animals. Additionally, cystic degeneration of the adrenal glands and increased ovarian primordial follicle counts were observed in F1 females. Also in the 2-generation study, in the offspring, increased spleen weight, delayed sexual maturation (F1), and decreased anogenital distance (AGD) and anogenital index (AGI) (F2) were observed in both sexes. Increased mortality in F1 males starting on post-natal day (PND) 45 was also observed. This mortality was preceded by severe clinical signs and coincident with markedly decreased body weight gains and hematology parameters; therefore the mortality was considered to be a result of repeated exposures. The extent of the changes in hematological parameters were greater in the F1 males than in the F0

animals, although a true comparison was not possible due to the different ages at sampling between the two groups. Due to increased mortality at the high-dose, the F1 males were removed from treatment and eventually terminated, and the F1 females were mated to the control animals. As a result, the study is limited in that the potential reproductive toxicity at the high dose level in the F1 animals could not be fully assessed. This study was considered acceptable with limitations. The increased mortality, delayed sexual maturation, and decreased AGD/AGI elicit concern for potential toxicity in developing young and young adults that were exposed throughout development. The applicant proposed that the observed delays in sexual maturation were a result of anemic conditions in the young animals rather than a directly toxic effect from epyrifenacil. A battery of in vivo and in vitro endocrine studies using epyrifenacil and S-3100-CA were negative. Supplemental reproductive toxicity studies with rats using an anemia-inducing positive control substance and blood withdrawal protocols to emulate anemia also resulted in delayed sexual maturation, but overall, there were insufficient data to decisively conclude that the observed delays in sexual maturation were solely due to anemia. While in vitro endocrine assays were negative, the cystic degeneration of the adrenal glands in F1 adults and the decreased anogenital distance in F2 pups suggested potential in vivo effects on the endocrine system. Furthermore, the observed statistically significant increase in offspring body weight at attainment of sexual maturation suggests that increased time to reach sexual maturity was not due to developmental delays.

In an oral gavage developmental toxicity study in rats, liver toxicity (focal hepatocyte necrosis, hepatocyte hypertrophy) and changes in hematological parameters (mainly decreased red blood cell parameters) were observed in maternal animals, consistent with target organ toxicity across the database. Developmentally, there was a decrease in fetal weights and increased variations (supernumerary cervical ribs, nodulated ribs) in fetuses at maternally toxic doses. In an oral gavage developmental toxicity study in rabbits, decreased red blood cell parameters were observed in maternal animals at the highest dose tested. At the same dose, an increased incidence of a malformation, supernumerary lumbar vertebra, was observed in fetuses in the presence of maternal toxicity.

Epyrifenacil showed no evidence of selective neurotoxicity in the oral acute neurotoxicity study in rats. Decreased activity level and decreased approach response were observed in females after acute exposure, but these findings were marginal and occurred at a very high dose level. There were no treatment-related neurotoxic effects in the 90-day dietary neurotoxicity study in rats. Decreased red blood cell parameters were observed in both sexes along with increased platelets and decreased eosinophils in males in the 90-day dietary neurotoxicity study.

An extensive set of non-guideline mechanistic data were generated by the applicant to explore the toxicology profile of epyrifenacil and the principal metabolite S-3100-CA. They included comparative in vitro assays using mouse, rat, rabbit, dog, and human hepatocytes. There were also in vivo studies in mice, rats, and chimeric mice with humanized livers. These chimeric mice were developed and validated independently by the applicant. The host mouse liver cells were replaced with healthy human donor liver cells, which provided an indication for potential human liver toxicity in an in vivo test system. Additionally, the applicant provided evidence that incorporated all of the available data to explain the proposed MOA. This dataset in its entirety was critical in evaluating species sensitivity associated with epyrifenacil treatment. In all test systems, there was evidence that rodents in general and mice specifically were considerably more sensitive to PPO inhibition from epyrifenacil than other tested species including humans.

Although the long-term mouse study demonstrated an effect that is qualitatively relevant to humans (liver toxicity), the balance of the toxicology database and a battery of in vivo and in vitro mechanistic data showed an increased mouse-specific quantitative sensitivity that undermined its suitability as the critical point of departure for human health risk assessment. The in vitro human and in vivo chimeric mouse data suggested that human sensitivity may be more comparable to non-rodents such as dogs and rabbits than to the rodent species due to measurable and consistent toxicokinetic and toxicodynamic differences. Human cells repeatedly showed lower epyrifenacil uptake, lower PPO inhibition (represented by higher IC_{50} values), lower PPIX accumulation, and lower resultant toxicity in the test system when compared to cells from mice.

To assess epyrifenacil's mechanism of toxicity (PPO inhibition), species-specific data were available at the whole body, tissue, cell, and sub-cellular levels. To complement data from mice and other test species, human donor mitochondrial fraction, hepatocyte, and liver tissue data were also available. The liver tissues were assayed within chimeric mice. All of the available data showed that mice were consistently significantly more sensitive to PPO inhibition from epyrifenacil than other tested species including humans. This broad set of mechanistic data considered alongside the standard toxicology studies was critical for selection of the point of departure. Based on the overall evidence from these studies, mouse PPO inhibition was not considered to be a suitable model for health risk assessment in humans nor for establishing toxicology reference values.

Waiver rationales were provided for the conditionally required immunotoxicity study, delayed neurotoxicity study, and developmental neurotoxicity study. The waivers were accepted based on the absence of relevant treatment-related effects in the toxicological database that would trigger the requirement for additional testing.

Nine downstream metabolites of epyrifenacil and its primary metabolite S-3100-CA were examined in short-term dietary toxicity studies and/or genotoxicity studies. The dietary studies frequently produced effects consistent with PPO inhibition, but at much higher dose levels than epyrifenacil or S-3100-CA, suggesting that these metabolites had lower potency. These results agreed with the findings from in vitro PPO inhibition assays. There was no evidence of genotoxicity in a battery of in vitro studies conducted with metabolites of epyrifenacil (S-3100-DA, S-3100-DP-Me, S-3100-CA-RD, S-3100-PR, 4"-OH-S-3100-CA, S-3100-CA-UR, S-3100-BFP, S-3100-DP, and APPE). For the purposes of risk assessment, the metabolites were considered to be of equivalent or lesser toxicity than epyrifenacil.

In silico genotoxicity and a general toxicity assessment of the impurities of epyrifenacil was considered. No additional concern was identified for any of the impurities in any of the endpoints in comparison to unchanged S-3100.

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 epyrifenacil and relevant metabolites and with its associated end-use products, are summarized in Appendix I, Tables 4, 5 and 6, respectively.

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 database contains the required studies including developmental toxicity studies in rats and rabbits and a 2-generation reproductive toxicity study in rats. Dose-range-finding studies were also available to support dose level selection in the main developmental toxicity and reproductive toxicity studies.

With respect to potential prenatal and postnatal toxicity, there was no evidence of sensitivity of the young in rats or rabbits, in that effects in the fetus or offspring occurred at dose levels at which maternal toxicity was also observed. However, the increased mortality in F1 males starting at PND 45 was considered to represent a generational sensitivity/effect as these descendant males exposed to epyrifenacil throughout development appeared to be more susceptible than F0 animals that only exhibited hematological and liver toxicity. Increased spleen weight, delayed sexual maturation in F1 and decreased anogenital distance in F2 were also observed in offspring at the same dose level. In a gavage developmental toxicity study in rats, supernumerary cervical ribs, nodulated ribs, and decreased fetal body weight were observed in fetuses in the presence of significant maternal toxicity (focal subcapsular (hepatocyte) necrosis and altered hematological parameters). Concern for these findings was tempered by the non-serious nature of the effects and the presence of maternal toxicity at the same dose level. In the gavage rabbit developmental toxicity study, the malformation of supernumerary lumbar vertebra was observed at the highest dose level in the presence of maternal toxicity (decreases in hemoglobin, hematocrit, and mean corpuscular hemoglobin).

Overall, the database is adequate for determining the sensitivity of the young. Effects in the young are well-characterized and occurred at dose levels also producing maternal toxicity. The fetal malformations in rabbits, decreased anogenital distance in F2 rats and increased mortality in young F1 rats were considered serious effects, though concern was tempered by the fact that they were observed at dose levels also producing maternal toxicity. Therefore, the *Pest Control Products Act* (PCPA) factor was reduced to threefold for scenarios in which these endpoints (supernumerary lumbar vertebra, reduced anogenital distance or F1 male mortality) are used to establish the point of departure for risk assessment. For all other scenarios, the PCPA factor may be reduced to onefold.

[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

For mixers, loaders and applicators, occupational exposure to S-3100 0.46 EC Herbicide or V-10488 0.94 SE Herbicide is characterized as short- to intermediate-term (<30 days to <6 months) in duration and is predominantly by the dermal and inhalation routes. For postapplication workers, occupational exposure to S-3100 0.46 EC Herbicide or V-10488 0.94 SE Herbicide is characterized as short- to intermediate-term in duration and is predominantly by the dermal route.

Acute and chronic dietary exposure to epyrifenacil is expected.

3.2.2 Occupational toxicology reference values

Short- and intermediate-term dermal and inhalation - Occupational

For short- and intermediate-term dermal and inhalation exposures, the offspring NOAEL of 6.8 mg/kg bw/day from the 2-generation reproductive toxicity study in rats was selected. At the LOAEL of 21 mg/kg bw/day, post-weaning F1 male deaths, delayed sexual maturation and decreased anogenital distance were observed in the presence of parental toxicity. The existing short-term dermal toxicity study did not address the endpoints of concern, thus necessitating the use of an oral study for risk assessment.

For occupational scenarios, the target MOE for this endpoint is 300. Ten-fold factors were applied each for interspecies extrapolation and intraspecies variability and a factor of threefold was applied 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 the unborn children and nursing infants of exposed female workers.

3.2.3 Acute reference dose (ARfD)

Females 13–49 years of age

To estimate acute dietary risk for females of reproductive age, the 2-generation reproductive toxicity study in rats with an offspring NOAEL of 6.8 mg/kg bw/day was selected for risk assessment. At the LOAEL of 21 mg/kg bw/day, decreased anogenital distance was observed in F2 offspring in the presence of parental toxicity. This effect was potentially the result of a single exposure within a critical window of development and is 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 threefold. The composite assessment factor (CAF) is thus 300.

The ARfD is calculated according to the following formula:

$$\text{ARfD} = \frac{\text{NOAEL}}{\text{CAF}} = \frac{6.8 \text{ mg/kg bw}}{300} = 0.02 \text{ mg/kg bw of epyrifenacil}$$

The selection of this study provides sufficient margins to the point of departure for malformations observed in the rabbit developmental toxicity study.

General population (excluding females 13–49 years of age)

Establishment of an acute reference dose for the general population (excluding females 13–49 years of age) is not required as an endpoint of concern attributable to a single exposure was not identified in the oral toxicity studies for this sub-population.

3.2.4 Acceptable daily intake (ADI)

To estimate risk following repeated dietary exposure, the lowest NOAEL of 1.4 mg/kg bw/day in females from the oncogenicity study in rats was selected. At the LOAEL of 8.3/9.5 mg/kg bw/day (males/females), observations included increased alkaline phosphatase and decreased mean cell volume and mean cell hematocrit with increased incidences of heart necrosis and cystic degeneration in males and increased hepatocellular hypertrophy in both sexes. This study represents the lowest NOAEL in the database for effects considered relevant to humans.

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 CAF is thus 100.

The ADI is calculated according to the following formula:

$$\text{ADI} = \frac{\text{NOAEL}}{\text{CAF}} = \frac{1.4 \text{ mg/kg bw/day}}{100} = 0.01 \text{ mg/kg bw/day of epyrifenacil}$$

The ADI provides a margin of 170 to the NOAEL for liver tumours observed in the mouse oncogenicity study and is considered to be protective of any concerns regarding potential carcinogenicity.

The ADI provides a margin of 680 to the NOAEL for the mortality observed in F1 generation males of the rat 2-generation reproductive toxicity study.

3.2.5 Cancer assessment

There was adequate evidence to support a threshold-based mechanism for the liver tumours in male mice in the dietary oncogenicity study. The ADI and the selected reference values for occupational exposure provide sufficient margins to not only the dose at which these tumours were observed, but also the precursor toxicological events that lead to tumour formation. Therefore, the toxicology reference values selected for use in the non-cancer risk assessment are considered to be protective of any concerns regarding potential tumourigenicity.

3.3 Dermal absorption

A human and rat in vitro dermal absorption study conducted with S-3100 5.5 EC Herbicide (which was confirmed to be equivalent to S-3100 0.46 EC Herbicide) was reviewed. Overall, the study was considered acceptable for the selection of a dermal absorption value for the exposure and risk assessment. Considering SPN2026-01, *Updated policy on the use of in vitro dermal*

absorption studies in risk assessment, based on an analysis of the factors that can impact absorption (such as formulation, product composition, and doses), the human in vitro data are considered acceptable for selecting a dermal absorption value for use in the exposure and risk assessment for epyrifenacil. In addition, based on the comparison of formulation type, product composition and irritation/sensitization properties of the two proposed products, the study conducted with S-3100 0.46 EC Herbicide is also adequate to represent the dermal absorption of the other proposed product V-10488 0.94 SE Herbicide.

As such, based on the data presented in the study (Appendix I, Table 7), a dermal absorption value of 12% was selected for the risk assessment of epyrifenacil from the mid-dose group (49.8 µg/cm^2), which had the highest dermal absorption of the human in vitro study.

3.4 Occupational and residential exposure assessment

3.4.1 Acute hazards of end-use products and mitigation measures

3.4.1.1 S-3100 0.46 EC Herbicide

The acute hazard assessment indicated that S-3100 0.46 EC Herbicide is of low acute toxicity via the oral, dermal and inhalation routes of exposure to rats. It is moderately irritating to the eyes and severely irritating to the skin in rabbits. The product is a skin sensitizer in the Buehler Test in guinea pigs. Based on these acute hazards, coveralls over a long-sleeved shirt and long pants, socks, chemical-resistant footwear, chemical-resistant gloves and goggles/face shield are required for workers during mixing, loading, application, clean-up and repair.

3.4.1.2 V-10488 0.94 SE Herbicide

The acute hazard assessment indicated that the toxicity of V-10488 0.94 SE Herbicide is low via the oral, dermal, and inhalation routes of exposure. V-10488 0.94 SE Herbicide is mildly irritating to the eyes and skin. It does not cause an allergic skin reaction. Based on these acute hazards, no additional personal protective equipment (PPE) is triggered for workers during mixing, loading, application, clean-up and repair. A long-sleeved shirt, long pants, socks, shoes, and chemical-resistant gloves are considered acceptable to protect against the acute hazard of V-10488 0.94 SE Herbicide.

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 epyrifenacil during mixing, loading, application, clean-up and repair. Dermal and inhalation exposure estimates were generated from the Agricultural Handlers Exposure Task Force (AHETF) database, the Pesticide Handlers Database (PHED, v1.1) for mixers, loaders and applicators applying S-3100 0.46 EC Herbicide to canola, field corn, soybean, wheat (spring and winter), fall burndown and fallow seedbed programs, and bare ground and industrial vegetation management using ground (field sprayer, right-of-way sprayer, mechanically-pressurized handgun, backpack sprayer, manually-pressurized handwand) and aerial equipment and V-10488 0.94 SE Herbicide to soybean, spring wheat, fall burndown and fallow land programs, and bare ground and industrial vegetation management using ground equipment (field sprayer, right-of-way sprayer, mechanically-pressurized handgun, backpack

sprayer, manually-pressurized handwand). The PPE in the risk assessment is based on handlers wearing a single layer and chemical-resistant gloves (gloves are not required within a closed cab or cockpit) (Appendix I, Tables 8 and 9).

Dermal exposure was estimated by combining the unit exposure values with the amount of product handled per day and the dermal absorption value of 12%. Inhalation exposure was estimated by combining the unit exposure values with the amount of product handled per day and 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 toxicological reference value to obtain the margin of exposure (MOE); the target MOE for epyrifenacil 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 labelled crops and sites, and are therefore not of health concern (Appendix I, Table 9).

Overall, to reduce the potential exposure of workers to epyrifenacil through direct skin contact or inhalation of sprays, workers mixing, loading and applying S-3100 0.46 EC Herbicide or V-10488 0.94 SE Herbicide and performing cleaning and repair activities must wear the PPE presented in Appendix I, Tables 10 and 11.

3.4.2.2 Postapplication exposure and risk assessment

The proposed crop uses of S-3100 0.46 EC Herbicide are preplant spring applications on fields where labelled crops will be growing, burndown fall treatment to fallow lands, and bare ground non-crop areas of farms and industrial settings. Similarly, the proposed non-crop uses of V-10488 0.94 SE Herbicide are as preplant/preemergent to labelled crops, burndown fall treatment to fallow lands, and bare ground non-crop areas of farms and industrial settings. It is expected that the main postapplication activity, if any, would be scouting for remaining weeds, and this visual inspection does not require the workers to be as close to the plants as they would be when scouting crops for fungi or insects. Consequently, the dermal exposure to workers scouting for weeds would be minimal, and therefore, a quantitative postapplication dermal risk assessment is not required.

Inhalation exposure is not expected and a quantitative risk assessment is not required, as epyrifenacil is considered non-volatile with a vapour pressure of 1.3×10^{-16} kPa (at 20°C), which is less than the North American Free Trade Agreement (NAFTA) criterion for a non-volatile product for outdoor scenarios [1×10^{-4} kPa at 20–30°C]. Inhalation risk is not of health concern for postapplication workers as epyrifenacil is considered to be non-volatile and the restricted-entry interval of 12 hours for agricultural crops and until sprays have dried for non-crop areas will allow residues to dry, suspended particles to settle and vapours to dissipate.

3.4.3 Residential exposure and risk assessment

3.4.3.1 Handler exposure and risk assessment

S-3100 0.46 EC Herbicide and V-10488 0.94 SE Herbicide are not domestic class products and are not permitted for use in residential settings; therefore, a residential handler exposure assessment is not required.

3.4.3.2 Postapplication exposure and risk assessment

S-3100 0.46 EC Herbicide and V-10488 0.94 SE Herbicide are not domestic class products and are not permitted for use in residential settings; therefore, a residential postapplication exposure assessment is not required.

3.4.4 Bystander exposure and risk assessment

Bystander exposure is considered negligible as application is limited when there is low risk of drift beyond the area to be treated, 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 and animal origin

The residue definition for risk assessment and enforcement in plant and animal food commodities is epyrifenacil. The data gathering and enforcement analytical methods are valid for the quantitation of epyrifenacil residues in crop and livestock matrices. The residues of epyrifenacil are stable in representative matrices from five commodity categories (high water, high oil, high protein, high starch and high acid content) for up to 13.5 months when stored at -20°C. Therefore, epyrifenacil residues are considered stable in all raw agricultural commodities and processed commodities for up to 13.5 months. The raw agricultural commodities of soybean, field corn, wheat, and canola were processed, but not further analyzed due to the lack of quantifiable epyrifenacil residues. As such, it can be concluded that epyrifenacil residues in processed fractions do not concentrate. Based on the estimated dietary burdens using residues from crop field trials, and data from the animal metabolism studies, quantifiable residues are not expected to occur in edible animal food commodities with the current use pattern. Crop field trials conducted throughout Canada and the United States using end-use products containing epyrifenacil at approved rates in or on soybeans, field corn, wheat, and canola are sufficient to support the proposed maximum residue limits. Field rotational crop studies were conducted in/on wheat, radish, and lettuce. The field accumulation data are adequate to demonstrate that a 30-day plantback interval for small grain cereals and a 60-day plantback interval for all other non-labeled crops are appropriate. Labeled crops may be replanted anytime.

Common environmental transformation product: Trifluoroacetic acid (TFA)

Epyrifenacil contains a $–CF_3$ group at the C4 position of the pyrimidine ring, where the electronic environment suggests the potential for TFA formation. However, whether $–CF_3$ cleavage actually occurs, and at what rate, depends on multiple factors, including ring electronics, substituent effects, metabolic pathways, and specific environmental degradation conditions.

In epyrifenacil soil metabolism studies (aerobic and anaerobic), TFA was not analyzed, but mass balance indicated that TFA did not form.

In confined rotational crop metabolism studies, TFA was identified as a major metabolite in rotational crops; however, these studies are designed as worst-case scenarios: plants are grown in pots where residues stay in the root zone, making them more available for uptake. As a result, residues in these studies are typically much higher than in field accumulation studies. Under real agricultural conditions, residues can dissipate, degrade, bind to soil, or move within the environment, reducing plant uptake.

The field accumulation results for epyrifenacil, reflective of real agricultural practice, showed that TFA residues in untreated samples (control plots) were at similar or higher levels (<0.07–0.64 ppm) than those in treated samples (<0.07–0.12 ppm), indicating background environmental TFA rather than formation from epyrifenacil.

Therefore, the available evidence indicates epyrifenacil, even with the potential to form TFA, is not a significant contributor to TFA levels in the environment.

As a result, TFA was not included in the residue definitions for epyrifenacil. Any TFA present in crops is expected to come from background environmental levels, not from pesticide application, and does not meaningfully contribute to dietary exposure.

Additional information on TFA in the environment

TFA is a degradation product formed from many chemicals containing a $C–CF_3$ group. The dominant global source of TFA is the atmospheric oxidation of volatile fluorinated refrigerants and blowing agents, which is then deposited onto land and water systems through precipitation.

Its high water solubility and low soil sorption allow it to move efficiently through the water cycle and appear in rain, surface water, groundwater, and even organic agricultural systems via precipitation. In plants, any observed TFA residues reflect passive uptake from the soil and transpiration rather than metabolic formation.

Some pesticides and fertilizers with CF_3 groups can form TFA, but not all CF_3 containing pesticides degrade to TFA. Since pesticides are not highly volatile, they degrade primarily in soils.

Several degradation pathways can theoretically produce TFA:

- Photolysis
- Combined photo-hydrolytic mechanisms

- Biological degradation
- Atmospheric oxidation
- Ozonation

Only certain CF_3 substituted structures efficiently form TFA. In particular, CF_3 groups directly attached to aromatic rings, especially in the ortho or para positions.

To date, no comprehensive overview exists quantifying TFA formation from the full range of CF_3 containing chemicals, and the degradation pathways are not completely understood.

3.5.2 Exposure from residues in drinking water

Concentrations in drinking water

Drinking water modelling follows a tiered approach consisting of progressive levels of refinement. Level 1 estimated environmental concentrations (EECs) are intended to screen out pesticides that are not expected to pose any concern related to drinking water. These are calculated using the highest proposed application rate, worst-case application methods, and widest application timing. This approach ensures that all potential use conditions are represented. A set of geographic scenarios, with regional weather and varying soil characteristics, is modelled to give the highest potential exposure across all agricultural regions of Canada. Level 2 EECs are based on crop-specific application timing and geographic scenarios, and do not cover all proposed/registered uses in all regions of Canada. EECs for epyrifenacil in drinking water sources were calculated using the Pesticide in Water Calculator (PWC) version 2.0. For surface water, PWC estimates the amount of pesticide entering a drinking water reservoir by runoff, soil erosion and spray drift, and the subsequent transformation and overflow of the pesticide in and from the water system. Groundwater EECs are estimated by simulating pesticide transformation, adsorption/desorption and movement through a layered soil profile. The model determines the mean pesticide concentration in the underlying aquifer within the upper 1 metre below the water table.

Level 1 EECs for the combined residue of epyrifenacil and six of its major transformation products (TPs), S-3100-CA, S-3100-DA, S-3100-CA-RD, S-3100-CA-UR, S-3100-DA-RD, S-3100-DA-UR, in drinking water sources were calculated. The major fate inputs for drinking water modelling and the Level 1 drinking water EECs are presented below, in Tables 3.1 and 3.2, respectively.

Refined Level 1 EECs for groundwater were also calculated using the same inputs with respect to the highest proposed application rate, worst-case application method, and widest application timing, and geographic scenarios as the Level 1 modelling. However, for the refined Level 1 EECs, separate parent and TP modelling was implemented, where the half-lives were calculated separately for parent (epyrifenacil) and daughter (S-3100-CA, S-3100-DA, S-3100-CA-RD, S-3100-CA-UR, S-3100-DA-RD, S3100-DA-UR). In addition, the adsorption coefficient (K_{oc}) of parent and daughter were used in the refined modelling, while in Level 1 modelling the lowest K_{oc} values among the combined residues were used. The fate inputs used in the refined Level 1 modelling are presented in Table 3.1. The refined Level 1 groundwater EECs cover all regions of Canada and are presented in Table 3.2.

Table 3.1 Major fate inputs for drinking water modelling of the combined residues of epyrifenacil plus six of its major transformation products (S-3100-CA, S-3100-DA, S-3100-CA-RD, S-3100-CA-UR, S-3100-DA-RD, S3100-DA-UR)

Parameter	Fate parameters for drinking water modelling		Details
Level 1			
K_{oc} (L/kg)	40.6		The 20th percentile of six values for the transformation product S-3100-CA (the lowest K_{oc} among all compounds of concern).
Water column metabolism half-life (day) at 20°C	Stable		Aerobic aquatic whole system half-life. Data for two water/sediment systems available.
Aqueous photolysis half-life (day) at 40°N	Stable		The aqueous phototransformation studies for epyrifenacil included reference standards for the identification of a limited number of TPs. At the end of the three studies, the total "unidentified products" ranged from 55.6 to 74% applied radioactivity (AR). The unidentified products may contain some of the TPs of concern. As such, the half-life of the combined residue was assumed to be stable.
Hydrolysis half-life (day) at 25°C (pH 7)	Stable		Only two TPs of concern, S-3100-CA and S-3100-DA, were identified in the epyrifenacil hydrolysis studies. The concentrations of both compounds were increasing at the end of the studies. The hydrolysis half-life for the combined residue was assumed to be stable because sufficient data on the hydrolysis of most of the TPs of concern were not available to refine this assumption.
Soil half-life (day) at 20°C	Stable		Three aerobic soil biotransformation studies using three ^{14}C radiolabels (phenyl, pyridyl and pyrimidinyl) are available. Only data from the phenyl label were used for drinking water modelling.
Refined level 1 (groundwater only)			
	Parent	**Daughter**	
K_{oc} (L/kg)	224	40.6	Parent: 20th percentile of six values. Daughter: 20th percentile of six values for the TP, S-3100-CA (the lowest K_{oc} among all compounds of concern).
Hydrolysis half-life (day) at 25°C (pH 7)	46.6	Stable	Since insufficient data on the hydrolysis of most of the TPs of concern are available, the half-life for daughter was assumed to be stable (most conservative assumption).
Soil half-life (day) at 20°C	0.33 and 0.12	1155.7	Only data from the phenyl label were used for drinking water modelling. The half-life values are the

Parameter	Fate parameters for drinking water modelling		Details
			90% upper and lower confidence bound on the mean of four American soils for each of the parent and daughter.
Foliar half-life (day)	10000	-	Default value
Molecular weight (g/mol)	517.81	517.81	The parent molecular weight is used for daughter residues because everything is expressed as "parent equivalent".
Vapour pressure (torr)	9.75×10^{-16}	3.51×10^{-14}	For daughter, the smallest value (S-3100-CA) among the TPs of concern was used.
Solubility (mg/L) at 20°C	3.91	1290	For daughter, the highest solubility (S-3100-DA-UR) among TPs of concern was used to generate conservative EECs.
Henry's law Constant	6.94×10^{-15}	6.07×10^{-15}	Calculated using molecular weight, solubility, and vapour pressure of parent and each TP in PWC. For daughter, the smallest value (S-3100-CA-RD) among the TPs of concern was used to generate conservative EECs.
Air Diffusion Coefficient (cm^2/d)	3.13×10^3	3.13×10^3	Value for parent.
Heat of Henry (J/mol)	5.49×10^4	5.49×10^4	Value for parent.

Table 3.2 Level 1 and Refined Level 1 EECs of combined residues of epyrifenacil, S-3100-CA, S-3100-DA, S-3100-CA-RD, S-3100-CA-UR, S-3100-DA-RD, S3100-DA-UR in potential sources of drinking water.

Use pattern	Groundwater (µg a.i./L)		Surface water (µg a.i./L)		
	Acute (1)	Chronic (2)	Daily (3)	Yearly (4)	Overall (5)
Level 1 EECs					
1 × 40 g a.i./ha annually (crop areas)	57	49	3.4	0.6	0.4
2 × 40 g a.i./ha annually (bare ground non-crop areas and industrial vegetation management)	113	98	5.1	1.0	0.7
Refined level 1 EECs					
1 × 40 g a.i./ha annually (crop areas)	56.3	48.8	NR	NR	NR
2 × 40 g a.i./ha annually (bare ground non-crop areas and industrial vegetation management)	112	97.6	NR	NR	NR

NR – not required
(1) The highest (peak) simulated average concentration (µg a.i./L) in 1 m below the water table.
(2) The temporal average concentration (µg a.i./L) in the 1 m below the water table over the post-breakthrough simulation period. The breakthrough time is the simulated time for the first application of a pesticide to reach groundwater. The post-breakthrough average is the average concentration of the pesticide from that time until the end of the simulation.
(3) 90th percentile of the highest 1-day average concentration from each year.
(4) 90th percentile of yearly average concentrations.
(5) Average of all yearly average concentrations.

3.5.3 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 epyrifenacil: 100% crop treated, default processing factors, and residues in/on crops and animal commodities at MRL levels.

The basic acute dietary exposure (food alone) from all supported and imported epyrifenacil food commodities is estimated to be less than 1% (0.000163 mg/kg bw) of the ARfD for females 13-49 years old (95th percentile, deterministic). Aggregate exposure from food and drinking water is considered acceptable: less than 30% of the ARfD for females 13–49 years old (0.005962 mg/kg bw).

For the general population and all population subgroups, except females 13–49 years old, an acute dietary exposure assessment was not required as an endpoint of concern attributable to a single dose was not identified in the oral toxicity studies.

3.5.3.2 Chronic dietary exposure results and risk characterization

The following assumptions were applied to the basic chronic (cancer and non-cancer) analysis for epyrifenacil: 100% crop treated, default processing factors, and residues in/on crops and animal commodities at MRL levels.

The basic chronic (cancer and non-cancer) dietary exposure (food alone) from all supported and imported epyrifenacil food commodities for the total population, including infants and children, and all representative population subgroups, is less than 6% of the acceptable daily intake (ADI). Aggregate exposure from food and drinking water is considered acceptable. The chronic (cancer and non-cancer) dietary exposure estimate to epyrifenacil from food and drinking water is less than 21% (0.002077 mg/kg bw/day) of the ADI for the total population. The highest exposure and risk estimate is for all infants (<1 year) at less than 76% (0.007526 mg/kg bw/day) of the ADI.

3.6 Aggregate exposure and risk assessment

For epyrifenacil, 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 Health Canada to consider the cumulative effects of pest control products that have a common mechanism of toxicity. Epyrifenacil belongs to a class of herbicides known as protoporphyrinogen IX oxidase (PPO) inhibitors. Within this class, there are several herbicides registered in Canada and internationally that all have the same mode of action (MOA), namely the inhibition of a key enzyme in the chlorophyll synthesis pathway, protoporphyrinogen oxidase (also referred to as Protox). The same enzyme and pathway are also involved in heme biosynthesis in mammals resulting in changes in hematopoietic parameters. Overall, based on the similar MOA of these compounds, further consideration for potential cumulative health effects was warranted. Only chronic exposure was assessed in the cumulative risk assessment (CRA) since PPO inhibition or any other associated blood effects were not considered relevant to acute exposure.

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 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

There are currently ten PPO inhibitors registered for use in Canada: acifluorfen-sodium, carfentrazone-ethyl, flumioxazin, fomesafen, oxyfluorfen, pyraflufen-ethyl, saflufenacil, sulfentrazone, tiafenacil and trifludimoxazin. In addition, three other PPO inhibitors are registered in the US, which have tolerances on food commodities: fluthiacet-methyl, lactofen and pyraclonil. As such, there is a potential for co-occurrence of exposure to PPO inhibitors from registered end-use products, as well as from imported food commodities.

3.7.2 Non-dietary exposure

There are no residential uses for the currently registered or proposed uses for active ingredients in this cumulative assessment group. Only one of the active ingredients (carfentrazone-ethyl) is registered for use on golf course tees and greens, from which postapplication exposure to golfers is expected to be intermittent and short-term in duration. Since no short-term dermal toxicological concerns were identified for carfentrazone-ethyl, postapplication exposure was not of concern for golfers coming in contact with treated golf course turf and an aggregate risk assessment (dermal exposure + dietary exposure) was not required. Accordingly, no significant residential (non-dietary) exposure of PPO inhibitors is anticipated.

3.7.3 Dietary exposure

3.7.3.1 Exposure from food

PPO inhibitors registered in Canada are used on food and feed crops. In addition, three other PPO inhibitors registered in the US (fluthiacet-methyl, lactofen and pyraclonil) have tolerances on food commodities.

Food monitoring data are available for most of the PPO inhibitors; however, none were available for tiafenacil (first registered in 2022). Of the remaining PPO inhibitors, PDP monitoring data are available, except for pyraclonil (registered in 2023 on rice only). CFIA monitoring data were available for acifluorfen, carfentrazone-ethyl, oxyfluorfen, pyraflufen-ethyl and sulfentrazone. Where available, a decade worth of monitoring data (~690,000 measurements combined from CFIA and PDP databases) for the Canadian registered PPO inhibitors and the other three PPO inhibitors registered in the US with food commodity tolerances were analyzed (Table 3.3). Only 0.021% of samples had residues above or equal to the limit of detection (LOD), but these were below the limit of quantification (LOQ), and well below the MRLs. For the PPO inhibitors that do not have monitoring data, quantifiable residues in treated crops are also not expected based on 1) the residue data reviewed in support of the epyrifenacil and tiafenacil registrations, and 2) the USEPA conclusion from crop field trials that pyraclonil residues were not detectable. As such, no co-occurrence of quantifiable residues originating from any of the herbicides in the PPO inhibitor group are expected on any food commodities.

Table 3.3 Summary of residue monitoring data by the Canadian Food Inspection Agency (CFIA, 2012–2021) and the USEPA Pesticide Data Program (PDP, 2015–2024) for PPO inhibitors for various food commodities.

Pest control product	Data source	# Samples tested	# Samples with residues greater than the LOD	% Positive	Residue range (ppm) in positive samples (greater than or equal to LOD)	LOD (ppm) range in different commodities
1. Acifluorfen[1]	CFIA	343	0	0%	NA	0.05
	PDP	4952	0	0%	NA	0.05
2. Carfentrazone-ethyl	CFIA	51 449	1	0.002%	0.0004	0.0029–0.008
	PDP	100 998	0	0%	NA	0.0001–0.02
3. Flumioxazin	CFIA	No data				
	PDP	87 149	8	0.009%	0.05–0.013	0.00004–0.12
4. Fluthiacet-methyl (No Canadian registration)	CFIA	No data				
	PDP	34 037	0	0%	NA	0.003–0.025
5. Fomesafen	CFIA	No data				
	PDP	11 933	0	0%	NA	0.005–0.03
6. Lactofen (No Canadian registration)	CFIA	No data				
	PDP	20 728	0	0%	NA	0.003–0.25
7. Oxyfluorfen	CFIA	40 621	17	0.042%	0.0011–0.008	0.0026–0.005
	PDP	79 666	108	0.136%	0.001–0.011	7E-06–0.2

Pest control product	Data source	# Samples tested	# Samples with residues greater than the LOD	% Positive	Residue range (ppm) in positive samples (greater than or equal to LOD)	LOD (ppm) range in different commodities
8. Pyraflufen-ethyl	CFIA	39 524	0	0%	NA	0.018–0.008
	PDP	49 575	0	0%	NA	0.001–0.03
9. Saflufenacil	CFIA	No data				
	PDP	72 533	0	0%	NA	0.002–0.25
10. Sulfentrazone	CFIA	39 524	11	0.028%	0.0005–0.005	0.0029–0.008
	PDP	58 486	0	0%	NA	0.001–0.06
11. Trifludimoxazin[2]	CFIA	No data				
	PDP	2856	0	0%	NA	0.005–0.025
Overall	**Canada (CFIA)**	171 461	29	0.017%	-	-
	US (PDP)	522 913	116	0.022%	-	-
	Overall	**694 374**	**145**	**0.021%**	-	-

LOD = limit of detection. Residues are below the limit of quantification (LOQ).
NA = not applicable

[1] Monitoring data for acifluorfen are available only for 2015–2021 (CFIA) and 2015–2017 (PDP).

[2] Monitoring data for trifludimoxazin are available only for 2022—2023 (PDP).

3.7.3.2 Exposure from drinking water

Water monitoring data are also available for most of the PPO inhibitors registered in Canada, except for trifludimoxazin, through the Canadian Water Monitoring Program for Pesticides (CWMPP) for the years 2022–2024 inclusive on the Monitoring water for pesticides webpage on Canada.ca. In the CWMPP data, of the 4877 unique water samples tested for PPO inhibitors, 36% had quantifiable levels of residues. Only acifluorfen-sodium, fomesafen, pyraflufen-ethyl, saflufenacil and sulfentrazone were detected at 3%, 43%, 0.1%, 78% and 26%, respectively of samples with positive detects. 13% of the samples had co-occurrence of more than one PPO inhibitor. From the samples with detections, maximum concentrations for individual pesticides (0.039 to 3.278 µg a.i./L) were 3–190× lower than the modelled EECs (1.4 to 323 µg a.i./L).

The PPO inhibitors included in this analysis have different toxicology reference values. As such, in order to assess the cumulative risk of the co-occurring PPO inhibitors, an index chemical was chosen, against which the other members of the group are compared. The index chemical should have a robust database and be representative of the chemicals in the assessment group. Fomesafen was chosen as an index chemical based on the criteria that, out of the detected PPO inhibitors, it had the lowest ADI and the highest maximum concentration found in the water monitoring data.

Using fomesafen as the index chemical, the maximum concentrations detected for each PPO inhibitor were adjusted for relative potency and molecular weight equivalency. In samples where co-occurrence was detected, concentrations of each PPO inhibitor were adjusted for relative potency and molecular weight equivalency, and then summed. The highest value from these adjusted concentrations was 3.72 µg/L. This concentration was then compared to the long-term human health reference value (HHRV) of fomesafen (60 µg/L). Based on this analysis, the

maximum contribution of cumulative exposure of PPO inhibitors from drinking water would be 6.2% of the HHRV.

Water monitoring data are not available for trifludimoxazin and epyrifenacil. The chronic dietary risks from drinking water estimated for the two active ingredients are 0.6% and 74% of the ADIs, respectively, when using a basic (Tier 1) analysis and modelled EECs. Dietary risks are expected to be much lower considering the conservatisms in the basic assessment, in comparison to the drinking water concentrations from the existing monitoring data of the other PPO inhibitors.

3.7.4 Summary and conservatisms of the semi-quantitative risk assessment of PPO inhibitors

As stated in SPN2018-02, a cumulative health risk assessment is aimed at identifying the human health risks associated with co-exposures to two or more pesticides (from non-occupational sources of exposure) that cause a common toxic effect(s) by the same, or essentially the same, sequence of major biochemical events (that is, a common mechanism of toxicity).

In the case of the PPO inhibitors, including epyrifenacil, no significant residential (non-dietary) exposure is anticipated. For dietary exposure from food, based on monitoring data and residue data, no co-occurrence of quantifiable residues originating from any of the herbicides in the PPO inhibitor group are expected on any food commodities. In addition, the risk assessment described above for dietary exposure from drinking water demonstrated that cumulative dietary exposure (food plus drinking water) to PPO inhibitor herbicides is unlikely to pose human health risks. The approach of using water monitoring data in this risk assessment has several conservatisms:

- It only considered samples with detection and co-occurrence.
- Maximum concentrations were used for the risk analysis from drinking water.
- The relative potency factors used for the risk assessment for each PPO inhibitor were calculated using the most conservative points of departure, that are not necessarily based on common effects of changes in hematopoietic parameters (which are likely to be higher and thus present lower toxicity).

As such, based on this semi-quantitative assessment, the cumulative health risks from potential co-exposure to more than one PPO inhibitor through food, drinking water and residential exposure, where relevant, are acceptable for all sub-populations.

3.8 Health risk assessment of common metabolite

Trifluoroacetic acid (TFA), an environmental transformation product of epyrifenacil, is also formed from several fluorinated pesticides. It is a common environmental degradate from both pesticide sources and non-pesticide sources (including chlorofluorocarbons). Other pesticides that are registered in Canada that may degrade to TFA include cyclobutrifluram, cyflumetofen, fluazinam, fomesafen, saflufenacil, tiafenacil, trifloxystrobin, and trifluralin.

As mentioned in section 3.5.1, available evidence (field accumulation results, reflective of agricultural practices) indicates that for epyrifenacil, even with the potential to form TFA, is not a significant contributor to TFA levels.

The human health risk assessment of TFA, taking into account the multiple pesticidal sources, is currently in the initial planning phase. The status of the TFA risk assessment is captured in the Cumulative Health Risk Assessment Operational Planning Framework that was published in December 2025.

3.9 Maximum residue limits

Dietary risks from the consumption of food commodities listed in Table 3.4 were shown to be acceptable when epyrifenacil is used according to the supported label directions. Therefore, foods containing residues at these levels are safe to eat, and the following MRLs will be specified for residues of epyrifenacil.

Table 3.4 Recommended maximum residue limits.

MRL (ppm)	Food Commodity
0.01	Eggs, milk, fat, meat, and meat byproducts of cattle, goats, horses, hogs, sheep, and poultry
0.005	Dry soybeans, field corn, wheat, rapeseeds (canola)

For additional information on maximum residue limits (MRLs) in terms of the international situation and trade implications, refer to Appendix II.

The nature of the residues in animal and plant commodities, analytical methodologies, field trial data, and acute and chronic dietary risk estimates are summarized in Appendix I, Tables 1b, 12 and 13.

3.10 Health incident reports

Epyrifenacil is a new active ingredient pending registration for use in Canada. As of 9 February 2026, no incidents involving epyrifenacil were submitted to Health Canada.

4.0 Impact on the environment

4.1 Fate and behaviour in the environment

A summary of the major transformation products (TPs) of epyrifenacil is provided in Appendix I, Table 14. The environmental fate parameters for epyrifenacil and its major TPs are provided in Appendix I, Table 15.

Terrestrial environment

The main dissipation pathways for epyrifenacil in the terrestrial environment are hydrolysis under alkaline conditions and biotransformation in soil. Phototransformation on soil is a negligible process for epyrifenacil.

The hydrolysis of epyrifenacil is temperature- and pH-dependent. Epyrifenacil is stable to hydrolysis at pH 4. The rate of hydrolysis at pH 7 is slow at 15 °C (half-life >100 days) but increases with temperature (half-life <2 days at 50 °C). At pH 9 (15-50 °C), the hydrolysis half-

lives of epyrifenacil are less than one day. Six major TPs are formed from the hydrolysis of epyrifenacil: S-3100-CA, S-3100-CA-UR, 4"-OH-S-3100-CA, S-3100-CA-RO1, S-3100-CA-RO2 and 1,1,1-trifluoroacetone. Hydrolysis of the TPs, S-3100-CA and S-3100-DA, is slower, with half-lives of 214 and 143 days, respectively.

Biotransformation in soil is a major route of transformation for epyrifenacil. It is non-persistent in aerobic and anaerobic soil, with half-lives of less than 0.5 days. Up to seven major TPs are formed in soil under aerobic conditions: S-3100-CA, S-3100-DA, S-3100-DA-RD, S-3100-CA-RD, S-3100-CA-UR, 4"-OH-S-3100-CA and S-3100-DP. Under anaerobic conditions, up to six major TPs are formed in soil, some of which are different from those formed under aerobic conditions: S-3100-CA, S-3100-CA-UR, S-3100-CA-RD-RO, S-3100-CA-RO1 and 1,1,1-trifluoroacetone. The TPs are more persistent than epyrifenacil, with half-lives ranging from less than 5 days to >1000 days. See Appendix I, Table 15 for the half-lives of each individual TP.

Two terrestrial field dissipation (TFD) trials on bare soil were conducted in ecoregions relevant to Canada (Ontario and North Dakota) using three applications of 40.4 g a.i./ha, with a 14-day retreatment interval. The TFD trials used one more application than the maximum proposed application rate in Canada of two applications of 40 g a.i./ha, with a 14-day retreatment interval. Epyrifenacil dissipated rapidly after application at both sites and was not detected in soil five days after the last application. Four major TPs were produced from the dissipation of epyrifenacil in the field: S-3100-CA, S-3100-CA-RD, S-3100-DA and S-3100-DA-RD. The major TPs dissipated over the course of the growing season; however, some major TPs were still detectable in soil at the start of the next growing season (360 days after the 3rd application (DA3A)). After one year, between 16.5 and 32.8% of the total residues of epyrifenacil measured on Day 0 after the third application, present as the sum of its TPs, remained at the sites. However, carryover of epyrifenacil residues into the next growing season is not expected to be an environmental concern as epyrifenacil dissipated rapidly in the field (<5 days after application), the environmental risk assessment and associated risk mitigation conservatively assumed that no dissipation of epyrifenacil or its TPs occurred to account for the persistence of the TPs, and no crop rotation or food residue concerns were identified for the TPs.

In the laboratory, epyrifenacil was observed to have moderate to high mobility in soils, while its major TPs have moderate to very high mobility. In contrast to the laboratory results, epyrifenacil and its major TPs were only measured in the top 0–15-cm soil layer in TFD studies and did not show any significant downward migration in the soil profile. Epyrifenacil is not expected to leach to groundwater; however, its major TPs may leach to groundwater based on the available weight-of-evidence (mobility information, groundwater modelling, groundwater ubiquity scores and the criteria of Cohen et al. (1984)). Based on this information, and because the major TPs are included in the drinking water residue definition, a precautionary label statement to inform users to avoid the use of products containing epyrifenacil in areas where the soils are permeable, particularly where the water table is shallow, is required.

Aquatic environment

Epyrifenacil residues in water are broken down via the combined processes of hydrolysis, phototransformation and biotransformation. Hydrolysis is an important transformation process for epyrifenacil, particularly under alkaline conditions (pH 9), such as those in the marine environment. Phototransformation in water is a route of dissipation for epyrifenacil near the

surface in waterbodies exposed to sunlight. Three major TPs are formed by phototransformation in water under laboratory conditions: S-3100-BFP, 4'-OH-S-3100 and CO_2. Other than CO_2, these TPs were not produced in soil or water by other transformation pathways.

Epyrifenacil is non-persistent in aerobic and anaerobic aquatic systems, with half-lives less than five days in the total system (water and sediment). In the laboratory, up to 13 major TPs were identified from the biotransformation of epyrifenacil in aquatic systems. Ten major TPs are formed under aerobic conditions: S-3100-CA, S-3100-CA-UR, S-3100-DA-RD, S-3100-DA, S-3100-DA-UR, S-3100-CA-RD, S-3100-DP, trifluoroacetic acid (TFA), 1,1,1-trifluoroacetone and CO_2. Thirteen major TPs are formed under anaerobic conditions: S-3100-CA, S-3100-CA-UR, S-3100-DA-UR, S-3100-DA, S-3100-DA-RD-RO, S-3100-DA-RO1, S-3100-DP-UR, S-3100-CA-RD, TFA, 1,1,1-trifluoroacetone and CO_2. Many of the major TPs in the tested aerobic and anaerobic aquatic systems were measured in higher concentrations in the sediment phase than in the water phase. This is contrary to what is expected based on their physical and chemical properties: all of the TPs are soluble in water, have low log octanol-water partitioning coefficient (log K_{ow}) values indicating an affinity for water and low K_{oc}/K_d values indicating low adsorption to soil/sediment and organic matter.

The log K_{ow} value of 3.42 for epyrifenacil indicates the potential to bioaccumulate. Bioaccumulation of the major TPs in animal tissues is not expected based on their log K_{ow} values (all <2). A study evaluating the bioconcentration of ^{14}C-epyrifenacil in bluegill sunfish showed that epyrifenacil was quickly metabolized in fish tissues, resulting in the formation of S-3100-CA and S-3100-DA. Epyrifenacil residues (as total radioactive residues (TRR)) were quickly eliminated from the fish tissues, with >99% depuration occurring within 3 days. Epyrifenacil and its TPs have a low potential to bioconcentrate in fish, with lipid- and growth-corrected kinetic bioconcentration factors (BCF_{KGL}), based on TRR, of 45.89 to 112.07 L/kg. This is well below the Toxic Substances Management Policy bioconcentration criteria of a BCF ≥ 5000.

Atmospheric fate

Epyrifenacil and its major TPs, with the exception of TFA and 1,1,1-trifluoroacetone, have low vapour pressures and low Henry's law constants, which indicate low potential for volatilization. TFA and 1,1,1-trifluoroacetone have intermediate to high volatilities based on their vapour pressures. TFA is expected to be slightly volatile from water surfaces and moist soils while 1,1,1-trifluoroacetone is expected to be rapidly lost from a water surface or moist soil.

4.2 Environmental risk characterization

An environmental risk assessment was conducted as described in the guidance document, Health Canada's Approach to Environmental Risk Assessment for Pest Control Products to estimate the potential for adverse effects on non-target species. Environmental exposure and ecotoxicology information were integrated by comparing estimated environmental concentrations (EECs) to effects-based values (effects metrics) used to assess risk. 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, Table 16.

Acute and chronic ecotoxicological data for non-target terrestrial, freshwater and marine organisms were submitted by the applicant and are summarized in Appendix I, Table 17. In the risk assessment, toxicity endpoints were adjusted via an uncertainty factor (UF) to calculate the effects metrics.

The effects metrics account for potential differences in species sensitivity as well as varying protection goals (in other words, protection at the community, population, or individual level). The toxicity endpoints and UFs used to establish the effects metrics, along with the level of concern (LOC) used in the risk assessment, are presented in Appendix I, Tables 18 and 19.

Initially, a screening-level risk assessment was performed using simple methods, conservative exposure scenarios and sensitive effects metrics. A risk quotient (RQ) was calculated by dividing the EEC by the effects metric and was then compared to the 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 considered additional effects metrics as well as more realistic exposure scenarios, including spray drift and runoff. 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, honeybees, beneficial arthropods, birds, small wild mammals, and non-target terrestrial plants may be exposed to epyrifenacil through direct contact with spray, spray drift, contact with sprayed surfaces, or from ingestion of contaminated food. A risk assessment of epyrifenacil (as technical grade active ingredient and formulated product) was undertaken based on available toxicity data for earthworms, honeybees and other beneficial arthropods, birds, small wild mammals and non-target terrestrial plants.

For soil exposure, screening level EECs are generally calculated based on a direct application of the active ingredient to soil at the maximum cumulative seasonal application rate, taking into account dissipation between applications. However, in soil, epyrifenacil rapidly transforms into major TPs that are more persistent and for which toxicity data for terrestrial organisms are not available. The EEC in soil was calculated assuming no dissipation of epyrifenacil to ensure that the screening level EEC represents a worst-case estimate of the concentration of epyrifenacil and any TPs in soil. While not directly applicable to terrestrial toxicity, epyrifenacil is expected to be more toxic than the TPs based on available data for aquatic organisms. The EEC in soil was calculated based on the maximum application rate of 80 g a.i./ha (two applications of 40 g a.i./ha). It was assumed that this total amount was evenly distributed in the 0–15-cm depth of the soil, which has a bulk density of 1.5 g/cm^3.

For foliar exposure, the screening level EEC was calculated based on two applications of 40 g a.i./ha, with a 14-day re-application interval, and assuming a default foliar half-life of 10 days. The use of the default foliar half-life was considered to be appropriate because dissipation and degradation of residues from plant material is expected to be more rapid than in other environmental media. The different routes of foliar residue decline include volatilization, wash-off, photolysis, abiotic and biotic transformation, and dilution due to plant growth.

The screening level risk assessment for terrestrial organisms, with the exception of birds and mammals, is presented in Appendix I, Table 18.

Earthworms

Earthworms may be exposed to epyrifenacil through contact with residues in soil. As such, the screening level risk assessment considered the soil EEC based on the maximum application rate of 80 g a.i./ha.

In the submitted 56-day earthworm toxicity test, epyrifenacil was applied to soil once at the beginning of the test. The formation of some of the major TPs in soil is expected to have occurred during the study, and any toxicity related to the TPs is included in the results of the study. However, the study would not include effects from exposure to TPs expected to form or persist later than 56 days after application of epyrifenacil to soil (in other words, 4”-OH-S-3100-CA, S-3100-CA-RD, S-3100-CA-UR). Although the toxicity of these major TPs to earthworms was not investigated, as discussed above, the EEC in soil is a worst-case estimate of the concentration of epyrifenacil and any TPs. The worst-case EEC in soil is orders of magnitude lower than the 56-day NOEC for earthworms (EEC of 0.036 mg a.i./kg dw soil compared to a NOEC of 484 mg a.i./kg dw soil). Given the above, the submitted earthworm toxicity test is considered to be sufficient to evaluate risks.

The screening level RQ of 0.0001 is below the LOC of 1 (Appendix I, Table 18), indicating that risks to earthworms are acceptable when epyrifenacil is used according to label directions.

Bees

Foraging bees could be exposed directly to epyrifenacil spray droplets during application, residues on the surface of the leaves (contact exposure), or ingestion of contaminated pollen or nectar (oral exposure). In addition, brood may be exposed to epyrifenacil if foraging bees bring contaminated pollen and nectar back to the hive. For the screening level risk assessment, it was assumed that epyrifenacil is systemic and expected to move through plants to pollen and nectar.

Individual flowers generally only bloom for a short period of time. Therefore, it is unlikely that the same forager bee would be exposed to a flower that was sprayed with epyrifenacil multiple times. Given this, the screening level risk assessment evaluated risk to bees using the maximum single application rate (40 g a.i./ha) to estimate the highest potential exposure.

Acute, chronic and larval honeybee toxicity tests are available for epyrifenacil. Epyrifenacil is classified as practically non-toxic to adult bees on an acute contact basis. Adverse effects on survival were observed in the larval toxicity and adult chronic toxicity laboratory tests at higher doses than bees are expected to be exposed to in the field.

The screening level RQs (maximum of 0.15) are below the LOCs of 0.4 for acute exposure and 1 for chronic exposure (Appendix I, Table 18). As such, risks to bees are acceptable when epyrifenacil is used according to label directions.

Beneficial arthropods

Foliar-dwelling beneficial arthropods could be exposed to epyrifenacil spray droplets during application, and to epyrifenacil residues on plant surfaces. Toxicity tests for the beneficial arthropods, *Typhlodromus pyri* and *Aphidius rhopalopsiphi*, were conducted with the formulated product, V-10456 0.46 EC (5.21% epyrifenacil), applied on glass plates. The screening level risk assessment evaluated risks to beneficial arthropods based on a foliar EEC derived from two applications of 40 g a.i./ha with a 14-day interval and the default foliar half-life of 10 days.

For *T.pyri* and *A.rhopalopsiphi*, the screening level risk assessment uses a LOC of 2 as recommended by Candolfi et al. (2001) when considering endpoints derived from spray application on glass plates. Significant ecological effects for these species at the population level are not expected to occur below the LOC of 2 based on an extensive empirical comparison of the risk quotients and known acceptable effects from field and semi-field studies.

The screening level RQs of <0.46 are below the LOC of 2 (Appendix I, Table 18), indicating that risks are acceptable when epyrifenacil is used according to label directions.

Birds and small wild mammals

A screening level risk assessment was conducted to evaluate acute and reproductive risks to birds and mammals based on the estimated concentration of epyrifenacil in various food items in the diet (the estimated daily exposure (EDE)) following two applications of 40 g a.i./ha with a 14-day interval and the default foliar half-life of 10 days. Exposure is dependent on the body weight of the animal, 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 epyrifenacil residue concentrations in food items;
- A diet that is composed entirely (100%) of a particular dietary item; and,
- The feeding guild assumed to have the highest exposure for each animal weight category.

The screening level RQs were below the LOC of 1 (range of <0.01 to 0.76). As such, risks to birds and wild mammals from the use of epyrifenacil are acceptable (Appendix I, Table 19).

Non-target terrestrial plants

The screening-level risk assessment assumed that non-target terrestrial plants would be exposed to a direct overspray of epyrifenacil as formulated product. Two modes of exposure were evaluated:

- Soil exposure: The effect of epyrifenacil in soil on seedling emergence was evaluated by comparing the EEC in soil to the most sensitive effects metric from the seedling emergence toxicity tests. The EEC was calculated based on the maximum seasonal application rate for epyrifenacil of 80 g a.i./ha. The seedling emergence toxicity tests evaluated effects in ten species (four monocots and six dicots); the most sensitive species was tomato.
- Foliar exposure: The effect of a foliar spray of epyrifenacil on the vegetative vigour of non-target terrestrial plants was evaluated by comparing the foliar EEC to the most sensitive effects metric from the vegetative vigour toxicity tests. The vegetative vigour toxicity tests evaluated effects in ten species (four monocots and six dicots); the most sensitive species was tomato.

The screening level RQs for both seedling emergence and vegetative vigour exceeded the LOC of 1 (RQs = 16 to 1839). As such, risks were further characterized to consider off-field spray drift of epyrifenacil one metre downwind from the point of application.

According to the proposed labels, epyrifenacil can be applied using a field sprayer or aerial application; both application methods use spray droplets equal to, or larger than, the American Society of Agricultural and Biological Engineers (ASABE) S572 (572.1 to 572.3) medium classification. Spray drift factors of 6% for field sprayer application, and 23 and 60% for aerial application to agricultural crops and non-crop areas, respectively, were used to calculate the off-field EECs (Appendix I, Table 20).

The refined RQs for both seedling emergence and vegetative vigour (RQs of 1.0 to 1103) continued to be equal to, or exceed, the LOC of 1 when considering spray drift at one metre downwind from the point of application. Spray buffer zones up to 275 metres are required to mitigate risk to non-target terrestrial plants and protect sensitive terrestrial habitat. Risks to non-target terrestrial plants are acceptable with the inclusion of spray buffer zones.

4.2.2 Risks to aquatic organisms

Aquatic organisms, such as invertebrates, fish, amphibians and aquatic plants could be exposed to epyrifenacil if spray drift or runoff enter aquatic habitats. For the screening level risk assessment, EECs were calculated as follows:

- The EECs for epyrifenacil in surface water were calculated based on a direct overspray to a one-hectare wetland at the maximum seasonal application rate for epyrifenacil of 80 g a.i./ha. No dissipation between applications was considered to ensure that the screening levels EECs represent a worst-case estimate of the concentration of epyrifenacil and any TPs in surface water.
- EECs for the major TPs with available aquatic toxicity studies (S-3100-CA, S-3100-DA, S-3100-DA-RD, S-3100-CA-RD, S-3100-CA-UR, 4”-OH-S-3100-CA, S-3100-DP, S-3100-DA-UR and TFA) were calculated assuming 100% transformation of epyrifenacil to each TP on a molar basis. No dissipation of the parent or TPs between applications was considered.

Water bodies of two different depths were evaluated: an EEC in surface water 15-cm deep was used to determine risk to amphibians while an EEC at an 80-cm depth was used to evaluate risks to all other aquatic organisms.

Epyrifenacil is classified as moderately to very highly toxic to freshwater and marine aquatic organisms (Appendix I, Table 17). A "toxic to aquatic organisms" label statement is required based on the inherent toxicity of epyrifenacil. Epyrifenacil is a light-dependent peroxidizing herbicide, which means its toxicity to aquatic organisms may be increased by UV light. The USEPA has developed a molar threshold approach with which to adjust fish chronic toxicity endpoints to account for potential increased toxicity under enhanced UV lighting conditions.[6] This approach was used to adjust the endpoints from the fish early-life stage toxicity tests that were used to assess risks to fish and amphibians (as a surrogate).

The available data show that the major TPs are less toxic than epyrifenacil. Toxicity tests using S-3100-CA are available for freshwater invertebrates, freshwater fish and freshwater algae. Freshwater algae toxicity tests are available for all major TPs expected to be produced in aquatic systems or transported from land via runoff, with the exception of S-3100-DA-RD-RO and 1,1,1-trifluoroacetone.

The partitioning of several of the major TPs from water to sediment was identified based on the environmental fate laboratory studies. Two 10-day tests evaluating the toxicity of epyrifenacil-spiked sediments to the chironomid, *Chironomus dilutus,* and the amphipod, *Hyalella azteca*, are available; toxicity tests with the major TPs were not submitted and are not required. NOEC values from the studies based on measured porewater concentrations were used to calculate effects metrics for the screening level risk assessment. Given the rapid dissipation of epyrifenacil in aerobic and anaerobic aquatic systems, the NOEC values account for the toxicity of the TPs formed during the 10-day toxicity study (for example, S-3100-CA, S-3100-CA-UR, S-3100-DA were formed within the first 10 days of the biotransformation of epyrifenacil in aquatic system studies).

For the screening level risk assessment (Appendix I, Table 18), the RQs for non-target organisms in overlying water and/or sediment for exposure to epyrifenacil and its TPs were below the LOC of 1, with the exception of the following:

- Chronic risks to freshwater fish (fathead minnow) from epyrifenacil (maximum RQ of 9.6);
- Chronic risks to amphibians (fathead minnow surrogate) from epyrifenacil (maximum RQ of 51);
- Risks to freshwater algae from epyrifenacil (maximum RQ of 39), S-3100-CA (maximum RQ of 2.4), S-3100-DA (maximum RQ of 11) and S-3100-DP (maximum RQ of 11);
- Chronic risks to the saltwater mysid (marine invertebrate) from epyrifenacil (RQ of 4.8);
- Chronic risks to the sheepshead minnow from epyrifenacil (maximum RQ of 9.6); and,
- Risks to marine diatoms from epyrifenacil (RQ of 43).

[6] US EPA, 2016. Guidance on Light-Dependent Peroxidizing Herbicides: Use of the Molar Threshold Value for Adjusting Fish Chronic Endpoints to Account for Ultraviolet Light-enhanced Toxicity (PMRA No. 3648570).

Applying epyrifenacil directly to water, as assumed in the screening level risk assessment, is not proposed by the applicant. To further characterize risk to amphibians, freshwater and marine fish, freshwater algae, marine invertebrates and marine diatoms, more realistic exposures to epyrifenacil via spray drift and runoff off-field were considered.

Spray drift to aquatic habitat

In order to evaluate risks from spray drift to aquatic organisms off-field, the screening level EECs were adjusted to account for deposition of spray drift one metre downwind from the point of application. As noted above for non-target terrestrial plants, spray drift factors of 6% for field sprayer application with medium sized spray droplets, and 23 and 60% for aerial application to agricultural crops and non-crop areas with medium sized spray droplets, respectively, were used to calculate the off-field EECs. The refined risk assessment for spray drift to aquatic habitat is presented in Appendix I, Table 21.

Freshwater

When considering spray drift from field sprayer application, RQs for exposure of freshwater fish to epyrifenacil and freshwater algae to S-3100-CA, S-3100-DA and S-3100-DP were below the LOC of 1; however, the RQs for amphibians (RQ = 3.1) and freshwater algae/diatoms (maximum RQ = 2.4) exposed to epyrifenacil exceeded the LOC. The RQs for aerial application to agricultural crops and non-crop areas exceeded the LOC for amphibians, freshwater fish and freshwater algae/diatoms (RQs of 2.2 to 31). As such, spray buffer zones of up to 125 metres are required to protect sensitive freshwater habitat. With the inclusion of the spray buffer zones, risks to non-target freshwater organisms from spray drift are acceptable.

Estuarine/marine

Estuarine and marine environments are dynamic systems characterized by tidal action. The size of estuaries can vary greatly. To ensure that the estuarine/marine risk assessment is protective of small, salt marshes as well as the larger estuarine and the marine environment, EECs were calculated based on a 1-ha, 80-cm deep water body (same size as freshwater). Given that small, salt marshes are expected to be flushed/recharged by tidal action, spray drift from multiple applications are not expected to accumulate in the water body due to tidal action. EECs were calculated considering spray drift from only one application of epyrifenacil at the highest rate of 40 g a.i./ha. Since only one application for spray drift is considered to refine the estuarine/marine EEC, the use of an acute endpoint is more appropriate to characterize risk as chronic exposure from spray drift is not expected. When considering only acute risk, the RQs of 1.3, 4.9 and 13 for marine diatoms exceeded the LOC of 1 for field sprayer, aerial application to agricultural crops and aerial application to non-crop areas, respectively. Spray buffer zones of up to 60 metres are required to protect sensitive marine habitat. With the inclusion of the spray buffer zones, risks to non-target estuarine/marine organisms are acceptable.

Runoff to aquatic habitat

Surface water can be contaminated with epyrifenacil residues via runoff of water from land. EECs for epyrifenacil residues in surface water from runoff were modelled using PWC version 2.0. The PWC model calculates the amount of pesticide entering the water body via runoff only, and the subsequent degradation of the pesticide in the water and sediment. Several application

scenarios in different regions of Canada were modelled. The EECs for each scenario were calculated by modelling runoff from a 10-ha field into 1-ha adjacent water bodies of two different depths: 15 and 80 cm. The model was run for 50 years using the combined residue of epyrifenacil and three major TPs (S-3100-CA, S-3100-DA, and S-3100-DP). The TPs were included in the residue definition based on the potential for exposure and toxicity in the environment, as shown by the LOC exceedances at the screening level. The fate parameters used in ecological runoff modelling are presented in Appendix I, Table 22. PWC calculates time-averaged concentrations by averaging the peak concentrations over different time periods (for example, 24-hour and 21-day). The highest value of these averages for each calendar year is then calculated. The 90th percentiles of the 50 yearly maxima are then reported as the EECs for each time period. The peak and 21-day EECs for each scenario were used to calculate acute and chronic risks, respectively. The EECs in surface water from runoff are presented in Appendix I, Tables 23 and 24.

Screening level RQs for epyrifenacil, S-3100-CA, S-3100-DA and/or S-3100-DP exceeded the LOC for amphibians, freshwater and estuarine/marine fish, freshwater algae, saltwater mysids and marine diatoms. Water modelling EECs were compared to the most sensitive effects metrics for each taxa available for epyrifenacil, which is more toxic to aquatic organisms than the TPs. The following effects metrics were used to represent each taxa:

- The fathead minnow effects metric adjusted for UV-light enhanced conditions was used as a surrogate for amphibians, freshwater fish and estuarine/marine fish;
- The marine diatom effects metric for *Skeletonema costatum* was used as a surrogate for freshwater algae and marine diatoms; and,
- The saltwater mysid effects metric was used as a surrogate for estuarine/marine invertebrates.

The results of the runoff risk assessment are summarized in Appendix I, Table 25. For brevity, three of the scenarios, that bound the risk estimates, are presented fully for the runoff risk assessment:

1) The exposure scenario resulting in the highest EECs for which RQs were below the LOC for all organisms. This corresponded to the second lowest EEC reported in the dataset, calculated based on two applications of 20 g a.i./ha for summer fallow in British Columbia. The results of the runoff risk assessment show that risks to aquatic organisms are acceptable for all EECs below or equal to 0.0007 mg a.i./L for 15-cm deep waterbodies and 0.0002 mg a.i./L for 80-cm deep waterbodies. EECs below, or equal to, these values are shaded grey in Appendix I, Tables 23 and 24;
2) The lowest EECs that resulted in RQs exceeding the LOC, corresponding to the third lowest EEC in the dataset, calculated based on one application of 40 g a.i./ha to winter wheat in British Columbia. EECs equal to, or greater than, 0.0019 mg a.i./L (15-cm depth) and 0.0006 mg a.i./L (80-cm depth) result in RQs above the LOC for freshwater and estuarine/marine organisms; and,
3) The exposure scenario that resulted in the maximum EECs (2 applications of 40 g a.i./ha to bare ground in Prince Edward Island). The maximum EECs resulted in maximum RQs of 27 for amphibians, 8.8 for freshwater and marine fish, 4.3 for saltwater mysids and 39 for freshwater algae and marine diatoms.

There are a number of conservative assumptions in the runoff modelling that may overestimate risk:

1) Several representative scenarios for each use pattern for different regions of Canada were modelled using the maximum application rate for each crop. The highest EEC for all modelled scenarios was used in the risk assessment.
2) The combined residue of epyrifenacil, S-3100-CA, S-3100-DA and S-3100-DP was used to calculate EECs in the runoff assessment. Given that epyrifenacil dissipates rapidly in the environment, the EEC would consist mostly of TPs rather than epyrifenacil. S-3100-CA, which was produced at >85% AR in the environmental fate studies, is expected to make up the majority of the EEC; S-3100-DA and S-3100-DP were measured at <30% AR and approximately 10% AR, respectively.
3) The runoff EECs were compared to effects metrics for epyrifenacil, which is demonstrated to be more toxic than the TPs. Ecotoxicity data for all of the TPs are only available for freshwater algae/diatoms (*Rhaphidocelis subcapitata* and *Navicula pelliculosa*). When considering the most sensitive freshwater algae endpoints for each TP, S-3100-CA is nine times less toxic than epyrifenacil while S-3100-DA and S-3100-DP are slightly less toxic than epyrifenacil (1.4 to 1.7 times less toxic). Acute freshwater invertebrate and fish toxicity data for S-3100-CA are also available. Compared to epyrifenacil, S-3100-CA is at least 15 times less toxic to *Daphnia magna* and 18 times less toxic to bluegill sunfish. When considering that the less toxic S-3100-CA is expected to make up most of the runoff EEC rather than epyrifenacil, the risk assessment likely overestimates risk to aquatic organisms from runoff.

When considering the conservative assumptions used in the runoff assessment, risks to aquatic organisms are acceptable when label directions, which include precautionary label statements to mitigate runoff, are followed.

4.3 Environmental incident reports

As of 9 February 2026, no environmental incident reports involving epyrifenacil have been submitted to Health Canada.

5.0 Value

Adequate weed control is one of the main concerns affecting the adoption and long-term management of conservation tillage systems. Epyrifenacil provides contact and systemic burndown control of a broad-spectrum of broadleaf and grassy weeds, including many that are considered to be the most damaging problematic weeds in conservation tillage production systems, with limited soil residual activity. Epyrifenacil allows conservation tillage users to start with clean fields.

Epyrifenacil is a Group 14 mode of action herbicide with a unique binding mechanism, which controls weed biotypes that are resistant to other chemical families within the same mode of action.

Pre-plant and pre-emergent applications of S-3100 0.46 EC Herbicide and V-10488 0.94 SE Herbicide fit well into Integrated Pest Management (IPM) programs. The applications of these herbicides provide early season weed control, which also helps to manage other pest issues, such as pathogens, insects, and rodents, thereby reducing the pest pressure from such pests and the need for multiple pesticide applications.

5.1 Support for efficacy claims

Efficacy information submitted for review consisted of data from 241 adequate field trials, scientific rationales, and precedent registrations for flumioxazin and pyroxasulfone. The field trials were conducted in Canada and the US between 2015 and 2021.

5.1.1 S-3100 0.46 EC Herbicide

In the 241 field trials for which efficacy data were reported for S-3100 0.46 EC Herbicide, it was demonstrated that the pre-plant or pre-emergent application of S-3100 0.46 EC Herbicide at 182-726 mL/ha, based on weed spectrum, host crops, and use site, provided acceptable burndown control or suppression of labelled weeds in croplands, fallow land, as well as bare ground non-cropland.

In the five trials for which the efficacy of S-3100 0.46 EC Herbicide applied with COC, MSO, or NIS for control of 10 weed species was compared to S-3100 0.46 EC Herbicide applied without an adjuvant, it was demonstrated that the level of weed control provided by S-3100 0.46 EC Herbicide applied with one of the adjuvants listed above was greater than that without an adjuvant.

In the five trials for which the efficacy of S-3100 0.46 EC Herbicide applied with COC or MSO at 1.0% v/v or NIS at 0.25% v/v was compared to each other for control of 13 weed species, it was demonstrated that the level of weed control provided by S-3100 0.46 EC Herbicide applied with COC, MSO, or NIS was not different. Carrier as an alternative adjuvant is also supported for use with S-3100 0.46 EC Herbicide based on data from the trials for which the efficacy of S-3100 0.46 EC Herbicide applied with Carrier was compared to that applied without an adjuvant.

The efficacy of S-3100 0.46 EC Herbicide applied with COC + NIS was evaluated in 34 trials for control of 30 weed species. However, S-3100 0.46 EC Herbicide applied with COC or NIS was only included in two of the 34 trials. As such, efficacy of S-3100 0.46 EC Herbicide applied with COC + NIS in the 34 field trials for control of 30 weed species was compared to that applied with COC, MSO, or NIS in all the field trials for control of the same 30 weed species. The trial results demonstrated that the level of weed control provided by S-3100 0.46 EC Herbicide applied with COC + NIS was improved when compared to that applied with COC, MSO, or NIS alone.

In the four trials for which the efficacy of S-3100 0.46 EC Herbicide applied with COC + NIS + ammonia sulfate (AMS) was evaluated for control of eight weed species, it was demonstrated that the level of weed control provided by S-3100 0.46 EC Herbicide applied with COC + NIS + AMS was similar to that applied with COC + NIS. However, the statement that AMS may be added to the spray mixture to negate the effect of hard water, which can reduce effectiveness of many herbicides, is considered acceptable for labelling based on scientific rationales.

The tank mix partners are supported for labelling if their respective registered use pattern is consistent with that proposed for the tank mixtures and there are no contradictory label statements on the tank mix partner labels.

In the one trial for which the efficacy of S-3100 0.46 EC Herbicide followed by a simulated rainfall of 12.5 mm at 20 minutes, 30 minutes, one hour, 2 hours, and 4 hours was investigated, it was demonstrated that the application of S-3100 0.46 EC Herbicide needed a rain-free period of 30 minutes to one hour for full efficacy potential.

5.1.2 V-10488 0.94 SE Herbicide

There are two lists of weeds controlled by V-10488 0.94 SE Herbicide: burndown weed control and residual weed control.

In the four trials for which the efficacy of V-10488 0.94 SE Herbicide was evaluated and compared to that of S-3100 0.46 EC Herbicide for burndown control of 11 weed species, it was demonstrated that the level of weed control provided by V-10488 0.94 SE Herbicide was acceptable and comparable to that by S-3100 0.46 EC Herbicide. Therefore, all weeds controlled by S-3100 0.46 EC Herbicide are expected to also be controlled by V-10488 0.94 SE Herbicide.

In the five trials for which the efficacy of V-10488 0.94 SE Herbicide was evaluated and compared to the tank mixture of S-3100 0.46 EC Herbicide + a precedent product containing flumioxazin and pyroxasulfone, it was demonstrated that the level of residual weed control averaged over nine species provided by V-10488 0.94 SE Herbicide was acceptable and comparable to that by the tank mixture of S-3100 0.64 EC Herbicide + the precedent product. In addition, it is well known that formulation variation of herbicides has minimal impact on residual weed control. It corroborated the trial results.

The tank mix partners are supported for labelling if their respective registered use pattern is consistent with that proposed for the tank mixtures and there are no contradictory label statements on the tank mix partner labels.

A 1-hour rainfastness is supported for V-10488 0.94 SE Herbicide since a 1-hour rainfastness was supported for S-3100 0.46 EC Herbicide and is registered for the precedent product.

5.2 Support for host crop claims

Crop tolerance information submitted included data from 71 adequate trials, 48 of which were dedicated crop tolerance trials, which were conducted in Canada between 2017 and 2021, and the remaining trials were combined efficacy and crop tolerance trials.

5.2.1 Soybean

In the 21 trials for which the tolerance of soybean to S-3100 0.46 EC Herbicide was investigated, it was demonstrated that injury to soybean following the pre-plant or pre-emergent application of S-3100 0.46 EC Herbicide at 726 mL/ha was acceptable throughout the field season. The yield data corroborated that soybean could exhibit an adequate margin of tolerance to S-3100 0.46 EC Herbicide applied as per the label.

In the 30 trials for which the tolerance of soybean to V-10488 0.94 SE Herbicide was investigated, it was demonstrated that injury to soybean was minor or not observed for the pre-plant or pre-emergent application of V-10488 0.94 SE Herbicide at 1.75 L/ha and minor or moderate for the same treatment at 3.5 L/ha early in the field season. All injuries observed in the early season declined overtime. Yield data corroborated that soybean could exhibit an adequate margin of tolerance to V-10488 0.94 SE Herbicide applied as per the label.

5.2.2 Spring and winter wheat

In the 19 trials for which the tolerance of spring wheat to S-3100 0.46 EC Herbicide was investigated, it was demonstrated that injury to spring wheat following the pre-plant application of S-3100 0.46 EC Herbicide at 726 mL/ha was acceptable throughout the field season. The yield data corroborated that spring wheat could exhibit an adequate margin of tolerance to S-3100 0.46 EC Herbicide applied as per the label.

Winter wheat as a host crop is also supported based on scientific rationales and crop tolerance data generated with spring wheat.

In the one trial for which the tolerance of spring wheat to V-10488 0.94 SE Herbicide was investigated, it was demonstrated that injury to spring wheat with the pre-plant application of V-10488 0.94 SE Herbicide at both 1.75 or 3.5 L/ha was not observed at the mid and late field ratings. Yield data confirmed that spring wheat could exhibit an adequate margin of tolerance to the application of V-10488 0.94 SE Herbicide as per the label instructions. In addition, spring wheat was tolerant to S-3100 0.46 EC Herbicide and the co-formulation of flumioxazin and pyroxasulfone when they were applied at the same active ingredient rates per hectare.

5.2.3 Field corn

In the nine trials for which the crop tolerance data were submitted for field corn, it was demonstrated that injury to field corn following the pre-plant application of S-3100 0.46 EC Herbicide at 726 mL/ha was acceptable throughout the field season. The yield data corroborated that field corn could exhibit an adequate margin of tolerance to S-3100 0.46 EC Herbicide applied as per the label.

5.2.4 Canola

In the 22 trials for which the crop tolerance data were submitted for canola, it was demonstrated that the pre-plant application of S-3100 0.46 EC Herbicide at 363 mL/ha caused minor to moderate injury at the early season ratings. However, the observed injury declined overtime and yield was not affected.

5.3 Support for rotational crop claims

Rotational crop tolerance information submitted included data from 15 field trials, which were conducted in Canada and the USA between 2015 and 2021. S-3100 0.46 EC Herbicide was applied several times as separate treatments in each trial to simulate different re-cropping intervals. In most cases, applications were made to bare soil and multiple crops were seeded in strips. Plots were kept weed-free in nine trials, preventing herbicide uptake and metabolism by weeds; weeds were not removed from the plots in the remaining six trials.

In the trials for which the rotational crop tolerance data were submitted for alfalfa, dry bean, flax, lentil, potato, and sorghum, it was demonstrated that injury to these crops planted one to three months after the application of S-3100 0.46 EC Herbicide at 363 and 726 mL/ha was minor or not detectable. Therefore, the re-cropping intervals of one month for 181.5 and 363 mL/ha and two months for 726 mL/ha for these crops are acceptable.

In the trials for which the rotational crop tolerance data were submitted for barley, chickpea, field pea, and oat, it was demonstrated that injury to these crops planted one to three months after the application of S-3100 0.46 EC Herbicide at 363 and 726 mL/ha were minor or not detectable. Therefore, the re-cropping interval of one month for S-3100 0.46 EC Herbicide at all three rates, in other words, 181.5, 363, and 726 mL/ha, for these crops is acceptable.

In the trials for which the rotational crop tolerance data were submitted for canola, it was demonstrated that moderate injury to canola planted one to three weeks and two months after the application of S-3100 0.46 EC Herbicide at 363 and 726 mL/ha, respectively, was observed. But the moderate injury observed in the early season declined over time. As such, the re-cropping intervals of 7 days and 2 months for S-3100 0.46 EC Herbicide at 363 and 726 mL/ha, respectively, for canola are acceptable with the inclusion of a precautionary label statement.

Although rotational crop tolerance information was not submitted to support canola that can be safely planted to fields three days after receiving an application of S-3100 0.46 EC at 182 mL/ha, it is supported based on the host crop tolerance data.

In the trials for which rotational crop tolerance data were submitted for sugar beet, it was demonstrated that injury to sugar beet planted two and three months after the application of S-3100 0.46 EC Herbicide at 363 and 726 mL/ha was not observed. Therefore, the re-cropping intervals of two months for S-3100 0.46 EC Herbicide at 182 and 363 mL/ha and four months for S-3100 0.46 EC Herbicide at 726 mL/ha are supported.

In the trials for which the rotational crop tolerance data were submitted for field corn, soybean and/or wheat, it was demonstrated that injury to field corn, soybean, and wheat (spring and winter) planted immediately after the application of S-3100 0.46 EC Herbicide at up to 726 mL/ha was minor or not detectable. In conjunction with the host crop tolerance data, field corn, soybean, and wheat as an immediate plant-back crop, in the event of a host crop failure, are supported for S-3100 0.46 EC Herbicide at all three rates.

Rotational crops for V-10488 0.94 SE Herbicide were supported for labelling based on the most restrictive rotational crop restrictions on the S-3100 0.46 EC Herbicide and the precedent product, which is co-formulated with pyroxasulfone and flumioxazin.

5.4 Value summary

Adequate weed control is one of the main concerns affecting the adoption and long-term management of conservation tillage systems. The registrations of S-3100 0.46 EC Herbicide and V-10488 0.94 SE Herbicide help conservation tillage users to start with clean fields. They provide contact and systemic burndown control of a broad-spectrum of broadleaf and grassy weeds, including many that are considered to be the most damaging problematic weeds in conservation tillage production systems.

Epyrifenacil is a Group 14 mode of action herbicide with a unique binding mechanism, which controls weed biotypes that are resistant to other chemical families within the same herbicide mode of action group.

Value information submitted for review included scientific rationales, precedent registrations, and efficacy data from 241 trials, crop tolerance data from 71 trials, and rotational crop tolerance data from 15 trials. S-3100 0.46 EC Herbicide was included in all trials while V-10488 0.94 SE Herbicide was included in a subset of these trials. Based on the weight of evidence, the use of S-3100 0.46 EC Herbicide and V-10488 0.94 SE Herbicide for pre-plant and/or pre-emergent control of the labelled weeds in field corn, soybean, spring and winter wheat, and/or canola, for use in fall burndown and fallow land programs, to maintain bare ground non-crop areas, and for IVM has been concluded to have acceptable value (Appendix I, Tables 26a, 26b, 26c and 26d).

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

During the review process, epyrifenacil and its transformation products were assessed in accordance with Regulatory Directive DIR99-03[7] and evaluated against the Track 1 criteria. Health Canada has reached the conclusion that epyrifenacil and its transformation products do not meet all of the TSMP Track 1 criteria.

Please refer to Appendix I, Table 27 for further information on the TSMP assessment.

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

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*.[8] The list is used as described in Science Policy Note SPN2020-01[9] and is based on existing policies and regulations, including the Toxic Substance Management Policy and *Formulants Policy*,[10] and taking into consideration the *Ozone-depleting Substances and Halocarbon Alternatives Regulations* under the *Canadian Environmental Protection Act, 1999*, (substances designated under the *Montreal Protocol*).

Health Canada has reached the conclusion that epyrifenacil and its end-use product, S-3100 0.46 EC Herbicide, do not contain any formulants or contaminants identified on Parts 1 or 3 of the *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern*. The end-use product, V-10488 0.94 SE Herbicide, has, as a component, the preservative 1,2-benzisothiazolin-3-one at 0.041%, which contains low levels of polychlorinated dibenzodioxins and furans (TSMP Track 1). No further action is required at this time. The use of this preservative in pest control products at a maximum of 0.1% was reassessed by Health Canada in 2012 and found to be acceptable because dioxin and furan levels are low/being managed as outlined in Regulatory Directive DIR99-03 for the implementation of TSMP. The use of formulants in registered pest control products is assessed on an ongoing basis through the Pesticides Regulatory Directorate's formulant initiatives and Regulatory Directive DIR2006-02.

7.0 Proposed regulatory decision

Health Canada, pursuant to subsection 28(1) of the *Pest Control Products Act*, is proposing registration for the sale and use of S-3100 Technical, S-3100 0.46 EC Herbicide and V-10488 0.94 SE Herbicide, containing the active ingredient epyrifenacil. S-3100 0.46 EC Herbicide provides burndown control of grass and broadleaf weeds in canola, field corn, soybean, and wheat. V-10488 0.94 SE Herbicide provides burndown control of the weeds controlled by epyrifenacil, and residual control of the weeds controlled by flumioxazin and pyroxasulfone, in soybean and wheat. Both products can also be used in fall burndown and fallow land programs, to maintain bare ground non-cropland, and for industrial vegetation management (IVM).

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.

[8] 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*.

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

[10] DIR2006-02, *Formulants Policy and Implementation Guidance Document*

Additional information being requested

Since the technical product S-3100 Technical is manufactured only at pilot scale before registration, five-batch data representing commercial-scale production and a final detailed commercial-scale manufacturing process will be required as post-market information after registration.

List of abbreviations

↑	increased
↓	decreased
#	number of
♀	female
♂	male
λ	wavelength
µg	microgram(s)
µL	microlitre(s)
µm	micrometre(s)
µM	micromolar
µPa	microPascal
°C	degree Celsius
°N	degree North
^{14}C	carbon-14
>	greater than
<	lesser than
≥	greater than, or equal to
%	percent
1/n	exponent for the Freundlich isotherm
a.i.	active ingredient
abs	absolute
AD	administered dose
ADD	absorbed daily dose
ADI	acceptable daily intake
A/G	albumin/globulin ratio
AGD	anogenital distance
AGI	anogenital index
AHETF	Agricultural Handlers Exposure Task Force
ALB	albumin
ALP	alkaline phosphatase
ALS	acetolactate synthase
ALT	alanine aminotransferase
AMS	ammonia sulfate
AOPWIN	Atmospheric Oxidation Estimation Program for Windows
AR	applied radioactivity
ASABE	American Society of Agricultural and Biological Engineers
AST	aspartate aminotransferase
ATPD	area treated per day
AUC	area under the curve
ARfD	acute reference dose
BAF	bioaccumulation factor
baso	basophil
BBCH	Biologishe Bundesanstalt, Bundessortenamt and Chemical industry
BCF	bioconcentration factor
BCF_{KLG}	growth and lipid corrected bioconcentration factor
BrdU	bromodeoxyuridine

bw	body weight
bwg	bodyweight gain
CAF	composite assessment factor
CAR	constitutive androstane receptor
CAS	Chemical Abstracts Service
CEPA	*Canadian Environmental Protection Act*
ChE	cholinesterase
chol	cholesterol
cm	centimetre(s)
cm^2	square centimetre
cm^3	cubic centimetre
conc'n	concentration
CO_2	carbon dioxide
CR	chemical-resistant
d	day(s)
DA3A	days after third application
DACO	data code
DAT	days after treatment
DEEM-FCID	Dietary Exposure Evaluation Model – Food Commodity Intake Database
DF	dry flowable
DFOP	double first order in parallel
DIR	Directive
DT_{50}	dissipation time 50% (dose required to observe 50% decline in concentration)
dw	dry weight
EC_{50}	effective concentration on 50% of the population
EDE	estimated daily exposure
EEC	estimated environmental concentration
eos	eosinophil
ER_{25}	effective rate for 25% of the population
EVOH	Ethylene vinyl alcohol
F1	first generation of offspring produced by a set of parents
F2	second generation
fc	food consumption
fe	food efficiency
FIR	food ingestion rate
FOB	functional observational battery
g	gram(s)
GB	groundboom
GI	gastrointestinal
GLP	Good Laboratory Practices
GSD	geometric standard deviation
GTP	glutamyl transpeptidase
h	hour(s)
H	Henry's law constant
ha	hectare(s)
HAFT	highest average field trial
Hb	hemoglobin
HC	historical control

Hct	hematocrit
HDPE	High Density Polyethylene
HPLC	high performance liquid chromatography
hr	hour(s)
ILV	independent laboratory validation
IORE	indeterminate order rate equation
IPM	Integrated Pest Management
IUPAC	International Union of Pure and Applied Chemistry
J	Joule(s)
K_d	soil-water partition coefficient
K_F	Freundlich adsorption coefficient
K_{FOC}	organic carbon normalized Freundlich distribution coefficient
kg	kilogram(s)
kPa	kilopascal(s)
K_{oc}	organic-carbon partition coefficient
K_{ow}	*n*–octanol-water partition coefficient
L	litre(s)
LAFT	lowest average field trial
LC_{50}	lethal concentration to 50% of the population
LDH	lactate dehydrogenase
LD_{50}	lethal dose to 50% of the population
LI	labelling index
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
LOQ	limit of quantitation
LR_{50}	lethal rate to 50% of the population
LSC	liquid scintillation counting
LUC	large unstained cell
M:E	myeloid to erythroid ratio
m	metre(s)
MBq	millibecquerel
mg	milligram(s)
mL	millilitre(s)
MAS	maximum average score for 24, 48 and 72 hours
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MIS	maximum irritation score
M/L	mixer/loader
mm	millimetre(s)
MMAD	mass median aerodynamic diameter
MOA	mode of action
MOE	margin of exposure
mol	mole(s)
mono	monocyte

MPHG	mechanically pressurized handgun
MPHW	manually pressurized handwand
MRID	US Master Record Identification Number
MRL	maximum residue limit
MS	mass spectrometry
MS/MS	tandem mass spectrometry
n	number
N/A	not applicable
NAFTA	North American Free Trade Agreement
neu	neutrophil
ng	nanogram(s)
NHANES/WWEIA	National Health & Nutrition Exam Survey/What We Eat in America
nm	nanometre(s)
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
NR	not required
NZW	New Zealand white
OATP	organic anion transporting polypeptide
OC	organic carbon content
OECD	Organisation for Economic Co-operation and Development
OH	hydroxyl radical
OM	organic matter content
P	parental generation
Pa	Pascal(s)
PBI	plantback interval
PCPA	*Pest Control Products Act*
PHED	Pesticide Handlers Exposure Database
PHI	preharvest interval
phos	inorganic phosphorus
p*K*a	dissociation constant
plt	platelet
PMRA	Pest Management Regulatory Agency
PMRL	Proposed Maximum Residue Limit
PND	postnatal day
PPARα	peroxisome proliferator-activated receptor alpha
PPE	personal protective equipment
PPIX	Protoporphyrin IX
ppm	parts per million
PRD	Proposed Registration Decision
prot	protein
PWC	Pesticide in Water Calculator
PXR	pregnane X receptor
QSAR	quantitative structure-activity relationship

RA	risk assessment
RAC	raw agricultural commodity
RBC	red blood cells
RBD	refined, bleached, and deodorized
RD	Registration Decision
RDW	red cell distribution width
RDW-CV	red cell distribution width %
REI	restricted-entry interval
rel	relative
RET	reticulocyte
RI	replacement index
ROW	right-of-way sprayer
RQ	risk quotient
S9	mammalian metabolic activation system
SDEV	standard deviation
SDH	succinate dehydrogenase
SFO	single first order
SL	single layer of clothing
SPN	Science Policy Note
$T_{1/2}$	half-life
T3	tri-iodothyronine
T4	thyroxine
TFA	trifluoroacetic acid
TFD	terrestrial field dissipation
T_{max}	time of peak effect
TP	transformation product
t_R	representative half-life
trig	triglyceride
TRR	total radioactive residue
TSMP	Toxic Substances Management Policy
UF	uncertainty factor
USEPA	United States Environmental Protection Agency
UV	ultraviolet
v.	version
v/v	volume per volume dilution
WBC	white blood cells
wt	weight
w/v	weight by volume

Appendix I Tables and Figures

Table 1a Residue analysis in environmental media

Matrix	Method ID	Analyte	Method Type	LOQ	Reference (PMRA No.)
Soil	RM-52S	active Metabolites: S-3100-CA S-3100-DA S-3100-CA-RD S-3100-CA-UR S-3100-DP 4″-OH-S-3100-CA S-3100-DA-RD	HPLC-MS/MS	0.010 mg/kg	3308401
	RM-52S-4	active Metabolites: S-3100-CA S-3100-DA S-3100-CA-RD S-3100-CA-UR S-3100-DP 4″-OH-S-3100-CA S-3100-DA-RD		0.00015 mg/kg 0.00015 0.00015 0.001 0.005 0.00015 0.001 0.001	3308403
	RM-52S-4A	active Metabolites: S-3100-CA S-3100-DA S-3100-CA-RD S-3100-CA-UR S-3100-DP 4″-OH-S-3100-CA S-3100-DA-RD	HPLC-MS/MS	0.00015 mg/kg 0.00015 0.00015 0.001 0.005 0.00015 0.001 0.001	3309629
	RM-52S-2	active Metabolites: S-3100-CA S-3100-DA S-3100-CA-RD S-3100-CA-UR	HPLC-MS/MS	0.01 mg/kg	3308404

Matrix	Method ID	Analyte	Method Type	LOQ	Reference (PMRA No.)
		S-3100-DP 4″-OH-S-3100-CA S-3100-DA-RD			
	RM-52S-3	active Metabolites: S-3100-CA S-3100-DA S-3100-CA-RD S-3100-CA-UR S-3100-DP 4″-OH-S-3100-CA S-3100-DA-RD	HPLC-MS/MS	0.00001 mg/kg	3420721
Ground water and surface waters	12709.6509	active Metabolites: S-3100-CA S-3100-CA-UR	HPLC-MS/MS	0.1 µg/L	3308405
Ground and Surface waters	12709.6529	Metabolites: S-3100-DA S-3100-DA-UR S-3100-DA-RD S-3100-DP S-3100-CA-RD 4″-OH-S-3100-CA	HPLC-MS/MS	0.1 µg/L	3308406

Table 1b Residue analysis in plant and animal matrices

Analytical methods	Matrix	Analyte	Method ID/ Type	LOQ	Reference
Livestock commodities					
Enforcement Method	Chicken breast	Epyrifenacil, S-3100-CA	RM-52T/ LC-MS/MS	0.01 ppm per analyte	Study Nos. V-21-202230; 202100234 MRID 51778734 PMRA No. 3309348

Analytical methods	Matrix	Analyte	Method ID/ Type	LOQ	Reference
	Liver, kidney, milk and eggs	Epyrifenacil, S-3100-CA	RM-52AM-1/ LC-MS/MS	0.01 ppm for all analytes in all matrices	Study Nos. V-21-202501; 202100485; 693SRUS21R0163 MRID 51778745 PMRA No. 3309347
ILV of Enforcement Method	Chicken breast	Epyrifenacil, S-3100-CA	RM-52T/ LC-MS/MS	0.01 ppm per analyte	Study Nos. V-21-202501; 202100485; 693SRUS21R0163 MRID 51778745 PMRA No. 3309347
	Pork kidney, chicken liver, milk, and eggs	Epyrifenacil, S-3100-CA	RM-52AM-1/ LC-MS/MS	0.01 ppm for all analytes in all matrices	Study No. 221118 MRID# 51494002 PMRA No. 3410278
Plant commodities					
Enforcement and Data-Gathering Method	Canola seed, corn stover, radish root, wheat forage, wheat grain	Epyrifenacil, S-3100-CA, S-3100-DA, S-3100-DP-Me, S-3100-PR	RM-52C-2b/ LC-MS/MS	0.005 ppm (canola seed, radish root, wheat grain; all analytes) 0.01 ppm (corn stover, wheat forage; all analytes)	Study Nos. V-18-200811; 202100439 MRID 51781205 PMRA No. 3309349 (Appendix E, pg. 325) Note: Method RM-52C-2b is a revised version of Method RM-52C-b.

Analytical methods	Matrix	Analyte	Method ID/ Type	LOQ	Reference
	Soybean oil	Epyrifenacil, S-3100-CA, S-3100-DA, S-3100-DP-Me, S-3100-PR	RM-52C-1a/ LC-MS/MS	0.005 ppm per analyte	Study Nos. V-18-200942; 202100467 MRID 51778744 PMRA No. 3309353 (Appendix A, pg. 64)
Data-Gathering Method	Canola seed, field corn stover, radish root, soybean forage, wheat grain	TFA	AM-2101/ LC-MS/MS	0.05 ppm (canola seed, field corn stover, radish root) 0.07 ppm (wheat grain) 0.1 ppm (soybean forage)	Study Nos. V-201300; 202100096 MRID 51778735 PMRA No. 3309346
	Corn cobs and grain, undelinted cotton seeds and soybean seed	Epyrifenacil, S-3100-CA, S-3100-DA, S-3100-DP-Me, S-3100-PR, TFA	**Epyrifenacil, S-3100-CA, S-3100-DA, S-3100-DP-Me, S-3100-PR:** bAdapted Method No. RM-52-C/ LC-MS/MS[2] **TFA:** Unnamed method/ HS GC-MS/MS[3]	**Epyrifenacil, S-3100-CA, S-3100-DA, S-3100-DP-Me, S-3100-PR:** 0.005 ppm for all matrices **TFA:** 0.05 ppm for corn (grain) and cotton undelinted seeds) 0.08 ppm for corn (cobs) and soybean (seeds)	Study No. S20-02453 (SUM-2002V) MRID# 51493309 PMRA No. 3379311

Analytical methods	Matrix	Analyte	Method ID/ Type	LOQ	Reference
ILV of Enforcement Method	Canola seed, corn stover, radish root, wheat forage, wheat grain	Epyrifenacil, S-3100-CA, S-3100-DA, S-3100-DP-Me, S-3100-PR	RM-52C-2b/ LC-MS/MS	0.005 ppm (canola seed, radish root, wheat grain; all analytes) 0.01 ppm (corn stover, wheat forage; all analytes)	Study Nos. V-21-202502; 202100483; 693SRUS32R0146 MRID 51781213 PMRA No. 3309352
	Soybean oil	Epyrifenacil, S-3100-CA, S-3100-DA, S-3100-DP-Me, S-3100-PR	RM-52C-1a/ LC-MS/MS	0.005 ppm per analyte	Study Nos. V-21-202601; 202100484; 693SRUS21R0164 MRID 51778744 PMRA No. 3309353
Radiovalidation of Methods	Kale, wheat straw	Epyrifenacil, S-3100-CA, S-3100-DA, S-3100-DP-Me, S-3100-PR	RM-52C-2b/ LC-MS/MS	Not applicable	Study Nos. V-201940; 202100419 MRID 51781205 PMRA No. 3309349
	Canola seed, corn stover, radish root, soybean forage	TFA	AM-2101/ LC-MS/MS	Not applicable	Study Nos. V-202440; 202100431 MRID 51778728 PMRA No. 3309351
Multiresidue Method Testing	Canola seed, lemon, lettuce, wheat hay	Epyrifenacil, S-3100-CA	EN 15662: 2008 (E)/ QuEChERS	0.01 ppm per analyte in all matrices	Study Nos. 21G0609; 202100400 MRID 51778746 PMRA No. 3309217

Table 2 Identification of select metabolites of epyrifenacil

Code	Chemical name	Source
S-3100-CA	2-((3-(2-chloro-4-fluoro-5-(3-methyl-2,6-dioxo-4-(trifluoromethyl)-3,6-dihydropyrimidin-1(2H)-yl) phenoxy)pyridin-2-yl)oxy)acetic acid	Rat, crops, livestock, environmental metabolite
S-3100-CA-UR	2-((3-(2-chloro-4-fluoro-5-(3-methylureido)phenoxy)pyridin-2-yl)oxy)acetic acid	Rat, environmental metabolite
S-3100-CA-RD	2-((3-(2-chloro-4-fluoro-5-(3-methyl-2,6-dioxo-4-(trifluoromethyl)tetrahydropyrimidin-1(2H)-yl) phenoxy)pyridin-2-yl)oxy)acetic acid	Rat, environmental metabolite
4"-OH-S-3100-CA	2-((3-(2-chloro-4-fluoro-5-(4-hydroxy-3-methyl-2,6-dioxo-4-(trifluoromethyl)tetrahydropyrimidin- 1(2H)-yl)phenoxy)pyridin-2-yl)oxy)acetic acid	Rat, environmental metabolite
S-3100-CA-AM	2-((3-(5-amino-2-chloro-4-fluorophenoxy)pyridin-2-yl)oxy)acetic acid	Rat, environmental metabolite
S-3100-DA	3-(4-chloro-2-fluoro-5-((2-oxo-1,2-dihydropyridin-3-yl)oxy)phenyl)-1-methyl-6-(trifluoromethyl) pyrimidine-2,4(1H,3H)-dione	Rat, environmental metabolite
S-3100-DP	3-(4-chloro-2-fluoro-5-hydroxyphenyl)-1-methyl-6-(trifluoromethyl)pyrimidine-2,4(1H,3H)-dione	Rat, environmental metabolite
S-3100-DA-UR	1-(4-chloro-2-fluoro-5-((2-oxo-1,2-dihydropyridin-3-yl)oxy)phenyl)-3-methylurea	Rat, environmental metabolite
(S)-TFP-Glu	(2S,3S,4S,5R,6S)-3,4,5-trihydroxy-6-(((S)-1,1,1-trifluoropropan-2-yl)oxy)tetrahydro-2H-pyran-2-carboxylic acid	Rat metabolite
APPE	ethyl 2-[3-(5-amino-2-chloro-4-fluorophenoxy)pyridin-2-yl]oxyacetate	Environmental metabolite
S-3100-DP-Me	3-(4-chloro-2-fluoro-5-methoxyphenyl)-1-methyl-6-(trifluoromethyl)pyrimidine2,4(1H,3H)-dione	Crop/livestock/water metabolite
S-3100-BFP	ethyl 2-((6-hydroxy-7-(3-methyl-2,6-dioxo-4-(trifluoromethyl)-3,6-dihydropyrimidin-1(2H)-yl)benzofuro[2,3-c]pyridin-1-yl)oxy)acetate	Environmental metabolite
S-3100-CA-RO1	2-((3-(2-chloro-4-fluoro-5-(4,4,4-trifluoro-3,3-dihydroxybutanamido)phenoxy)pyridin-2-yl)oxy)acetic acid	Crop/livestock/water metabolite
S-3100-DA-RD	3-(4-chloro-2-fluoro-5-((2-oxo-1,2-dihydropyridin-3-yl)oxy)phenyl)-1-methyl-6-(trifluoromethyl)dihydropyrimidine-2,4(1H,3H)-dione	Crop/livestock/water metabolite

Code	Chemical name	Source
S-3100-CA-RO2	(E)-3-(3-(5-((2-(carboxymethoxy)pyridin-3-yl)oxy)-4-chloro-2-fluorophenyl)-1-methylureido)-4,4,4-trifluorobut-2-enoic acid	Crop/livestock/water metabolite
4'-OH-S-3100	ethyl 2-((3-(2-chloro-4-hydroxy-5-(3-methyl-2,6-dioxo-4-(trifluoromethyl)-3,6-dihydropyrimidin-1(2H)-yl)phenoxy)pyridin-2-yl)oxy)acetate	Crop/livestock/water metabolite
S-3100-PR	1-methyl-6-(trifluoromethyl)dihydropyrimidine-2,4(1H,3H)-dione	Crop/livestock/water metabolite
S-3100-DA-RO1	N-(4-chloro-2-fluoro-5-((2-oxo-1,2-dihydropyridin-3-yl)oxy)phenyl)-4,4,4-trifluoro3,3-dihydroxybutanamide	Crop/livestock/water metabolite
S-3100-CA-RD-RO	3-(3-(5-((2-(carboxymethoxy)pyridin-3-yl)oxy)-4-chloro-2-fluorophenyl)-1-methylureido)-4,4,4-trifluorobutanoic acid	Crop/livestock/water metabolite
S-3100-DA-RD-RO	3-(3-(4-chloro-2-fluoro-5-((2-oxo-1,2-dihydropyridin-3-yl)oxy)phenyl)-1-methylureido)-4,4,4-trifluorobutanoic acid	Crop/livestock/water metabolite

Table 3 Toxicology reference values for use in health risk assessment for epyrifenacil

Exposure Scenario	Study	Point of departure and endpoint	CAF[1] or Target MOE
Acute dietary general population	Establishment of an acute reference dose is not required as an endpoint of concern attributable to a single exposure was not identified in the oral toxicity studies.		
Acute dietary Females 13–49 years of age	2-generation reproductive toxicity study in rats	NOAEL = 6.8 mg/kg bw Decreased anogenital distance in F2 male and female offspring	300
ARfD (females 13–49 years) = 0.02 mg/kg bw			
Repeated dietary	Oncogenicity study in rats	NOAEL = 1.4 mg/kg bw/day Liver, heart effects, decreased MCV and MCH, increased ALP	100
ADI = 0.01 mg/kg bw/day			
Short- and intermediate-term dermal[2]	2-generation reproductive toxicity study in rats	NOAEL = 6.8 mg/kg bw/day Post-weaning F1 male pup death, delayed sexual maturation and decreased anogenital distance in offspring	300

Exposure Scenario	Study	Point of departure and endpoint	CAF[1] or Target MOE
Short- and intermediate-term inhalation[3]	2-generation reproductive toxicity study in rats	NOAEL = 6.8 mg/kg bw/day Post-weaning F1 male pup death, delayed sexual maturation and decreased anogenital distance in offspring	300
Cancer	Evidence of tumourigenicity; there was adequate evidence to support a threshold-based mechanism to the liver tumours in male mice. The selected reference values provide a sufficient margin to the dose at which these tumours were observed.		

[1] CAF (composite assessment factor) refers to a total of uncertainty and PCPA factors for dietary assessments; MOE (margin of exposure) refers to a target MOE for occupational assessments.
[2] Since an oral NOAEL was selected, a dermal absorption factor of 12% 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 epyrifenacil

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.

Note: unless otherwise specified, studies listed in this table are considered Acceptable according to Information Note: Determining Study Acceptability for use in Pesticide Risk Assessments

Study Type/ Animal/PMRA No.	Study results
Toxicokinetic Studies	
Absorption, distribution, excretion and metabolism in the rat (single and repeated oral gavage administration) Crl:CD(SD) rats PMRA No. 3410757	**Treatment:** [phenyl-^{14}C]S-3100, [pyrimidinyl-4-^{14}C]S-3100, or [pyridyl-4(6)-^{14}C]S-3100 were administered (4/sex/dose or 12/sex/dose for distribution groups) in single oral administration in 0.5% w/v methylcellulose in water via gavage at dose levels of 1 or 50 mg/kg bw. Additionally, a group of animals was given a single oral administration of [phenyl-^{14}C]S-3100 at 1 mg/kg bw following 13-day repeated doses (once a day) of non-radiolabeled test compound, S-3100 AS, at 1 mg/kg bw/day. **Absorption:** The absorption rates were ~73% of the AD at 1 mg/kg bw, based on radioactivity recovered in bile, urine, and carcass, in both sexes without significant reabsorption from bile. T_{max} was 2-8 hours at low dose and 1-2 hours at high dose. No significant dose-related change in absorption or metabolism. No remarkable sex-related difference was observed in ^{14}C-concentrations in blood and plasma of a single dose. The AUC and $T_{1/2}$ were larger (twofold) in the repeat-dose female group. ^{14}C in bile was excreted into feces (18-19%).

Study Type/ Animal/PMRA No.	Study results
	Distribution: Radioactivity distributed in most organs and tissues reached the highest level at 2 or 8 hours after administration at low dose and at 1 or 2 hours at high dose, and then decreased with time. At 72 hours post-administration, the administered ^{14}C was almost completely eliminated from organs and tissues. The concentrations in liver and kidney were higher than other organs except for GI tract and its contents. No significant radiolabel- or sex-dependent differences were observed. **Elimination:** The excretion of radioactivity was extensive and mostly via feces within 48 hours following administration. There were no significant dose- or radiolabel-related changes on the excretion profiles. The excretion in urine was higher in females. The excretion with the pyrimidinyl label showed higher excretion via urine and expired air, and with the pyridyl label, showed higher excretion via urine, compared to phenyl label. **Metabolism:** Nine metabolites (S-3100-CA, S-3100-CA-UR, S-3100-CA-RD, 4"-OH-S-3100-CA, S-3100-CA-AM, S-3100-DA, S-3100-DP, S-3100-DA-UR, and (S)-TFP-Glu) as well as unchanged S-3100 were identified in the rat. S-3100-CA (42.7-67.8%) was the most predominant metabolite in bile, feces, and urine with all radiolabels. The amount of S-3100-CA in urine of females was remarkably higher while it was barely detected in males. More unchanged S-3100 and less S-3100-CA (about 10%) were detected in feces at high dose. In plasma, liver and kidney, the unchanged S-3100 was not detected, and no dose-related difference was observed. The concentrations of major metabolites (S-3100-CA and 4"-OH- S-3100-CA) were noticeably higher in liver than in kidney and plasma.
Acute toxicity studies (S-3100 TG; Epyrifenacil technical)	
Acute oral Crl:CD(SD) rats PMRA No. 3308309	LD_{50} > 2000 mg/kg bw (♀) No clinical signs of toxicity **Low toxicity**
Acute dermal Crl:CD(SD) rats PMRA No. 3308310	LD_{50} > 2000 mg/kg bw (♂♀) No clinical signs of toxicity **Low toxicity**
Acute inhalation Crl:CD(SD) rats	LC_{50} > 2.2 mg/L (♂♀) No clinical signs of toxicity

Study Type/ Animal/PMRA No.	Study results
PMRA No. 3308311	**Low toxicity** MMAD = 3.57 µm GSD = 2.75
Eye irritation NZW rabbits PMRA No. 3308312	Washed: MAS $_{\text{at 24, 48 and 72 hours}}$ = 0/110 MIS $_{\text{at 1 hour}}$ = 0/110 (No reaction) Unwashed: MAS $_{\text{at 24, 48 and 72 hours}}$ = 0.2/110 MIS $_{\text{at 1 and 24 hour}}$ = 0.7/110 **Minimally irritating**
Dermal irritation NZW rabbits PMRA No. 3308313	MAS $_{\text{at 24, 48 and 72 hours}}$ = 0.2/8 MIS $_{\text{at 1 hour}}$ = 0.7/8 **Minimally irritating**
Dermal sensitization (Maximization) Slc:Hartley guinea pigs PMRA No. 3308314	**Negative**
Short-term toxicity studies	
90-Day oral (dietary) Crl:CD1(ICR) mice PMRA No. 3308316	NOAEL= 3.4/4.1 mg/kg bw/day ♂/♀ LOAEL= 14/15 mg/kg bw/day ♂/♀ Effects at the LOAEL: ↑RDW, ↑plt, ↑SDH, ↑ALP, ↓RBC, ↓Hb, ↓Hct, ↓MCV, ↓MCH, ↓MCHC, pale liver and single cell degeneration/necrosis (♂/♀); ↑ALT, hepatocellular hypertrophy, hepatocellular single cell necrosis/apoptosis (♂); liver mixed cell infiltrate (♀)
90-Day oral (dietary) Crl:CD(SD) rats PMRA No. 3308315	NOAEL= 3/19 mg/kg bw/day ♂/♀ LOAEL= 17/51 mg/kg bw/day ♂/♀ TK (days 1, 57, 84): ↑ S-3100-CA conc'n proportional to dose, no sex difference, no signs of accumulation over course of study, unchanged S-3100 was not observed in the plasma samples Effects at the LOAEL: ↓bw/bwg, ↓fc, ↑RET, ↑RDW, ↑ALT, ↑SDH, ↑ALP, ↑ urine bilirubin, pale pancreas/lungs, enlarged spleen, ↑femur and sternum bone marrow erythropoiesis, spleen/liver extramedullary hematopoiesis, liver bile duct

Study Type/ Animal/PMRA No.	Study results
	hyperplasia, multifocal hepatocellular degeneration/necrosis (♂); ↑bone marrow erythroid cells, ↓M:E, ↓Hb, ↓Hct, ↓MCV, ↓MCH, ↑RET, ↑RDW, ↑incidence of ≥ 1+ urine bilirubin, ↑liver wt, ↑femur and sternum bone marrow erythropoiesis (♀) Note: all males at 52 mg/kg bw/day were sacrificed on day 58 due to poor condition
28-Day oral range-finding (capsule) Beagle dogs PMRA No. 3308318	Acceptable with limitations NOAEL and LOAEL not established **1000 mg/kg bw/day:** ↓bw/bwg, an immature ovary, uterus, and vagina, with pituitary cyst (♀) Limitations: Dose range-finding study with limited sample size and endpoints assessed
90-Day oral (capsule) Beagle dogs PMRA No. 3308317	NOAEL= 100/300 mg/kg bw/day ♂/♀ LOAEL= 300/1000 mg/kg bw/day ♂/♀ TK: The majority of S-3100 was transformed to S-3100-CA, but small amounts of S-3100 were still detectable in plasma. ↑ S-3100-CA conc'n proportional to dose, no sex difference, no evidence for accumulation over 90 days Effects at the LOAEL: ↑femur bone marrow erythropoiesis (♂/♀); ↓Hb, MCV and MCH at Days 37 and 90 with increased severity evident at Day 90, ↑liver wt, (♂); ↑sternum marrow erythropoiesis, ↑liver glycogen, ↓MCHC at Day 90, mucoid feces, yellow mucoid feces, emesis containing white material (♀)
28-Day dermal Crl:CD(SD) rats PMRA No. 3308325	NOAEL= 200 mg/kg bw/day ♂/♀ LOAEL= 1000 mg/kg bw/day ♂/♀ Effects at the LOAEL: ↑RET, ↑RDW, ↑WBC, ↑plt, ↑bone marrow erythroid cells, ↑sternum and femur bone marrow erythropoiesis, ↑spleen extramedullary hematopoiesis, ↓MCV, ↓MCH, ↓MCHC, ↓Hb, ↓Hct, ↓M:E, ↓segmented neutrophils and lymphocytes (♂/♀);↓ bw, ↑ALP, ↑liver wt, ↓RBC, ↓total prot, ↓ALB, ↓GLOB (♂); ↑SDH (♀)
90-Day inhalation Crl:CD(SD) rats PMRA No. 3308326	NOAEC= 0.05 mg/L (13 mg/kg bw/day) ♂/♀ LOAEC= 0.14 mg/L (36 mg/kg bw/day) ♂/♀ Effects at the LOAEL: ↑A/G, ↑urine bilirubin, ↑darkness of urine, ↑incidences of eosinophilic globules of the olfactory epithelium and increased/hypertrophied mucous cells of the respiratory epithelium in nasal turbinates, ↑incidences of increased/hypertrophied mucous cells and eosinophilic globules of

Study Type/ Animal/PMRA No.	Study results
	the respiratory epithelium (nasopharyngeal duct) in nasopharynx, ↓total plasma chol (♂/♀); ↑ALP, ↑liver wt, ↓α-1 globulin conc'n (♂)
Chronic toxicity/Oncogenicity studies	
Oncogenicity dietary, 18-month CD-1 mice PMRA No. 3308327	NOAEL= 0.1/0.1 mg/kg bw/day ♂/♀ LOAEL= 0.5/0.7 mg/kg bw/day ♂/♀ Effects at the LOAEL: ↑ karyocytomegaly, ↑centrilobular fibrosis (♂/♀); ↑ALT, ↑foci of cellular alteration, ↑chronic centrilobular inflammation (♂) ≥1.7 mg/kg bw/day: Hepatocellular adenoma/carcinoma in males Evidence of carcinogenicity
Combined chronic/oncogenicity dietary, 24-month with 12-month satellite group Crl:CD(SD) rats PMRA No. 3308328 HC: PMRA No. 3410756, 3492581	NOAEL= 2.4/1.4 mg/kg bw/day ♂/♀ LOAEL= 8.3/9.5 mg/kg bw/day ♂/♀ Effects at the LOAEL: **52 weeks:** heart necrosis, **104 weeks**: heart necrosis, hepatocellular hypertrophy, cystic degeneration (♂); hepatocellular hypertrophy (♀) No evidence of tumourigenicity
Developmental/Reproductive toxicity studies	
One-generation reproductive toxicity, dietary (range-finding) Crl:CD(SD) rats PMRA No. 3308330	Acceptable with limitations NOAEL and LOAEL not established Parental toxicity **≥ 20/20 mg/kg bw/day** ♂/♀**:** cool and pale extremities or pale body (♂/♀); ↑liver wt (♂); ↑RET, ↓Hct, ↑RDW, ↓Hb, ↓MCV, ↓MCH, ↑WBC, ↑eos/neu/lymphocyte/mono/LUC, ↑spleen wt (♀) **40/40 mg/kg bw/day** ♂/♀**:** ↑RET, ↑RDW, ↓Hct, ↓Hb, ↓MCV, ↓MCH, ↑liver wt (♂); ↓RBC, enlarged/swollen spleen (♀) **Offspring toxicity** No treatment-related effects were observed on offspring toxicity (viability, bw, organ wt of 1 pup/litter, necropsy of 1 pup/litter were assessed)

Study Type/ Animal/PMRA No.	Study results
	Reproductive toxicity No treatment-related effects were observed on reproductive parameters examined (standard reproductive performance indices were assessed) Limitations: Dose range-finding study with limited sample size and endpoints assessed.
Two-generation reproductive toxicity, dietary Crl:CD(SD) rats PMRA No. 3308329	**Parental toxicity** NOAEL= 6.6/7.7 mg/kg bw/day in ♂/♀ LOAEL= 20/23 mg/kg bw/day in ♂/♀ Effects at the LOAEL: pale and cool extremities/body (F1), P: ↑bile duct hyperplasia, ↑hepatocellular hypertrophy, ↑Kupffer cell pigment, all generations: ↑RET, ↑RDW, ↑NRBC (F1 and F2, disproportionate to # RET), ↑stomatocytes, ↑liver wt (F1), F1 and F2: ↓Hb, ↓Hct, ↓MCV, ↓MCH, ↓MCHC (F1 and F2) (♂/♀); P: hepatocellular necrosis, F1: ↑mortality (starting PND 45), ↑morbidity, ↑neu, large changes in bw/bwg/fc, ↓RBC, ↓WBC, ↓lymphocyte, ↓plt (F1) (♂); ↑spleen wt (F1 and F2), ↑adrenal glands cystic degeneration (F1), F2: ↑WBC, ↑lymphocyte/neu, ↓RBC (♀) **Offspring toxicity** NOAEL= 6.8 mg/kg bw/day in ♂/♀ LOAEL= 21 mg/kg bw/day in ♂/♀ Effects at the LOAEL: ↑spleen wt, delayed sexual maturation, ↓anogenital distance, ↓anogenital distance relative to cube root of pup body wt (♂/♀); ↑mortality (starting PND 45) (♂) **Reproductive toxicity** NOAEL= 6.6/23 mg/kg bw/day in ♂/♀ LOAEL= not determined No treatment-related effects were observed on reproductive parameters. **No evidence of sensitivity of the young** **Limitations:** F1 males at 300 ppm were removed from treatment on PND 55 and then terminated PND 80-84, F1 females in this group were mated to control males. No measure of growing ovarian follicles.

Study Type/ Animal/PMRA No.	Study results
Developmental toxicity (gavage) Range-finding Crl:CD(SD) rats PMRA No. 3308339	Acceptable with limitations NOAEL and LOAEL not established **Maternal toxicity** **≥100 mg/kg bw/day:** one treatment-related mortality, though none at higher doses, ↑RET, ↑erythroid precursor, ↑mature WBC, ↓WBC precursor, ↓immature RBC, ↑liver wt **≥200 mg/kg bw/day:** ↑plt, ↑WBC, ↑lymphocyte, ↓Hb, ↓Hct, ↑spleen wt, ↑liver and spleen extramedullary hematopoiesis **300 mg/kg bw/day:** ↓MCV, ↓MCH **Developmental toxicity** No treatment-related effects on developmental toxicity parameters examined (bw, sex, and external examination) **Limitations:** Dose range-finding study with limited sample size and endpoints assessed.
Developmental toxicity (gavage) Crl:CD(SD) rats PMRA No. 3308338	**Maternal toxicity** NOAEL= 20 mg/kg bw/day LOAEL= 60 mg/kg bw/day Effects at the LOAEL: ↑RET, ↓Hb, ↓Hct, ↑neu/lymphocyte/baso/mono, ↑liver wt, centrilobular hepatocyte hypertrophy, focal subcapsular (hepatocyte) necrosis, liver extramedullary hematopoiesis, spleen extramedullary hematopoiesis **Developmental toxicity** NOAEL= 20 mg/kg bw/day LOAEL= 60 mg/kg bw/day Effects at the LOAEL: ↑supernumerary cervical ribs **No evidence of treatment-related malformations** **No evidence of sensitivity of the young**
Developmental toxicity (gavage) Range-finding NZW rabbits	Acceptable with limitations NOAEL and LOAEL not established **Maternal toxicity**

Study Type/ Animal/PMRA No.	Study results
PMRA No. 3308341	**≥250 mg/kg bw/day:** ↑RET, ↑liver wt, ↑centrilobular hepatocyte hypertrophy, ↑femur cellularity marrow **≥500 mg/kg bw/day:** ↓RBC, ↓Hb, ↓Hct **1000 mg/kg bw/day:** ↓bw, ↓bwg, ↓fc, ↓gravid uterine wt **Developmental toxicity** **1000 mg/kg bw/day:** ↓fetal wt Limitations: Dose range-finding study with limited sample size and endpoints assessed.
Developmental toxicity (gavage) NZW rabbits PMRA No. 3308340	**Maternal toxicity** NOAEL= 250 mg/kg bw/day LOAEL= 750 mg/kg bw/day Effects at the LOAEL: ↓Hb, ↓Hct, ↓MCV **Developmental toxicity** NOAEL= 250 mg/kg bw/day LOAEL= 750 mg/kg bw/day Effects at the LOAEL: supernumerary lumbar vertebra **Evidence of treatment-related malformations** **No evidence of sensitivity of the young**
Genotoxicity studies	
In vitro bacterial reverse mutation assay *S. typhimurium* *Escherichia coli* PMRA No. 3308342	Negative up to the limit concentration ± metabolic activation
In vitro mammalian cell assay Chinese Hamster V79 cells PMRA No. 3308351	Negative up to a precipitating concentration ± metabolic activation
In vitro chromosome aberration test	Negative up to a precipitating concentration ± metabolic activation

Study Type/ Animal/PMRA No.	Study results
Chinese hamster lung (CHL/IU) cells PMRA No. 3308352	
Micronucleus test CD-1 mice PMRA No. 3308360	Negative No mortality or clinical signs of toxicity Tested up to a limit dose
Neurotoxicity studies	
Acute neurotoxicity (gavage) Range-finding Crl:CD (SD) rats PMRA No. 3308331	Acceptable with limitations NOAEL and LOAEL not established **≥500 mg/kg bw :** ↓pupil size 1 to 4 hours after the treatment (♂) **≥1000 mg/kg bw:** ↓pupil size 1 to 4 hours after the treatment (♀) **Limitations:** Dose range-finding study with limited sample size and endpoints assessed.
Acute neurotoxicity (gavage) Crl:CD (SD) rats PMRA No. 3308332, 3308333	NOAEL= 2000/1000 mg/kg bw ♂/♀ LOAEL= not determined/2000 mg/kg bw ♂/♀ Effects at the LOAEL: ↓ activity levels and approach response (♀) **No evidence of selective neurotoxicity**
28-Day repeated dose neurotoxicity (dietary) Range-finding Crl:CD (SD) rats PMRA No. 3308334	Acceptable with limitations NOAEL and LOAEL not established **≥39 mg/kg bw/day:** ↑AST, ↓creatinine, ↓total prot, ↓ALB, ↓total bilirubin (♀) **38/65 mg/kg bw/day:** ↑liver wt, ↑dark colour in liver, ↓Hct, ↓Hb, ↓MCV, ↓MCH (♂/♀); ↑MCHC, ↑plt, ↑ALP, ↑ALT, ↑phos (♂) **Limitations:** Dose range-finding study with limited sample size and endpoints assessed.
90-Day repeated dose neurotoxicity (dietary) Crl:CD (SD) rats PMRA No. 3308335, 3308336	NOAEL= 3.3/20 mg/kg bw ♂/♀ LOAEL= 17/54 mg/kg bw ♂/♀ Effects at the LOAEL: ↓Hct, ↓Hb, ↓MCV, ↓MCH (♂/♀); ↑plt, ↓eos (♂) **No evidence of neurotoxicity**

Study Type/ Animal/PMRA No.	Study results
Delayed Neurotoxicity and Developmental Neurotoxicity Study (Waiver request) PMRA No. 3308319	Request to waive the conditional requirement for delayed neurotoxicity and developmental neurotoxicity testing accepted based on lack of triggering criteria.
Immunotoxicity Studies	
Immunotoxicity (Waiver request) PMRA No. 3308337	Request to waive the conditional requirement for immunotoxicity testing accepted based on the absence of immunotoxic effects in the database.
Special Studies	
Mechanistic in vitro study (effect on protoporphyrinogen oxidase (PPO) activity) PXB mice PMRA No. 3308371	**Objective:** To validate the appropriateness of using PXB mice for the evaluation of PPO inhibition as a human model, inhibitory activity of S-3100-CA against PPO were examined in vitro using hepatic mitochondrial fraction of chimeric mice with humanized liver (PXB mice), then compared to those of wild type mice, host mice of PXB mice, and humans **Results:** IC_{50} values of the PXB mice were comparable to that of humans, but higher than those in wild type mice and the host mice
Mechanistic oral (dietary) study in the mouse (effect on liver alteration), 7, 28, or 90 days Crl:CD1(ICR) mice PMRA No. 3308374	**Objective:** To investigate time course and dose response of key events of postulate MOAs involving porphyria-mediated cytotoxicity (PPIX accumulation, followed by hepatocyte injury and subsequent regenerative hepatocyte proliferation) and/or PPARα activation (PPARα activation followed by enhanced cell proliferation, associated with peroxisome proliferation) **Results:** **7d** **5.1/8.6 mg/kg bw/day:** ↑liver wt, centrilobular hepatocellular hypertrophy, increased mitosis (♂/♀); focal necrosis, centrilobular hepatocellular vacuolation (♂); ↑LDH, ↑ALT (♀) **28d** **5.3/8.5 mg/kg bw/day:** ↓RBC, ↓Hb, ↓Hct, ↓RET, ↑liver wt, enlarged liver, centrilobular hepatocellular hypertrophy, focal necrosis, centrilobular hepatocellular vacuolation (♂/♀); ↑plt, ↑ALT, single cell necrosis, Kupffer cell pigmentation, ↑BrdU (♂) **90d** **≥0.7 mg/kg bw/day:** centrilobular hepatocellular hypertrophy (♂); ↑plt (♀)

Study Type/ Animal/PMRA No.	Study results
	≥2.0/2.9 mg/kg bw/day: ↓RBC, ↓Hb, ↓Hct, ↓MCHC, ↓RET, centrilobular hepatocellular hypertrophy, ↑Cyp4a10 expression (♂/♀); ↑ALP, centrilobular hepatocellular vacuolation (♂); ↑eos (♀) **5.6/9.6 mg/kg bw/day:** ↑ALT, ↑liver wt, enlarged liver (3/4), centrilobular hepatocellular hypertrophy, centrilobular hepatocellular vacuolation, focal and single cell necrosis, Kupffer cell pigmentation, ↑lipid droplet, ↑BrdU (♂/♀); pale liver (♂); ↑WBC, ↑lymphocyte, ↑ALP (♀)
Mechanistic oral (dietary) study in the rat (effect on liver alteration) , 7, 28, or 90 days Crl:CD(SD) rats PMRA No. 3308390	**Objective:** To investigate the time-dependent changes of key events of the postulate MOAs, involving porphyria-mediated cytotoxicity (PPIX accumulation, followed by hepatocyte injury and subsequent regenerative hepatocyte proliferation) and/or PPARα activation (PPARα activation followed by enhanced cell proliferation, associated with peroxisome proliferation) **Results:** ↑liver wt (28 and 90d), enlarged liver, ↑BrdU labeling index, ↑S9 (7d), ↑lauric acid hydroxylation (7d), ↑PPIX conc'n (♂/♀); ↓bwg (90d), ↓Hb, ↓Hct, ↑plt, ↑LDH(28d), ↑AST/ALT (90d), ↑cyp4a1, cyp2b1/2, and cyp3a2 mRNA expression (3.2-11 fold), ↑S9 (28d) (♂); ↓MCV, ↓MCH, ↑RDW-CV, ↑liver wt (7d), ↑cyp4a1, cyp2b1/2, and cyp3a1/2 mRNA expression, ↓lauric acid hydroxylation (28 and 90d) (♀)
Mechanistic 90-day oral (dietary) study in the mouse (effect on liver alteration) Crl:CD1(ICR) mice PMRA No. 3308375	**Objective:** To assess the potential toxicity of S-3100 and investigate causal relationship to the postulated mode-of-action (MOA) for potential toxicity of S-3100. **Results:** **7d** **≥0.6 mg/kg bw/day:** ↓RBC, ↓Hb, ↓RET, diffuse hepatocellular hypertrophy, ↑PPIX conc'n **≥6.3 mg/kg bw/day:** ↓Hct, ↑liver wt, enlarged liver, increased mitosis, ↑Cyp2b10/Cyp3a11/Cyp4a10 expression **12 mg/kg bw/day:** single cell and focal necrosis, ↑BrdU **28d** **≥0.7 mg/kg bw/day:** diffuse hepatocellular hypertrophy, ↑PPIX conc'n **≥6.5 mg/kg bw/day:** ↓Hb, ↓Hct, ↑liver wt, enlarged liver, pale liver, increased mitosis, single cell necrosis, vacuolar degeneration of hepatocytes, ↑Cyp2b10/Cyp3a11/Cyp4a10 expression **13 mg/kg bw/day:** ↓RET, yellowish-brown pigmentation in Kupffer cells, hepatocytes and bile duct, ↑peroxisome, ↑lipid droplet, ↑BrdU

Study Type/ Animal/PMRA No.	Study results
	90d **≥0.6 mg/kg bw/day:** diffuse hepatocellular hypertrophy, ↑PPIX conc'n **≥6.1 mg/kg bw/day:** ↓Hb, ↓Hct, ↓MCH, ↑liver wt, enlarged liver, pale liver, single cell necrosis, yellowish-brown pigmentation in Kupffer cells, hepatocytes and bile duct, vacuolar degeneration of hepatocytes, ↑Cyp2b10/Cyp3a11/Cyp4a10 expression **13 mg/kg bw/day:** ↓RET, ↓MCV, ↑mitosis, ↑peroxisome, ↑lipid droplet, ↑BrdU
Mechanistic 32-day oral (dietary) study in the mouse (effect on liver alteration) chimeric PXB mice with humanized liver PMRA No. 3308372	**Objective:** To assess whether there were quantitative differences in key events (accumulation of PPIX, hepatocyte injury and subsequent regenerative hepatocyte proliferation) of carcinogenicity MOA involving porphyria-mediated cytotoxicity and liver concentration of test item, which are the basis for analyzing relevance of carcinogenicity MOA for humans **Results:** Slight diffuse hepatocyte hypertrophy observed in mouse-origin hepatocytes of one treated male. ↑PPIX (1.8-fold) in treated animals. No S-3100 detected in liver and plasma. Plasma and liver concentration levels of S-3100-CA were 34.6±20.86 ng/mL and 157.9±63.46 ng/mL, respectively, and liver/plasma ratio was 6.4±5.18.
Mechanistic 28-day oral (dietary) study in the mouse (effect on liver alteration) chimeric PXB mice with humanized liver PMRA No. 3308383	**Objective:** To assess whether there were quantitative species difference in key events of carcinogenicity MOA involving porphyria-mediated cytotoxicity and liver concentration of test item between mice and PXB mice with additional donor of human hepatocytes. **Results:** ↑liver wt, hepatocyte proliferative lesion in mouse-origin area, ↑PPIX. S-3100-CA conc'n: plasma=77.7 ng/mL, liver=118.7 ng/g liver, liver/plasma=1.7
Mechanistic 28-day oral (dietary) study in the mouse (effect on liver alteration) chimeric PXB mice with humanized liver PMRA No. 3308382	**Objective:** To assess whether there were quantitative species differences in key events of carcinogenicity MOA involving porphyria-mediated cytotoxicity and liver concentration of test item between mice and PXB mice with additional donor of human hepatocytes. **Results:** White focus in liver confirmed to be hepatocyte proliferative lesion (carcinoma) originated from mouse. ↑PPIX. S-3100-CA conc'n: plasma=74 ng/mL, liver=265.4 ng/g liver, liver/plasma=3.7

Study Type/ Animal/PMRA No.	Study results
	No change in liver enzymes including hALT1 nor histopathological findings indicative of hepatocyte injury in human hepatocytes, and also no ↑ in BrdU LI
Mechanistic 7-day oral (dietary) study in the mouse (effect on liver alteration) chimeric PXB mice with humanized liver PMRA No. 3308384	**Objective:** To confirm a no-observed-effect level (NOEL) of PPIX accumulation in the PXB mouse liver, and also assess species difference in both PPIX accumulation and hepatocellular uptake of S-3100-CA between mice and humans **Results:** No change in PPIX level. **0.2 mg/kg bw/d:** S-3100-CA conc'n in plasma=0.9 ng/mL, liver=37.9 ng/g liver **1.4 mg/kg bw/d**: S-3100-CA conc'n in plasma=2.5 ng/mL, liver=135.6 ng/g liver
Mechanistic 7-day oral (dietary) study in the mouse (effect on liver alteration and S-3100-CA and PPIX distribution by Mass Spectrometry Imaging analysis) chimeric PXB mice with humanized liver with low replacement index of human hepatocyte PMRA No. 3308373 and 3308377	**Objective:** PPIX concentration in the liver were analyzed, and liver and plasma concentrations of S-3100 and its causal metabolite S-3100-CA were measured after 7-day treatment of S-3100 TG to detect PPIX accumulation. It has been identified that there are significant species differences in the PPO inhibition and the hepatic uptake of the major causal metabolite, S-3100-CA, between human and rodents. To identify the species differences in the PPO inhibition and the hepatic uptake of the major causal metabolite, S-3100-CA, between humans and mice in vivo, samples were analyzed with mass spectrometry. **Results:** Compared to a previous study with high RI mice (PMRA No. 3308372), the hepatic PPIX level was increased as well as the concentration of S-3100-CA metabolite in liver and liver/plasma ratio. S-3100-CA and PPIX were similarly localized on the serial liver slices at the region that represented host mouse hepatocytes.
Mechanistic study in the mouse (PPIX measurement by LC-MS/MS analysis) chimeric PXB mice with humanized liver with low replacement index of human hepatocyte PMRA No. 3308376	**Objective:** To determine basal hepatic PPIX levels of chimeric mice with humanized liver (PXB mice) with low replacement index (RI) of human hepatocytes and host mice **Results:** PPIX conc'n of PXB mice with low RI and host mice were 39 and 106 ng/g liver, respectively.
Mechanistic 28-day oral (dietary) study in the mouse (effect on liver alteration)	**Objective:** To assess the adequacy of PXB mice, chimeric mice with human hepatocytes, as an in vivo experimental model to evaluate the key events of the porphyria-mediated carcinogenicity mode of action (MOA) in humans, which could be required to

Study Type/ Animal/PMRA No.	Study results
chimeric PXB mice with humanized liver PMRA No. 3308386	assess human relevance of findings in animals for human risk assessment **Results:** **686 mg/kg bw/d:** Four animals found dead/terminated prematurely after showing moribundity, red urine, stain at abdomen and genital region, and/or colored stool in all animals, ↓bw/bwg, ↓fc, ↓WBC, ↓RET, ↓plt, ↓mono, ↑ALT, ↑AST, ↑ALP, ↑LDH, ↑γ-GTP, ↑hALT1, ↓A/G, ↓glucose, ↓abs liver wt, single cell necrosis, ↑ mitoses, yellowish-brown pigmentation in hepatocytes and macrophages, ↑BrdU LI, ↑PPIX, ↑HMOX1/UROS gene expression, ↓ABCG2 gene expression
Mechanistic 28-day oral (dietary) study in the mouse (effect on liver alteration) chimeric PXB mice with humanized liver PMRA No. 3308387	**Objective:** To assess the adequacy of PXB mice, chimeric mice with human hepatocytes, as an in vivo experimental model to evaluate the key events of the porphyria-mediated carcinogenicity mode of action (MOA) in humans, which could be required to assess human relevance of findings in animals for human risk assessment **Results:** **≥381 mg/kg bw/d**: red urine, ↓bw/bwg, ↓fc, ↓glucose, single cell necrosis, ↑BrdU LI, ↑PPIX, ↑HMOX1 gene expression **537 mg/kg bw/d**: ↑ALT, ↑AST, ↑ALP, ↑LDH, ↑γ-GTP, ↑hALT1, ↑phospholipids, yellowish-brown pigmentation in hepatocytes and macrophages, ↑mitoses, positive stains (Berlin blue/Schmorl), ↑PPIX, ↑ABCB6 gene expression
In vitro S-3100-CA hepatic uptake assay study primary hepatocytes PMRA No. 3308378	**Objective:** To compare the active uptake clearance of S-3100-CA in liver via organic anion transporting polypeptides (OATPs) between rodents and human, S-3100-CA hepatic uptake assay was performed using male rat, female rat, male mouse, female mouse and human (both genders) cryopreserved primary hepatocytes **Results:** Hepatic uptake rate of S-3100-CA: Human: 3.8 μL/10^6 cells/min Mouse (♂/♀): 50 μL/10^6 cells/min; 22 μL/10^6 cells/min Rat (♂/♀): 8.1 μL/10^6 cells/min; 6.7 μL/10^6 cells/min
In vitro S-3100-CA hepatic uptake assay study (OATP inhibition) primary hepatocytes treated with OATP inhibitors	**Objective:** To investigate the contribution of organic anion transporting polypeptides (OATPs) to the hepatic uptake of S-3100-CA **Results:** The active uptake of S-3100-CA was observed, and both inhibitors of OATPs, especially rifampicin, inhibited the S-3100-CA uptake in a dose-dependent manner in all species tested. The

Study Type/ Animal/PMRA No.	Study results
PMRA No. 3308379	inhibition with 100 µM rifampicin was the largest in mice, followed in order by rats and humans.
In vitro S-3100-CA hepatic uptake assay study primary hepatocytes PMRA No. 3308380	**Objective:** To investigate the possible gender difference in the hepatic uptake of S-3100-CA in humans **Results:** The average active uptake volume: 2.0 ± 0.55 µL/10^6 cells in 3 ♂donors 3.3 ± 1.07 µL/10^6 cells in 4 ♀ donors There was no statistically significant difference between the sexes.
In vitro S-3100-CA hepatic uptake assay study primary hepatocytes PMRA No. 3308381	**Objective:** To validate the appropriateness of using PXB mice for the evaluation of hepatic uptake of S-3100-CA as a human model **Results:** The active uptake volume: 2.6 to 3.7 µL/10^6 cells The average active uptake volume: 2.0 ± 0.5 µL/10^6 cells
Mechanistic oral (gavage) study in the mouse (metabolite profiling and distribution), single dose Crl:CD1(ICR) mice PMRA No. 3308388	**Objective:** To investigate the influence of organic anion transporting polypeptide (OATP) inhibitors on tissue distribution of S-3100-CA in mice after single oral administration of S-3100 with or without OATP inhibitors in plasma, liver, and kidney **Results:** S-3100 conc'n rapidly distributed and excreted. T_{max} = 4 hr♂/1 hr ♀; $T_{1/2}$ = 8 hours ♂/♀; $AUC_{0-\infty}$ in ♀s were 2-3 times higher than ♂s Without inhibitors: liver/plasma = 73-fold ♂/35-fold ♀ With rifampicin: ↓conc'n in liver; liver/plasma = 11-fold ♂/fourfold ♀ With digoxin: ↓conc'n in liver; no change in liver/plasma The major metabolite, S-3100-CA was highest in liver. Without inhibitors: liver/plasma = 88-fold ♂/52-fold ♀ With rifampicin: ↓conc'n in liver; liver/plasma = 18-fold ♂/4.6-fold ♀ With digoxin: slight ↓conc'n in liver; no change in liver/plasma
In vitro S-3100-CA hepatic uptake assay study hepatic OATP expressing cells PMRA No. 3308389	**Objective:** To identify whether the species differences in the active uptake of S-3100-CA is caused by the difference in the selectivity toward various hepatic OATPs **Results:** No remarkable selectivity differences toward OATP isoforms among human, mouse, and rat OATPs. S-3100-CA transported by all the tested OATPs. Rifampicin and rifamycin SV inhibited all OATPs except human OATP2B1. Digoxin inhibited mouse Oatp1a4 in high rate, and mouse Oatp1a1 and human

Study Type/ Animal/PMRA No.	Study results
	OATP1B3 in moderate rate. All OATP inhibitors reduced the update of S-3100-CA in a dose-dependent manner.
Anemia and sexual maturation study (the effects of anemia induced by repeated blood removal on sexual maturation) Crl:CD (SD) rats PMRA No. 3308393	**Objective:** To assess the effect of anemia during juvenile period on sexual maturation in female rats **Results:** ↑Ret, ↑MCV, ↓RBC, ↓Hb, ↓Hct, ↓MCHC, delayed sexual maturation
In vitro aromatase assay Human Recombinant Microsomes PMRA No. 3492582	Negative Tested S-3100 TG and S-3100-CA up to precipitating concentrations
Transactivation activation assay (Human estrogen receptor) human hERα-HeLa-9903 PMRA No. 3492583	Negative Tested S-3100-CA up to precipitating concentrations
Transactivation activation assay (Human androgen receptor) AR-EcoScreen™ PMRA No. 3492584	Negative Tested S-3100-CA up to precipitating concentrations
In vitro aromatase inhibition Human Recombinant Microsomes PMRA No. 3738215	Negative for aromatase inhibition Tested S-3100 TG and S-3100-CA up to precipitating concentrations
Androgen receptor agonist/antagonist assay Stably transfected AR-CALUX cells	Negative for both androgen agonism and antagonism Tested S-3100 TG up to the limit of solubility

Study Type/ Animal/PMRA No.	Study results
PMRA No. 3738216	
Androgen receptor agonist/antagonist assay Stably transfected human androgen receptor transcriptional activation assay AR-EcoScreen PMRA No. 3738217	Negative for both androgen agonism and antagonism Tested S-3100-CA up to the limit of solubility
Estrogen receptor agonist/antagonist assay Stably transfected human estrogen receptor-α transactivation assay hERα-HeLa9903 cell line PMRA No. 3738218	Negative for both estrogen agonism and antagonism Tested S-3100-CA up to the limit of solubility
Estrogen receptor agonist/antagonist assay Stably transfected human estrogen receptor-α transactivation assay hERα-HeLa9903 cell line PMRA No. 3738219	Negative for both estrogen agonism and antagonism Tested S-3100 TG up to the precipitating concentrations Some cytotoxicity was observed at 1.0×10^{-5} M
Endocrine disruptor steroidogenesis assay Human cell line H295R PMRA No. 3738220	Negative for induction or inhibition of both testosterone and 17β-estradiol Tested S-3100 TG up to the precipitating concentrations
Endocrine disruptor steroidogenesis assay Human cell line H295R PMRA No. 3738221	Negative for induction or inhibition of both testosterone and 17β-estradiol Tested S-3100-CA up to the precipitating concentrations
Anemia and sexual maturation study (the	Periodic venous blood removal was performed to induce an anemic state. No test substances were employed in this study

Study Type/ Animal/PMRA No.	Study results
effects of anemia induced by repeated blood removal on sexual maturation) Crl:CD (SD) rats PMRA No. 3738222	Age at vaginal opening was delayed by 1.8 and 2.3 days for the 1.0 and 1.5% blood removal groups, respectively There were no effects on uterine or ovary weights, gross pathology, or histopathology of the ovaries, uterus, or vagina at PND 57/58
Anemia and sexual maturation study (the effects of anemia induced by phenylhydrazine on sexual maturation) Crl:CD (SD) rats PMRA No. 3738223	Phenylhydrazine administration was performed as a positive control inducer of anemia. No S-3100-related test substances were employed in this study Age at vaginal opening was delayed by 1.3 and 2.5 days for the 10 and 20 mg/kg bw groups, respectively There were no effects on uterine or ovary weights, gross pathology, or histopathology of the ovaries, uterus, or vagina at PND 55/56
Inhibition of protoporphyrinogen oxidase (PPO) activity Mouse ♂/♀ and human ♂/♀ liver mitochondria PMRA No. 3738224	S-3100 and S-3100-CA had similar inhibitory activity, though in this particular study, S-3100-CA had upwards of fourfold more potency than unchanged S-3100, whereas S-3100-DA and the other downstream metabolites (-CA-RD, DA-RD, -CA-UR, and -DA-UR) were much weaker Across the most active compounds, the mouse fractions were approximately 10-fold more sensitive to PPO inhibition than the human fractions
Hepatic uptake assay for degradates of S-3100 Mouse ♂ and human ♂/♀ primary hepatocytes PMRA No. 3738225	Mouse hepatocytes showed nearly 10-fold more uptake clearance of the main metabolite S-3100-CA than human cells. In all other metabolites/degradates, uptake was always greater in mouse than human, but the difference was less pronounced Uptake generally increased with both time and temperature The active uptake positive control substance [6, 7-3H(N)]Estrone sulfate ammonium salt was used to confirm assay validity
Metabolite studies	
S-3100-DA	
28-Day oral (dietary) Crl:CD1(ICR) mice PMRA No. 3308320	**S-3100 TG** NOAEL= 1.7/2.0 mg/kg bw/day ♂/♀ LOAEL= 20/21 mg/kg bw/day ♂/♀ **S-3100-DA** NOAEL= 349/353 mg/kg bw/day ♂/♀ LOAEL= 1148/1390 mg/kg bw/day ♂/♀

Study Type/ Animal/PMRA No.	Study results
	Effects at the LOAEL **S-3100 TG**: ↑liver wt, ↑hepatocellular hypertrophy, ↑ liver single cell degeneration/necrosis, ↑liver apoptosis/single cell necrosis (♂/♀); ↑plt, ↑SDH (♂); ↑pale liver, ↑spleen extramedullary hematopoiesis, ↓RBC, ↓Hb, ↓Hct (♀) Effects at the LOAEL **S-3100-DA**: ↑liver wt, ↑hepatocellular hypertrophy, ↑ liver single cell degeneration/necrosis, ↑liver apoptosis/single cell necrosis (♂/♀); ↑trig (♂); ↑spleen wt, ↑thyroid/parathyroid wt, ↑spleen extramedullary hematopoiesis, ↓RBC, ↓Hb, ↓Hct (♀)
In vitro bacterial reverse mutation assay *S. typhimurium* *Escherichia coli* PMRA No. 3308344	Negative ± metabolic activation Tested up to limit concentration
In vitro Micronucleus test Human Lymphoblast TK6 cells PMRA No. 3308361	Negative ± metabolic activation Tested up to cytotoxic concentrations
S-3100-DP-Me	
28-Day oral (dietary) Crl:CD1(ICR) mice PMRA No. 3308321	NOAEL= 60/72 mg/kg bw/day ♂/♀ LOAEL= 229/301 mg/kg bw/day ♂/♀ Effects at the LOAEL: ↑spleen extramedullary hematopoiesis, ↑RDW, ↑liver wt, ↑spleen wt, ↓RBC, ↓Hb, ↓Hct (♂/♀); ↑hepatocellular hypertrophy, ↑RET (♂); ↓MCV, ↓MCH (♀)
In vitro bacterial reverse mutation assay *S. typhimurium* *Escherichia coli* PMRA No. 3308345	Negative ± metabolic activation Tested up to limit concentration
In vitro Micronucleus test Human Lymphoblast TK6 cells	Negative ± metabolic activation Tested up to cytotoxic concentrations

Study Type/ Animal/PMRA No.	Study results
PMRA No. 3308363	
S-3100-CA-RD	
28-Day oral (dietary) Crl:CD1(ICR) mice PMRA No. 3308323	NOAEL= 267/1244 mg/kg bw/day ♂/♀ LOAEL= 1032 mg/kg bw/day/not determined ♂/♀ Effects at the LOAEL: ↑ALP (♂)
In vitro bacterial reverse mutation assay *S. typhimurium* *Escherichia coli* PMRA No. 3308343	Negative ± metabolic activation Tested up to limit concentration
In vitro Micronucleus test Chinese hamster lung (CHL/IU) cells PMRA No. 3308365	Negative ± metabolic activation Tested up to the limit concentration
S-3100-PR	
28-Day oral (dietary) Crl:CD1(ICR) mice PMRA No. 3308324	NOAEL= 947/1341 mg/kg bw/day ♂/♀ LOAEL= not determined
In vitro bacterial reverse mutation assay *S. typhimurium* *Escherichia coli* PMRA No. 3308346	Negative ± metabolic activation Tested up to limit concentration
In vitro Micronucleus test Human Lymphoblast TK6 cells PMRA No. 3308362	Negative ± metabolic activation Tested up to cytotoxic concentrations
4"-OH-S-3100-CA	
28-Day oral (dietary)	NOAEL= 109/145 mg/kg bw/day ♂/♀ LOAEL= 610/657 mg/kg bw/day ♂/♀

Study Type/ Animal/PMRA No.	Study results
Crl:CD1(ICR) mice PMRA No. 3308322	Effects at the LOAEL: ↑hepatocytes necrosis, ↑SDH, ↓RBC, ↓Hb, ↓Hct (♂/♀); ↑ALT, ↑plt, ↑thyroid/parathyroid wt (♂)
In vitro bacterial reverse mutation assay *S. typhimurium* *Escherichia coli* PMRA No. 3308349	Negative ± metabolic activation Tested up to the limit concentration
In vitro micronucleus test Chinese hamster lung (CHL/IU) cells PMRA No. 3308364	Negative ± metabolic activation Tested up to cytotoxic concentrations
S-3100-CA-UR	
In vitro bacterial reverse mutation assay *S. typhimurium* *Escherichia coli* PMRA No. 3308348	Negative ± metabolic activation Tested up to the limit concentration
APPE	
In vitro bacterial reverse mutation assay *S. typhimurium* *Escherichia coli* PMRA No. 3308350	Negative ± metabolic activation Tested up to the limit concentration
S-3100-BFP	
In vitro bacterial reverse mutation assay *S. typhimurium* *Escherichia coli* PMRA No. 3308347	Negative ± metabolic activation Tested up to the limit concentration
In vitro micronucleus test Human Lymphoblast TK6 cells	Negative ± metabolic activation Tested up to the limit concentration

Study Type/ Animal/PMRA No.	Study results
PMRA No. 3308367	
S-3100-DP	
In vitro micronucleus test Human Lymphoblast TK6 cells PMRA No. 3308366	Negative ± metabolic activation Tested up to cytotoxic concentrations
Metabolite PPO activity	
Mechanistic in vitro study (effect on PPO activity) PMRA No. 3308369	**Objective:** Inhibitory activity of S-3100 and its major metabolites, S-3100-CA and S-3100-DA, against PPO were examined in vitro using mouse, rat, rabbit, dog and human liver mitochondrial fractions. **Results/conclusions:** S-3100 and S-3100-CA had similar inhibitory activity, whereas S-3100-DA was about 24.5 to 82.2 times weaker in all species tested. When compared among the species, mice and rats are 3- to 16-fold more sensitive than dogs, rabbits and humans.
Mechanistic in vitro study (effect on PPO activity) PMRA No. 3308370	**Objective:** To compare the inhibitory activity of S-3100 and its metabolites/degradates against PPO, an in vitro enzyme inhibition assay was performed using mouse liver mitochondrial fraction. **Results/conclusions:** S-3100 and S-3100-CA demonstrated the strongest inhibitory activity, with complete inhibition of PPO at the concentration tested, followed by S-3100-DA, 4''-OH-S-3100-CA, S-3100-DP and S-3100-DP-Me.

Table 5 Toxicity profile of S-3100 0.46 EC Herbicide containing epyrifenacil

Effects are known or assumed to occur in both sexes unless otherwise noted; in such cases, sex-specific effects are separated by semi-colons.

Study Type/Animal/PMRA No.	Study results
Acute oral toxicity Crl:CD(SD) rats PMRA No. 3307091	LD_{50} > 2000 mg/kg bw (♂♀) **Low acute toxicity**
Acute dermal toxicity Crl:CD(SD) rats PMRA No. 3307092	LD_{50} > 2000 mg/kg bw (♂♀) **Low acute toxicity**

Study Type/Animal/PMRA No.	Study results
Acute inhalation toxicity Crl:CD(SD) rats PMRA No. 3307093	LC_{50} > 5.68 mg/L (♂♀) **Low acute toxicity** MMAD = 3.92 µm GSD = 2.01 ↓bw and ↓bwg on Day 1
Eye irritation NZW rabbits PMRA No. 3307094	Washed: MAS $_{\text{at 24, 48 and 72 hours}}$ = 23.4/110 MIS $_{\text{at 24 hour}}$ = 30.7/110 Unwashed: MAS $_{\text{at 24, 48 and 72 hours}}$ = 28/110 MIS $_{\text{at 24 hour}}$ = 30.7/110 **Moderately irritating**
Dermal irritation Japanese White rabbits PMRA No. 3307095	MAS $_{\text{at 24, 48 and 72 hours}}$ = 5.6/8 MIS $_{\text{at 48 and 72 hours}}$ = 5.7/8 **Severely irritating**
Dermal sensitization (Buehler test) Slc:Hartley guinea pigs PMRA No. 3307096	**Positive** 4/20 test animals with score of 1 for erythema.

Table 6 Toxicity profile of V-10488 0.94 SE Herbicide containing epyrifenacil, flumioxazin, pyroxasulfone

Effects are known or assumed to occur in both sexes unless otherwise noted; in such cases, sex-specific effects are separated by semi-colons.

Study Type/Animal/PMRA No.	Study results
Acute oral toxicity SD albino rats PMRA No. 3307132	LD_{50} > 5000 mg/kg bw (♀) **Low acute toxicity**

Study Type/Animal/PMRA No.	Study results
Acute dermal toxicity SD albino rats PMRA No. 3307133	LD_{50} > 5000 mg/kg bw (♂♀) **Low acute toxicity**
Acute inhalation toxicity SD albino rats PMRA No. 3307134	LC_{50} > 2.2 mg/L (♂♀) **Low acute toxicity** MMAD = 3.08 µm GSD = 2.22 Clinical signs: hypoactivity and irregular respiration
Eye irritation NZW rabbits PMRA No. 3307135	MAS $_{\text{at 24, 48 and 72 hours}}$ = 13.9/110 MIS $_{\text{at 24 hour}}$ = 20/110 Persistence of eye irritation until Day 4 (reactions disappeared by Day 7) **Mildly irritating**
Dermal irritation NZW rabbits PMRA No. 3307136	MAS $_{\text{at 24, 48 and 72 hours}}$ = 1.6/8 MIS $_{\text{at 48 and 72 hour}}$ = 1.7/8 **Mildly irritating**
Dermal sensitization (LLNA) CBA/J mice PMRA No. 3307137	**Negative**

Table 7 Comparison of mean percent recovery of epyrifenacil absorbed through the skin after six hours of exposure to S-3100 5.5 EC Herbicide (in other words, S-3100 0.46 EC Herbicide), measured at 18 hours post-exposure

	Human skin			Rat skin		
	Low dose	Mid dose	High dose	Low dose	Mid dose	High dose
Actual Dose (µg/cm²)	5.01	49.8	547	4.98	49.9	552
Dislodgeable or Unabsorbed Dose[1] (% Total Dose)	90.23 ± 8.44	88.92 ± 7.41	99.31 ± 1.29	76.93 ± 3.76	81.78 ± 7.82	88.03 ± 11.66

	Human skin			Rat skin		
	Low dose	**Mid dose**	**High dose**	**Low dose**	**Mid dose**	**High dose**
Absorbed Dose[2] (% Total Dose)	10.84 ± 8.65	**11.70 ± 8.49**	1.84 ± 0.32	23.36 ± 3.77	19.03 ± 7.90	11.41 ± 8.74
All Tape Strips (% Total Dose)	9.86 ± 8.62	11.00 ± 8.89	1.77 ± 0.31	12.38 ± 4.19	12.41 ± 6.76	5.89 ± 4.35
Recovery (% Total Dose)	101.07 ± 1.01	100.61 ± 1.86	101.15 ± 1.18	100.29 ± 1.24	100.80 ± 1.08	99.45 ± 3.55

[1] Dislodgeable or Unabsorbed Dose = % total dose found in Membrane Wash + Donor Cell Wash
[2] Absorbed Dose = % total dose found in Skin Membrane + All Tape Strips + Receptor Fluid + Receptor Cell Rinse
[3] Recovery = dislodgeable dose + absorbed dose
NOTE: A dermal absorption of 12% was chosen for epyrifenacil, based on the **bolded** absorbed dose (from the mid-dose group of the human in vitro results).

Table 8 AHETF/PHED unit exposure estimates for mixer/loaders and applicators handling epyrifenacil (µg/kg a.i. handled)

Exposure scenario and PPE		**Dermal**	**Dermal absorbed[1]**	**Inhalation[2]**
PPE for all scenarios: Single layer and chemical-resistant gloves				
Mixer/loader AHETF estimates				
A	Open Mix/Load Liquids, Single Layer, CR Gloves (AHETF)	58.5	7.02	0.63
Applicator AHETF/PHED estimates				
B	Open Cab Groundboom, SL, CR Gloves	25.4	3.05	1.68
C	Aerial, closed cockpit (AHETF)	2.67	0.32	0.00969
D	ROW (SL, CR Gloves) (PHED)	852.54	102.3	5.0
Mixer/loader + applicator AHETF/PHED estimates				
A+B	Open M/L (SL, CR Gloves), Open Cab Groundboom (SL, CR Gloves)	83.9	10.1	2.31
A+D	Open M/L (SL, CR Gloves), ROW (SL, CR Gloves)	931.34	111.8	5.63
E	Open M/L (SL, gloves), MPHG	5585.49	670.3	151.0
F	Open M/L (SL, gloves), Backpack	5445.85	653.5	62.1
G	Open M/L (SL, gloves), MPHW	943.37	113.2	45.2

CR: chemical-resistant; SL: single layer of clothing; GB: groundboom; ROW: right-of-way sprayer; MPHW – manually pressurized handwand; MPHG – mechanically pressurized handgun.
[1] Dermal unit exposure (µg/kg a.i. handled) × 12% dermal absorption
[2] Light inhalation rate (except for backpack= moderate inhalation rate)

Table 9 Mixer/Loader/Applicator risk assessment for epyrifenacil

Exposure scenario	Unit exposure (µg/kg a.i. handled)[1]		ATPD (ha/day)[2]	Rate (kg a.i./ha)	Exposure (µg/kg bw/day)[3]		MOE (Target 300)		
	Dermal	Inhalation			Dermal	Inhalation	Dermal[4]	Inhalation[4]	Combined[5]
PPE: Single layer and chemical-resistant gloves (unless otherwise specified)									
A: Open Mix/Load Liquid (Aerial)	7.02	0.63	400	0.04	1.40	0.13	4843	53 968	4444
C: Aerial, closed cockpit	0.32	0.00969	400	0.04	0.064	0.002	106117	3 508 772	103 002
A+B: Open M/L, Open Cab Groundboom	10.1	2.31	360	0.04	1.81	0.42	16354	16 354	3052
A+D: Open M/L, ROW	111.8	5.63	38	0.04	2.08	0.11	63569	63 569	3113
E: Open M/L (SL, gloves), MPHG	670.3	151.0	38	0.04	12.7	2.87	534	2370	436
F: Open M/L (SL, gloves), Backpack	653.5	62.1	1.5	0.04	0.49	0.047	13874	146 001	12 670
G: Open M/L (SL, gloves), MPHW	113.2	45.2	1.5	0.04	0.085	0.034	80091	200 590	57 237

[1] Unit exposure based on AHETF/PHED from Table 8

[2] Standard Area Treated per Day values; for handheld equipment. ATPD was calculated using the maximum L handled per day from th e summary table (3800 L/day for ROW and MPHG and 150 L/day for backpack and MPHW) ÷ Spray volume (100 L water/ha)

[3] Dermal or Inhalation Exposure (µg/kg bw/day) = Dermal or Inhalation Unit Exposure (µg/kg a.i. handled) × ATPD (ha/day) × Rate (kg a.i./ha)) / 80 kg bw

[4] Dermal or Inhalation MOE = Dermal and Inhalation NOAEL of 6.8 mg/kg bw/day ÷ (Dermal Exposure or Inhalation Exposure (µg/kg b w/day) × Unit Conversion (mg/1000 µg)); Target MOE = 300

[5] Combined MOE = 1/((1/Dermal MOE)+(1/Inhalation MOE))

Table 10 Required personal protective equipment based on exposure and risk to epyrifenacil and the acute hazards of S-3100 0.46 EC Herbicide

Application equipment and engineering controls	Personal protective equipment	
	Mixer/Loader/Clean-up and repair	Applicator
Aerial	Coveralls over a long-sleeved shirt and long pants, chemical-resistant gloves, socks, and chemical-resistant footwear and protective eyewear (goggles or face shield).	Long-sleeved shirt, long pants, chemical-resistant gloves,[1] socks and shoes.
Groundboom – Open Cab		Coveralls over a long-sleeved shirt and long pants, chemical-resistant gloves, socks, and chemical-resistant footwear.
Groundboom – Closed Cab		Long-sleeved shirt, long pants, socks and shoes.
Handheld application equipment – fine to very coarse spray[2]		Coveralls over a long-sleeved shirt and long pants, chemical-resistant gloves, socks, and chemical-resistant footwear.

[1] Gloves are not required within a closed cockpit.
[2] Based on the American Society of Agricultural and Biological Engineers (ASABE) ASABE S572.1 Droplet Size Classification

Table 11 Required personal protective equipment based on exposure and risk to the active ingredients and the acute hazards of V-10488 0.94 SE Herbicide

For crop uses			
Application equipment and engineering controls	Personal protective equipment		Restricted amount of product handled per day per person
	Mixer/Loader/Clean-up and repair	Applicator	
Groundboom – Open Cab	Long-sleeved shirt, long pants, chemical-resistant gloves, socks and shoes.	Long-sleeved shirt, long pants, chemical-resistant gloves, socks and shoes.	Less than 514 L
	Coveralls over a long-sleeved shirt and long pants, socks and shoes.		Greater than or equal to 514 L
Groundboom – Closed Cab	Long-sleeved shirt, long pants, chemical-resistant gloves, socks and shoes.	Long-sleeved shirt, long pants, socks and shoes.	Less than 665 L
	Coveralls over a long-sleeved shirt and long pants, chemical-resistant gloves, socks and shoes.		Greater than or equal to 665 L

For non-crop uses			
Application equipment and engineering controls	**Personal protective equipment**		**Restricted amount of product handled per day per person**
	Mixer/Loader/Clean-up and repair	**Applicator**	
Groundboom – Open Cab	Long-sleeved shirt and long pants, chemical-resistant gloves, socks and shoes.	Long-sleeved shirt and long pants, chemical-resistant gloves, socks and shoes.	Less than 360 L
	Coveralls over long-sleeved shirt and long pants, chemical-resistant gloves, socks and shoes.		Greater than or equal to 360 L; less than 650 L
	Chemical-resistant coveralls over long-sleeved shirt and long pants, chemical-resistant gloves, socks and chemical-resistant footwear.		Greater than or equal to 650 L; less than 785 L
Groundboom – Closed Cab	Long-sleeved shirt and long pants, chemical-resistant gloves, socks and shoes.	Long-sleeved shirt and long pants, socks and shoes	Less than 442 L
	Coveralls over long-sleeved shirt and long pants, chemical-resistant gloves, socks and shoes.		Greater than or equal to 442 L; less than 722 L
	Chemical-resistant coveralls over long-sleeved shirt and long pants, chemical-resistant gloves, socks and chemical-resistant footwear.		Greater than or equal to 722 L; less than 834 L
Right-of-Way Sprayer	Long-sleeved shirt and long pants, chemical-resistant gloves, socks and shoes.		Less than 34 L
	Coveralls over long-sleeved shirt and long pants, chemical-resistant gloves, socks and shoes.		Greater than or equal to 34 L; less than 55 L
	Chemical-resistant coveralls over long-sleeved shirt and long pants, chemical-resistant gloves, socks and chemical-resistant footwear.		Greater than or equal to 55 L; less than 64 L
Mechanically-pressurized handgun- fine to very coarse spray[1]	Long-sleeved shirt and long pants, chemical-resistant gloves, socks and shoes.		Less than 5 L
	Coveralls over long-sleeved shirt and long pants, chemical-resistant gloves, socks and shoes.		Greater than or equal to 5 L; less than 12 L
	Chemical-resistant coveralls over long-sleeved shirt and long pants, chemical-resistant gloves, socks and chemical-resistant footwear.		Greater than or equal to 12 L; less than 16 L
All other handheld application equipment	Long-sleeved shirt and long pants, chemical-resistant gloves, socks and shoes.		No restriction

[1] Based on the American Society of Agricultural and Biological Engineers (ASABE) ASABE S572.1 Droplet Size Classification

NOTE: The mitigation measures required for V-10488 0.94 SE Herbicide were driven by the risk assessments of the co-formulated active ingredients flumioxazin and pyroxasulfone.

Table 12 Integrated food residue chemistry summary

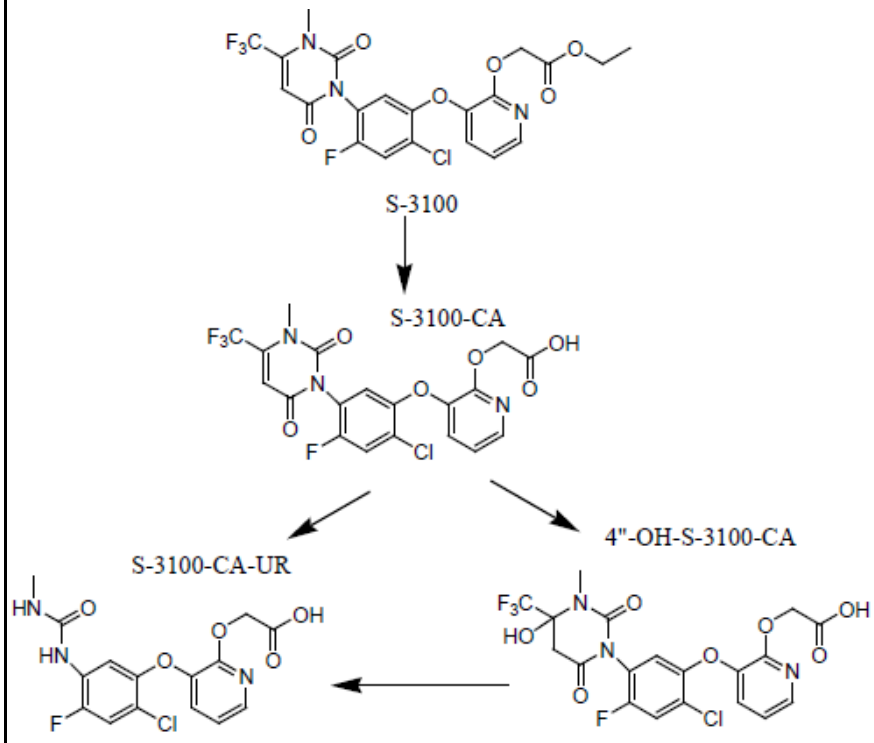
Nature of the residue in laying hen	**PMRA No. 3307063**
Species and Numbers	3 groups of laying hens (10 hens/group) (Hyline brown)
Radiolabel positions	[phenyl-U-^{14}C]epyrifenacil (PH label) (specific activity as received: 8.37 MBq/mg) [pyridyl-4(6)-^{14}C]epyrifenacil (PY label) (specific activity as received: 4.08 MBq/mg) [pyrimidinyl-4-^{14}C]epyrifenacil (PMD label) (specific activity as received: 4.00 MBq/mg)
Average doses	PH-label: 9.6 mg/kg feed (corresponding to 0.585 mg/kg bw/day) PY-label: 9.4 mg/kg feed (corresponding to 0.581 mg/kg bw/day) PMD-label: 10.3 mg/kg feed (corresponding to 0.587 mg/kg bw/day)
Treatment Regimen	Once daily/Oral/Corn oil-coated capsules
Study period	7 consecutive days
Collection times	Eggs: 2/day (morning and afternoon); Excreta: 2/day (morning and afternoon)
Tissues collected	Eggs, liver, breast and leg muscle, abdominal and subcutaneous fat, and GI tract with contents
Interval from last dose to sacrifice	6 hours
Plateau of residues in eggs	Egg white: 0.002-0.007 ppm on Day 4-5 Egg yolk: None reached
Extraction solvents	Liver and muscle: 2× acetonitrile (ACN):water (1:1, v:v) and 1× ACN Composite fat and egg yolk: 2× hexane:acetone (4:1, v:v) and 1× acetone PES (liver and egg yolk (PY-label)): Further characterized by sequential extraction with ACN:0.1 M HCl (1:1, v:v), ACN:0.1 M NaOH (1:1, v:v), and 0.1 M phosphate buffer (pH 7.5) with 0.01 M $CaCl_2$, with each extract being isolated by centrifugation. Solids remaining after the buffer extraction were sequentially subjected to protease and

	strong acid (4 N HCl) hydrolyses; however, the conditions for these hydrolyses were illegible in the study submission.					
Matrices	**phenyl-U-^{14}C**		**pyridyl-4(6)-^{14}C**		**pyrimidinyl-4-^{14}C**	
	TRRs (ppm)[1]	**% of administered dose**	**TRRs (ppm)[1]**	**% of administered dose**	**TRRs (ppm)[1]**	**% of administered dose**
Egg white (Day 1–7)	<0.001–0.005	<0.01	<0.001-0.005	<0.01	<0.001–0.007	<0.01
Egg yolk (Day 1–7)	<0.001–0.015	<0.01	<0.001-0.043	<0.01	<0.001–0.029	<0.01
Liver	0.088 (0.092)	<0.1	0.130 (0.129)	<0.1	0.129 (0.137)	<0.1
Muscle, leg	0.011	<0.1	0.014	<0.1	0.025	<0.1
Muscle, breast	0.009	<0.1	0.010	<0.1	0.020	<0.1
Muscle, composited	0.010 (0.010)	<0.1	0.012 (0.012)	<0.1	0.022 (0.020)	<0.1
Fat, abdominal	0.007	<0.1	0.011	<0.1	0.012	<0.1
Fat, subcutaneous	0.020	<0.1	0.015	<0.1	0.022	<0.1
Fat, composited	0.010 (0.009)	<0.1	0.011 (0.010)	<0.1	0.015 (0.012)	<0.1
GI tract with contents	0.824	2.0	0.976	2.4	0.990	2.4
Excreta (Day 1–7)	<1.329–8.920	91.6	1.515–9.348	89.7	1.622–10.776	88.8
Composited excreta (Day 1 pm–7 pm)	5.394 (5.362)	NA	5.367 (5.154)	NA	7.517 (6.280)	NA
Cage wash	Not applicable	0.2	Not applicable	0.1	Not applicable	0.1

[1] TRR were determined by LSC (cage wash), solubilization/LSC (tissues and egg white and yolk) or combustion/LSC (excreta) and are reported in parent equivalents. For samples that were subjected to extraction, TRR calculated by summing extractable and nonextractable radioactivity are presented in parentheses; these values were used for all further determinations.

Summary of major identified metabolites in hen matrices			
Radiolabel position	**Major metabolites** (>10% of the TRRs and >0.01 ppm)		
Metabolites identified	**phenyl-U-^{14}C**	**pyridyl-4(6)-^{14}C**	**pyrimidinyl-4-^{14}C**
Liver	S-3100-CA, 4″-OH-S 3100 CA	S-3100-CA, 4″-OH-S 3100 CA	S-3100-CA, 4″-OH-S 3100 CA
Muscle	-	-	-
Fat	-	-	-
Egg yolk	-	-	-

Proposed Metabolic Scheme in Hen



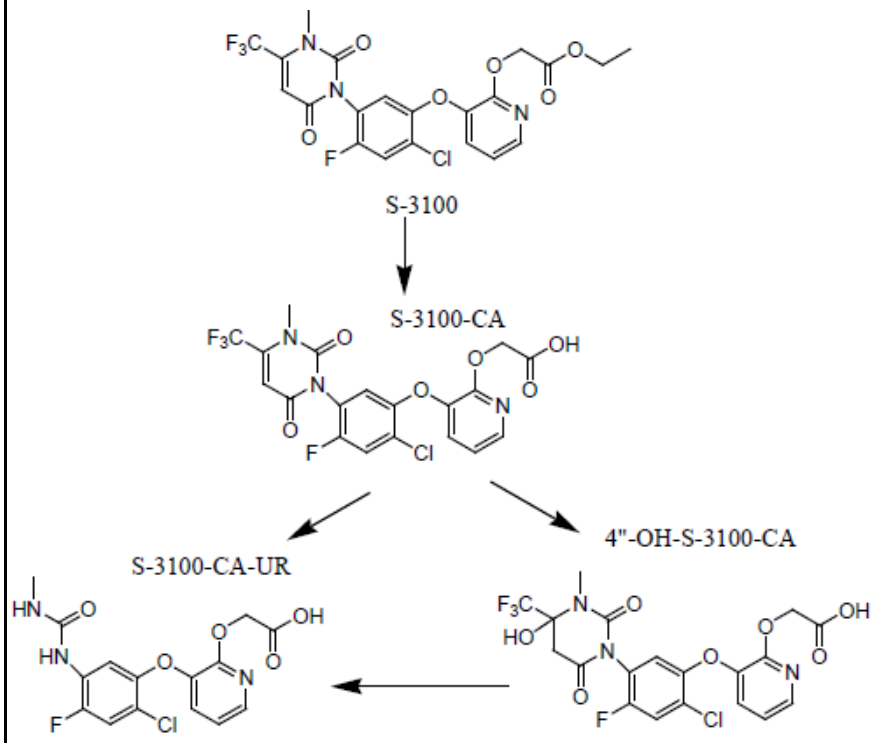
S-3100 = epyrifenacil

Nature of the residue in lactating goat	**PMRA No. 3307062**
Species and numbers	Dairy goats (one goat/group) (American alpine)
Radiolabel positions	[phenyl-U-^{14}C]epyrifenacil (PH label) (specific activity as received: 8.37 MBq/mg) [pyridyl-4(6)-^{14}C]epyrifenacil (PY label) (specific activity as received: 4.08 MBq/mg) [pyrimidinyl-4-^{14}C]epyrifenacil (PMD label) (specific activity as received: 4.00 MBq/mg)
Average doses	PH-label: 10.4 mg/kg feed (corresponding to 0.196 mg/kg bw/day) PY-label: 14.1 mg/kg feed (corresponding to 0.189 mg/kg bw/day) PMD-label: 11.9 mg/kg feed (corresponding to 0.186 mg/kg bw/day)
Treatment Regimen	Once daily/Oral/Capsule
Study period	5 consecutive days
Collection times	Milk: 2/day; Urine and feces: 2/day
Tissues collected	Milk; liver; kidney; loin and flank muscle; renal, omental, and subcutaneous fat; GI tract with contents; blood; and bile.
Interval from last dose to sacrifice	8 hours
Plateau of residues in milk	TRR in whole milk plateaued within 2 days for the PH- and PY-labels at 0.001-0.003 ppm, and began to plateau by Day 4 for the PMD-label at 0.018 ppm, although the highest residues in PMD-label milk occurred in the final Day 5 sample (0.020 ppm). As with whole milk, TRR in skim milk and milk fat from the PMD-label began to plateau by Day 4 at 0.018 and 0.025 ppm respectively.
Extraction solvents	Liver, kidney, and muscle: 2× acetonitrile (ACN):water (1:1, v:v) and 1× ACN Skim milk: 2× acetone/water (1:1, v/v) and 1× acetone The acetone/water extract was concentrated, and an aliquot of the extract was dissolved in acetonitrile/water for HPLC analysis.

	Milk fat and composited fat: 2× hexane:acetone (4:1, v:v) and 1× acetone Combined extract fractions were concentrated to remove the acetone, and the remaining hexane fraction was partitioned with ACN.					
Matrices	**phenyl-U-^{14}C**		**pyridyl-4(6)-^{14}C**		**pyrimidinyl-4-^{14}C**	
	TRRs (ppm)[1]	**% of administered dose**	**TRRs (ppm)[1]**	**% of administered dose**	**TRRs (ppm)[1]**	**% of administered dose**
Whole milk (Day 1–5)	0.001-0.003	<0.01	<0.001–0.002	<0.01	0.004–0.020	0.26
Liver	0.325 (0.348)	0.5	0.112 (0.117)	0.2	0.375 (0.418)	0.6
Kidney	0.205 (0.214)	<0.1	0.160 (0.163)	<0.1	0.198 (0.211)	<0.1
Muscle, loin	0.004	<0.1	0.002	<0.1	0.018	<0.1
Muscle, flank	0.005	<0.1	0.001	<0.1	0.017	<0.1
Muscle, composited	Not applicable	-	Not applicable	-	0.018 (0.023)	<0.1
Fat, renal	0.004	<0.1	0.002	<0.1	0.012	<0.1
Fat, omental	0.003	<0.1	0.001	<0.1	0.011	<0.1
Fat, subcutaneous	0.003	<0.1	0.002	<0.1	0.014	<0.1
Fat, composited	Not applicable	-	Not applicable	-	0.012 (0.016)	<0.1
Blood	0.018	<0.1	0.011	<0.1	0.028	<0.1
Bile	3.098	0.1	1.557	<0.1	4.543	0.3
GI tract with contents	1.596	41.6	0.826	23.4	1.854	49.2
Urine (Day 1–5)	2.395–8.828	41.3	0.646–2.578	24.6	0.929–2.660	33.7
Composited urine (Day 1-5)	5.399	Not applicable	1.322	Not applicable	2.023	Not applicable
Feces (Day 1–5)	0.091–11.095	29.1	0.033–9.049	24.5	0.042–6.218	24.2

Composited feces (Day 1–5)	7.608 (8.091)	Not applicable	4.310 (4.546)	Not applicable	2.973 (2.972)	Not applicable
Cage wash	0.449	0.3	0.155	0.1	0.236	0.2
[1] TRR were determined by LSC (urine, bile, and cage wash), solubilization/LSC (tissues and milk) or combustion/LSC (blood, feces, and GI tract) and are reported in parent equivalents. For samples that were subjected to extraction, TRR calculated by summing extractable and nonextractable radioactivity are presented in parentheses; these values were used for all further determinations.						
Summary of major identified metabolites in goat matrices						
Radiolabel position	**Major metabolites** (>10% of the TRRs and >0.01 ppm)					
Metabolites identified	**phenyl-U-^{14}C**		**pyridyl-4(6)-^{14}C**		**pyrimidinyl-4-^{14}C**	
Liver	S-3100-CA, 4″-OH-S-3100-CA		S-3100-CA, 4″-OH-S-3100-CA		S-3100-CA, 4″-OH-S-3100-CA	
Kidney	S-3100-CA, 4″-OH-S-3100-CA		S-3100-CA, 4″-OH-S-3100-CA, S-3100-CA-UR		S-3100-CA, 4″-OH-S-3100-CA	
Composited muscle	-		-		-	
Composited fat	-		-		-	
Skim milk	-		-		-	

Proposed Metabolic Scheme in Goat



S-3100 = epyrifenacil

Livestock feeding – Laying hens

A feeding study was not required based on the low dietary burden. Therefore, the poultry metabolism study was used to estimate the anticipated residues in the relevant livestock matrices.

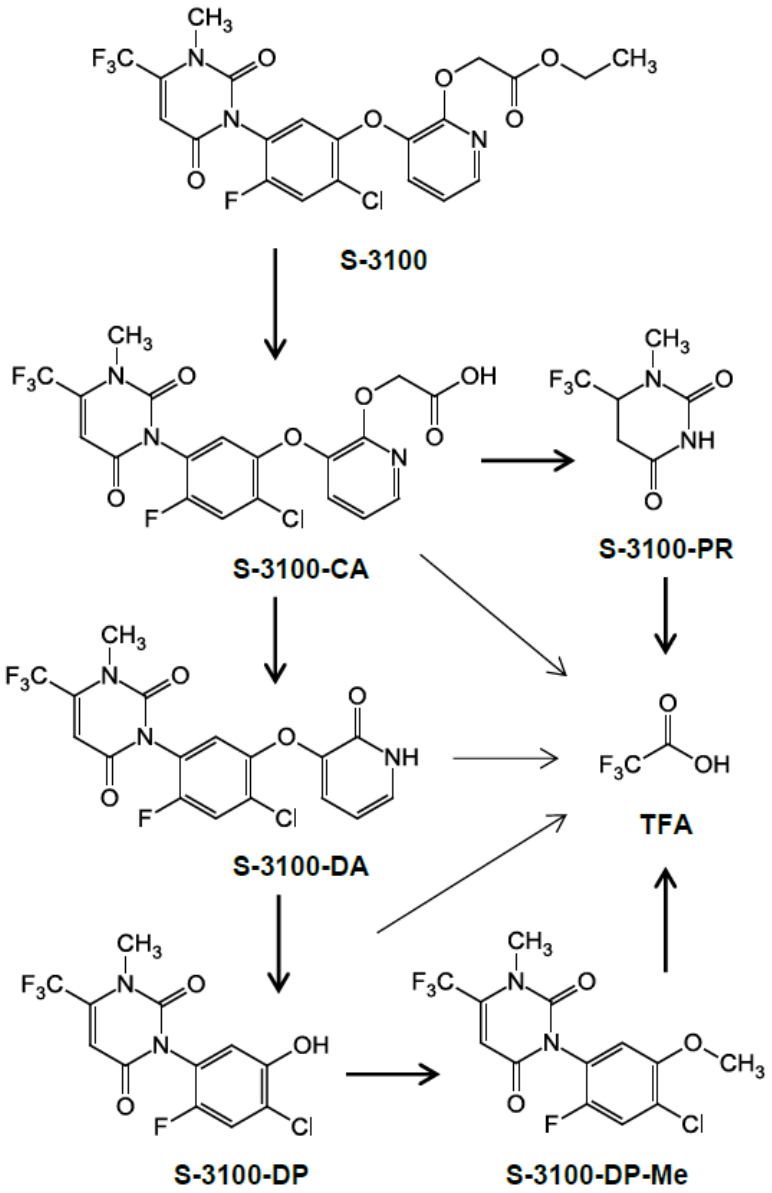
Anticipated residues in poultry matrices

Matrices	Residue definition	Dietary burden (ppm)	Anticipated residues (ppm)
Eggs	Epyrifenacil	0.006	0
Fat			0
Liver			0
Muscle			0

Note: Residues of epyrifenacil were not detected in any matrix.			
Livestock feeding – Goat			
A feeding study was not required based on the low dietary burden. Therefore, the goat metabolism study was used to estimate anticipated residues in the relevant livestock matrices.			
Anticipated residues in animal matrices			
Matrices	**Residue definition**	**Dietary burden (ppm)**	**Anticipated residues (ppm)**
Beef Cattle			
Fat	Epyrifenacil	0.009	7.6×10^{-7}
Liver			Not quantifiable in the metabolism
Kidney			Not quantifiable in the metabolism
Muscle			Not quantifiable in the metabolism
Dairy cattle			
Whole milk	Epyrifenacil	0.02	Not quantifiable in the metabolism
Fat			1.7×10^{-5}
Liver			Not quantifiable in the metabolism
Kidney			Not quantifiable in the metabolism
Muscle			Not quantifiable in the metabolism
Swine			
Fat	Epyrifenacil	0.006	5.0×10^{-7}
Liver			Not quantifiable in the metabolism
Kidney			Not quantifiable in the metabolism
Muscle			Not quantifiable in the metabolism
Note: Residues of epyrifenacil were only identified at <0.001 ppm in the composited fat of goat with the [pyrimidinyl-4-^{14}C]epyrifenacil (PMD) radiolabel.			
NATURE OF THE RESIDUE IN CANOLA			**PMRA No. 3307066**
Radiolabel positions	[phenyl-U-^{14}C]epyrifenacil (PH label) (specific activity: 8.31 MBq/mg) [pyridyl-4(6)-^{14}C]epyrifenacil (PY label) (specific activity: 4.06 MBq/mg) [pyrimidinyl-4-^{14}C]epyrifenacil (PMD label)		

	(specific activity: 4.14 MBq/mg)			
Treatment				
Test site	Outdoor plots. Treatment plots were designated 0 DAT and 7 DAT. The 7 DAT plots were intended to serve as back-up in case insufficient RAC samples were harvested from the 0 DAT plots.			
Treatment	Spray application to bare soil prior to seeding (BBCH 00).			
Total rates	PH label: 1× 44.5 g a.i./ha (0 and 7 DAT) PY label: 1× 44.5 g a.i./ha (0 and 7 DAT) PMD label: 1× 44.4 g a.i./ha (0 DAT); 1× 44.5 g a.i./ha (7 DAT)			
Formulation	Emulsifiable concentrate (EC) formulation of epyrifenacil			
Harvest	Mature canola seeds were harvested at maturity (191-204 DAT).			
Extraction solvents	Homogenized samples: 2× with acetonitrile (ACN), 2× with water, and 1× with ACN (ACN rinse).			
Matrices	**PHI (days)**	**phenyl-U-^{14}C TRR (ppm)[1]**	**pyridyl-4(6)-^{14}C TRR (ppm)[1]**	**pyrimidinyl-4-^{14}C TRR (ppm)[1]**
Mature seed	0	0.003	0.002	0.062 (0.058)
	7	0.007	0.004	0.058
[1] Determined by combustion/LSC. For the sample that was subjected to extraction, TRR calculated by summing extractable and nonextractable radioactivity are presented in parentheses. This value was used for all further determinations.				
Summary of major identified metabolites in plant matrices				
Radiolabel position	**Major metabolites** (>10% of the TRR and >0.05 ppm for TFA)			
Metabolites identified	**phenyl-U-^{14}C**	**pyridyl-4(6)-^{14}C**	**pyrimidinyl-4-^{14}C**	
Canola seed	-	-	TFA	

Proposed metabolic scheme in canola



S-3100 = epyrifenacil

Nature of the residue in corn				**PMRA No. 3307064**
Radiolabel positions	[phenyl-U-^{14}C]epyrifenacil (PH label) (specific activity: 8.31 MBq/mg) [pyridyl-4(6)-^{14}C]epyrifenacil (PY label) (specific activity: 4.06 MBq/mg) [pyrimidinyl-4-^{14}C]epyrifenacil (PMD label) (specific activity: 4.14 MBq/mg)			
Treatment				
Test Site	Outdoor plots. Treatment plots were designated 0 DAT and 7 DAT. The 7 DAT plots were intended to serve as back-up in case insufficient RAC samples were harvested from the 0 DAT plots.			
Treatment	Spray application to bare soil prior to seeding (BBCH 00).			
Total Rates	PH label: 1× 44.5 g a.i./ha (0 and 7 DAT) PY label: 1× 44.5 g a.i./ha (0 and 7 DAT) PMD label: 1× 44.4 g a.i./ha (0 DAT); 1× 44.5 g a.i./ha (7 DAT)			
Formulation	Emulsifiable concentrate (EC) formulation of epyrifenacil			
Harvest	Kernel + cob were harvested at BBCH 79; milk/succulent (84–89 DAT). Forage was harvested at BBCH 85; late dough/early dent (104–108 DAT). Stover and grain were harvested at BBCH 99; maturity (139–146 DAT).			
Extraction solvents	Homogenized samples: 2× with acetonitrile (ACN), 2× with water, and 1× with ACN (ACN rinse).			
Matrices	**PHI (days)**	**phenyl-U-^{14}C TRR (ppm)[1]**	**pyridyl-4(6)-^{14}C TRR (ppm)[1]**	**pyrimidinyl-4-^{14}C TRR (ppm)[1]**
Kernel + cob	0	<0.001	<0.001	0.002
	7	<0.001	<0.001	0.005
Forage	0	0.008	0.005	0.026 (0.026)
	7	0.011	0.004	0.030

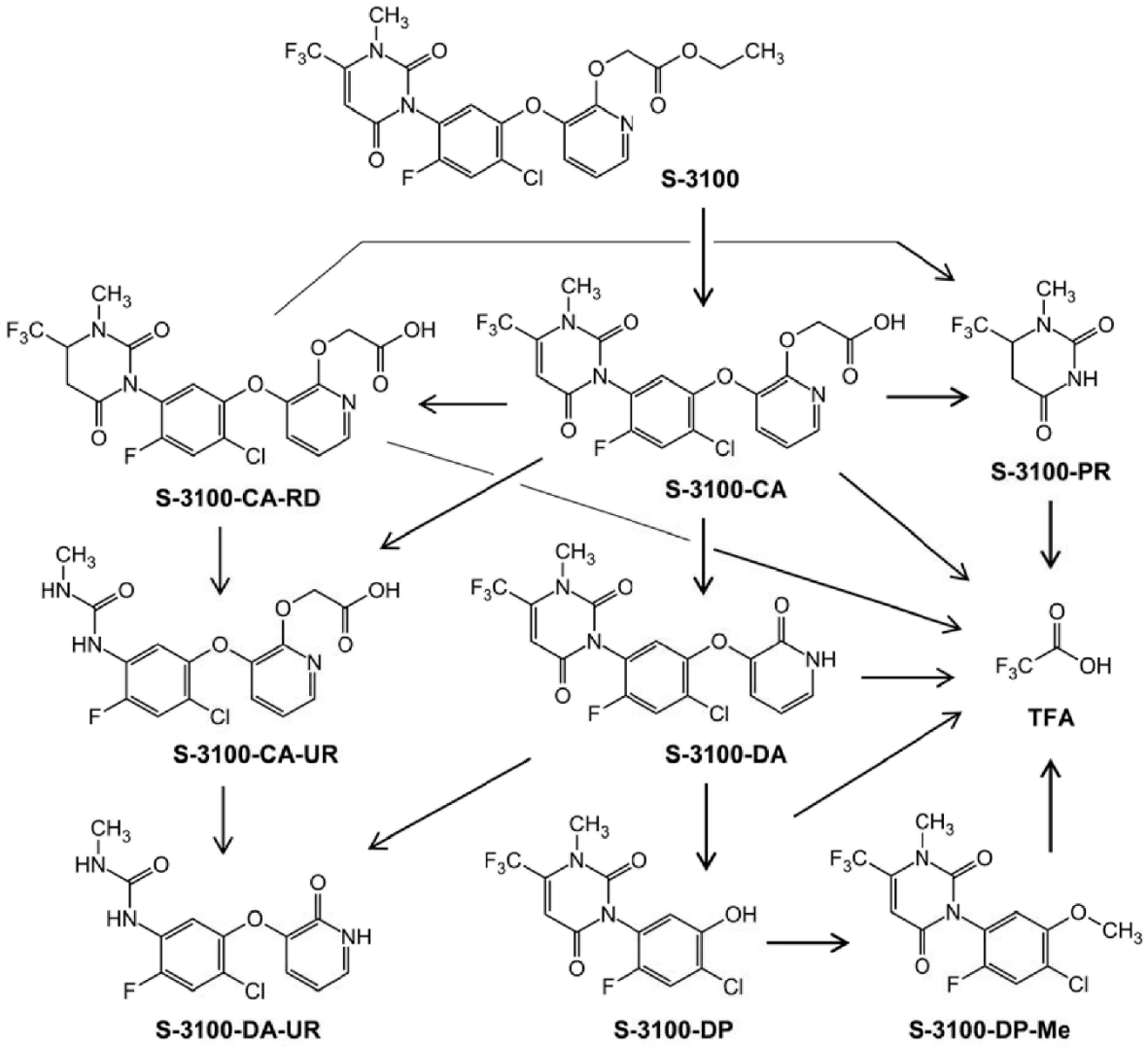
Stover	0	0.014 (0.014)	0.009 (0.006)	0.045 (0.046)
	7	0.019	0.004	0.056
Grain	0	<0.001	<0.001	0.004 (0.005)
	7	<0.001	<0.001	0.008

[1] Determined by combustion/LSC. For samples that were subjected to extraction, TRR calculated by summing extractable and nonextractable radioactivity are presented in parentheses. These values were used for all further determinations.

Summary of major identified metabolites in plant matrices

Radiolabel position	**Major metabolites** (>10% of the TRRs and >0.01 ppm for feed commodities for epyrifenacil and related metabolites (except TFA) or >0.05 ppm for TFA)		
Metabolites identified	**phenyl-U-^{14}C**	**pyridyl-4(6)-^{14}C**	**pyrimidinyl-4-^{14}C**
Corn stover	-	-	-
Corn forage	-	-	-

Proposed metabolic scheme in corn



S-3100 = epyrifenacil

Nature of the residue in soybean				**PMRA No. 3307065**
Radiolabel position	[phenyl-U-^{14}C]epyrifenacil (PH label) (specific activity: 8.31 MBq/mg) [pyridyl-4(6)-^{14}C]epyrifenacil (PY label) (specific activity: 4.06 MBq/mg) [pyrimidinyl-4-^{14}C]epyrifenacil (PMD label) (specific activity: 4.14 MBq/mg)			
Treatment				
Test Site	Outdoor plots. Treatment plots were designated 0 DAT and 7 DAT. The 7 DAT plots were intended to serve as back-up in case insufficient RAC samples were harvested from the 0 DAT plots.			
Treatment	Spray application to bare soil prior to seeding (BBCH 00).			
Total Rate	PH label: 1× 44.4 g a.i./ha (0 DAT); 1× 36.6 g a.i./ha (7 DAT) PY label: 1× 44.4 g a.i./ha (0 DAT); 1× 34.4 g a.i./ha (7 DAT) PMD label: 1× 44.5 g a.i./ha (0 DAT); 1× 34.4 g a.i./ha (7 DAT)			
Formulation	Emulsifiable concentrate (EC) formulation of epyrifenacil			
Harvest	Forage was harvested at BBCH 606; ~60% of flowers open (53-59 DAT). Hay was harvested at BBCH 700; ~10% of pods final length (74 DAT). Green pods with seeds were harvested at BBCH 707; ~70% of pods final length (88 DAT). Mature seeds were harvested at BBCH 909; maturity (123–125 DAT).			
Extraction solvents	Homogenized samples: 2–3× with acetonitrile (ACN), 2× with water, and 1× with ACN (ACN rinse)			
Matrices	**PHI (days)**	**phenyl-U-^{14}C TRR (ppm)[1]**	**pyridyl-4(6)-^{14}C TRR (ppm)[1]**	**pyrimidinyl-4-^{14}C TRR (ppm)[1]**
Forage	0	0.008 (0.008)	0.003	0.088 (0.087)
	7	0.007	0.003	0.069
Hay	0	0.038 (0.037)	0.017 (0.017)	0.249 (0.253)
	7	0.024	0.013	0.259

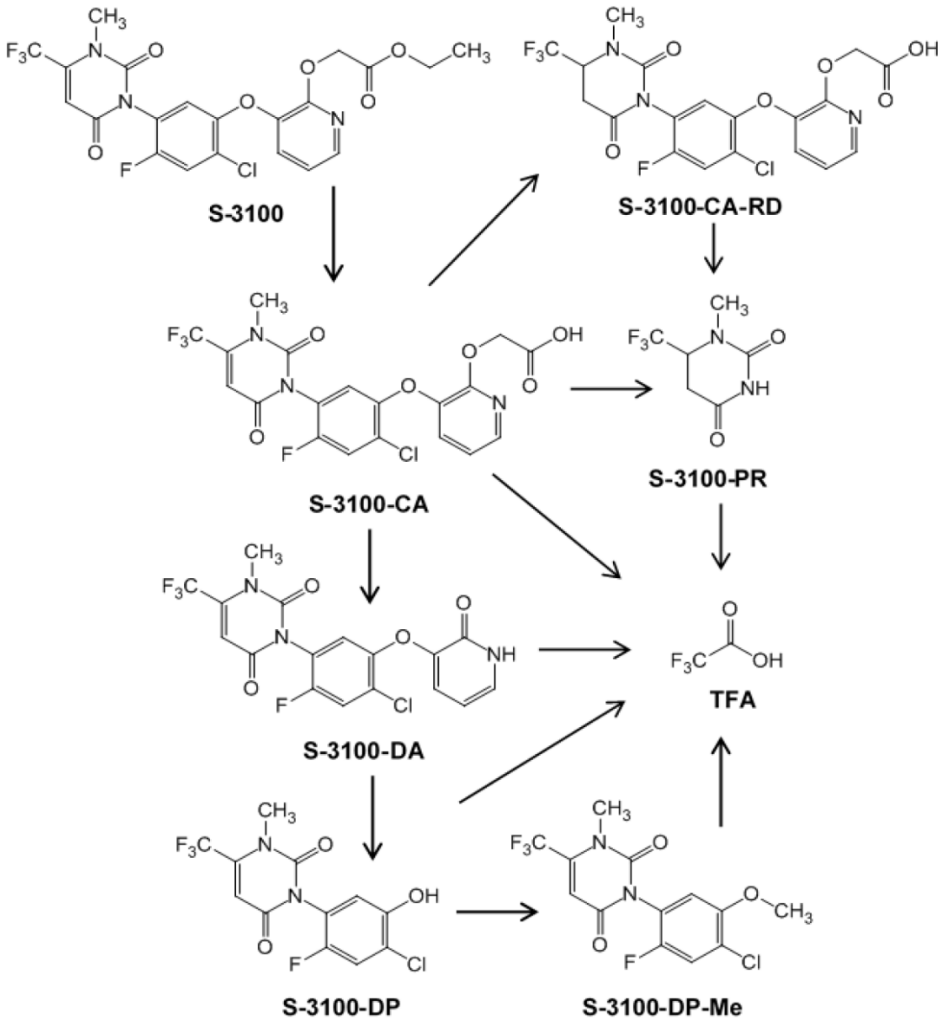
Green pods with seeds	0	0.002	0.001	0.037 (0.034)
	7	0.001	<0.001	0.038
Mature seed	0	0.003	0.004	0.020 (0.017)
	7	0.003	0.003	0.022

[1] Determined by combustion/LSC. For samples that were subjected to extraction, TRR calculated by summing extractable and nonextractable radioactivity are presented in parentheses. These values were used for all further determinations.

Summary of Major Identified Metabolites in Plant Matrices

Radiolabel Position	**Major Metabolites** (>10% of the TRRs and >0.01 ppm in feed or >0.005 ppm in food for epyrifenacil and related metabolites (except TFA); or >0.05 ppm for TFA)		
Metabolites Identified	**phenyl-U-^{14}C**	**pyridyl-4(6)-^{14}C**	**pyrimidinyl-4-^{14}C**
Soybean forage	-	-	TFA
Soybean hay	S-3100-DP-Me	-	TFA
Green pods with seeds	-	-	-
Mature seed	-	-	-

Proposed metabolic scheme in soybean



S-3100 = epyrifenacil

Freezer storage stability in plant matrices			PMRA No. 3309331, 3309334, 3309336, 3309332, 3309333, 3309337	
Tested matrices	**Analyte**	**Tested intervals**	**Temperature**	**Category**
Lettuce, soybean seed, dried bean seed, corn grain, orange	Epyrifenacil, S-3100-CA, S-3100-DA, S-3100-PR, S-3100-DP-Me	0, 1, 3, 6, 8, 14 months	-20°C	High-water, High-oil, High-protein, High-starch, High-acid
Radish root, soybean seed, corn stover, wheat forage, wheat grain, and corn oil	Epyrifenacil, S-3100-CA, S-3100-DA, S-3100-PR, S-3100-DP-Me	0, 1-2, 4-5, 7, 9-10, and 10-11 or 13-14 months Note: S-3100-DA declined by 46% in soybean seed after 11.0 months of storage, by 40% in corn stover after 12.5 months of storage, and by 54% in wheat forage after 13.5 months of storage.	-20°C	High-starch, High-oil, High-water
Lettuce, soybean seed, dried bean seed, corn grain, orange	TFA	0, 1, 3, 8, and 9 months	-20°C	High-water, High-oil, High-protein, High-starch, High-acid
Canola seed, corn stover, radish root, soybean forage	TFA	Rationale (31–44 months)	Not applicable	High-starch, High-oil, High-water

Crop field trials and residue decline on soybean	PMRA No. 3309439

Crop field trials were conducted in 2019 in Canada and the United States. Trials were conducted in North American growing regions 2 (1 trial), 4 (2 trials) and 5 (17 trials) for a total of 20 trials. A 55 g a.i./L emulsifiable concentrate (EC) formulation of epyrifenacil was applied as a single broadcast application at a rate of 39–41 g a.i./ha/application immediately prior to planting soybeans. A non-ionic surfactant was added to the spray mixture for each application. Samples of soybean forage were harvested at the 15–20 cm to beginning pod formation stage (BBCH 15–71, full flowering), and hay samples were harvested at mid to full bloom to 50% pod development (BBCH 64–85, first pods visible); at five trials, hay was cut on the same day as the forage was harvested. Samples of seed (dried) were harvested at normal crop maturity. At two trials, additional samples were collected 10 and 5–6 days before and 10–11 days after target harvest to assess residue decline. Hay samples were allowed to dry for 1–10 days prior to collection.

Crop	Total application rate (g a.i./ha)	PHI (days)	Analyte	Residue levels[2,3] (ppm)						
				n[1]	LAFT	HAFT	Median	Mean	SDEV	Range of TFA residues in/on control samples
Soybean forage	39–41	37–78	Epyrifenacil	20	<0.010	<0.010	0.010	0.010	-	-
			S-3100-CA		<0.011	<0.011	0.011	0.011	-	-
			S-3100-DA		<0.012	<0.012	0.012	0.012	-	-
			S-3100-DP-Me		<0.015	<0.015	0.015	0.015	-	-
			S-3100-PR		<0.026	<0.026	0.026	0.026	-	-
			TFA		<0.10	0.94	0.10	0.23	0.22	<0.10–0.918
Soybean hay		48–104	Epyrifenacil	20	<0.010	<0.010	0.010	0.010	-	-
			S-3100-CA		<0.011	<0.011	0.011	0.011	-	-
			S-3100-DA		<0.012	<0.012	0.012	0.012	-	-
			S-3100-DP-Me		<0.015	<0.015	0.015	0.015	-	-
			S-3100-PR		<0.026	0.029	0.026	0.026	<0.001	-
			TFA		<0.10	3.0	0.27	0.61	0.73	<0.10–2.982
Soybean seed		108–169	Epyrifenacil	20	<0.005	<0.005	0.005	0.005	-	-
			S-3100-CA		<0.005	<0.005	0.005	0.005	-	-
			S-3100-DA		<0.006	<0.006	0.006	0.006	-	-
			S-3100-DP-Me		<0.007	<0.007	0.007	0.007	-	-
			S-3100-PR		<0.013	<0.013	0.013	0.013	-	-
			TFA		<0.10	0.58	0.10	0.17	0.14	<0.10–0.455

[1] n = number of independent trials.
[2] For computation, values <LOQ are assumed to be at the LOQ (0.005 ppm for epyrifenacil and S-3100-CA, 0.006 ppm for S-3100-DA, 0.007 ppm for S-3100-DP-Me, and 0.013 ppm for S-3100-PR in seed; 0.010 ppm for epyrifenacil, 0.011 ppm for S-3100-CA, 0.012 ppm for S-3100-DA, 0.015 ppm for S-3100-DP-Me, and 0.026 ppm for S-3100-PR in forage and hay; and 0.10 ppm for TFA in all matrices).
[3] Residues of the metabolites were converted to epyrifenacil equivalents using molecular weight conversion factors: S-3100-CA (1.06), S-3100-DA (1.20), S-3100-DP-Me (1.47), and S-3100-PR (2.64). TFA residues reported as analyte (NOT converted to epyrifenacil equivalents).

Crop field trials and residue decline on field corn | **PMRA No. 3309436**

Crop field trials were conducted in 2019 in Canada and the United States. Trials were conducted in North American growing regions 1 (1 trial), 5 (17 trials), 7 (1 trial) and 8 (1 trial) for a total of 20 trials. A 55 g a.i./L emulsifiable concentrate (EC) formulation of epyrifenacil was applied as a single broadcast application at a rate of 39–41 g a.i./ha/application immediately prior to planting field corn. A non-ionic surfactant was added to the spray mixture for each application. Samples of field corn forage were harvested at the late dough/early dent stage (BBCH 85–87), and samples of grain and stover were harvested at normal crop maturity. At two trials, additional samples were collected 7–9 and 3–5 days before and 7–8 days after target harvest to assess residue decline.

Crop	Total application rate (g a.i./ha)	PHI (days)	Analyte	Residue levels[2,3] (ppm)						
				n[1]	LAFT	HAFT	Median	Mean	SDEV	Range of TFA residues in/on control samples
Corn forage	39–41	84–127	Epyrifenacil	20	<0.010	<0.010	0.010	0.010	-	-
			S-3100-CA		<0.011	<0.011	0.011	0.011	-	-
			S-3100-DA		<0.012	<0.012	0.012	0.012	-	-
			S-3100-DP-Me		<0.015	<0.015	0.015	0.015	-	-
			S-3100-PR		<0.026	<0.026	0.026	0.026	-	-
			TFA		<0.050	0.37	0.068	0.12	0.098	<0.050–0.360
Corn grain		116–174	Epyrifenacil	20	<0.005	<0.005	0.005	0.005	-	-
			S-3100-CA		<0.005	<0.005	0.005	0.005	-	-
			S-3100-DA		<0.006	<0.006	0.006	0.006	-	-
			S-3100-DP-Me		<0.007	<0.007	0.007	0.007	-	-
			S-3100-PR		<0.013	<0.013	0.013	0.013	-	-
			TFA		<0.050	0.14	0.050	0.066	0.032	<0.050–0.232
Corn stover		116–174	Epyrifenacil	20	<0.010	<0.010	0.010	0.010	-	-
			S-3100-CA		<0.011	<0.011	0.011	0.011	-	-
			S-3100-DA		<0.012	<0.012	0.012	0.012	-	-

			S-3100-DP-Me		<0.015	<0.015	0.015	0.015	-	-
			S-3100-PR		<0.026	<0.026	0.026	0.026	-	-
			TFA		<0.050	0.51	0.083	0.13	0.14	<0.050–0.323

[1] n = number of independent trials.
[2] For computation, values <LOQ are assumed to be at the LOQ (0.005 ppm for epyrifenacil and S-3100-CA, 0.006 ppm for S-3100-DA, 0.007 ppm for S-3100-DP-Me, and 0.013 ppm for S-3100-PR in grain; 0.010 ppm for epyrifenacil, 0.011 ppm for S-3100-CA, 0.012 ppm for S-3100-DA, 0.015 ppm for S-3100-DP-Me, and 0.026 ppm for S-3100-PR in forage and stover; and 0.050 ppm for TFA in all matrices).
[3] Residues of the metabolites were converted to epyrifenacil equivalents using molecular weight conversion factors: S-3100-CA (1.06), S-3100-DA (1.20), S-3100-DP-Me (1.47), and S-3100-PR (2.64). TFA residues reported as analyte (NOT converted to epyrifenacil equivalents).

Crop field trials and residue decline on wheat | **PMRA No. 3309441**

Crop field trials were conducted in 2018–2019 in Canada and the United States. Trials were conducted in North American growing regions 2 (1 trial), 5 (5 trials), 6 (2 trials), 7 (5 trials), 8 (1 trial), 11 (2 trials), and 14 (4 trials) for a total of 20 trials. A 55 g a.i./L emulsifiable concentrate (EC) formulation of epyrifenacil was applied as a single broadcast application at a rate of 39–41 g a.i./ha/application one day prior to planting of wheat. A non-ionic surfactant was added to the spray mixture for each application. Samples of wheat forage were harvested at the 15–20 cm to stem elongation stage (BBCH ≤39) and samples of hay were harvested at the early flowering (boot, BBCH 41-45) to soft dough stage (BBCH ~85). Samples of grain and straw were harvested at normal crop maturity. At two trials, additional samples were collected 6-8 days before and 6–9 and 13–15 days after target harvest to assess residue decline. Hay samples were allowed to dry for 1–13 days prior to collection.

Crop	Total application rate (g a.i./ha)	PHI (days)	Analyte	Residue levels [2,3] (ppm)						
				n[1]	LAFT	HAFT	Median	Mean	SDEV	Range of TFA residues in/on control samples
Wheat forage	39–41	26-203	Epyrifenacil	20	<0.010	<0.010	0.010	0.010	-	-
			S-3100-CA		<0.011	<0.011	0.011	0.011	-	-
			S-3100-DA		<0.012	<0.012	0.012	0.012	-	-
			S-3100-DP-Me		<0.015	<0.015	0.015	0.015	-	-
			S-3100-PR		<0.026	<0.026	0.026	0.026	-	-
			TFA		<0.070	0.28	0.071	0.098	0.054	<0.070–0.451
Wheat hay		46–230	Epyrifenacil	20	<0.010	<0.010	0.010	0.010	-	-
			S-3100-CA		<0.011	<0.011	0.011	0.011	-	-
			S-3100-DA		<0.012	<0.012	0.012	0.012	-	-
			S-3100-DP-Me		<0.015	<0.015	0.015	0.015	-	-
			S-3100-PR		<0.026	<0.026	0.026	0.026	-	-

			TFA		<0.070	0.82	0.14	0.20	0.18	<0.070–1.01
Wheat grain		94–262	Epyrifenacil	20	<0.005	<0.005	0.005	0.005	-	-
			S-3100-CA		<0.005	<0.005	0.005	0.005	-	-
			S-3100-DA		<0.006	<0.006	0.006	0.006	-	-
			S-3100-DP-Me		<0.007	<0.007	0.007	0.007	-	-
			S-3100-PR		<0.013	<0.013	0.013	0.013	-	-
			TFA		<0.070	0.24	0.073	0.11	0.059	<0.070–0.452
Wheat straw		94–262	Epyrifenacil	20	<0.010	<0.010	0.010	0.010	-	-
			S-3100-CA		<0.011	<0.011	0.011	0.011	-	-
			S-3100-DA		<0.012	<0.012	0.012	0.012	-	-
			S-3100-DP-Me		<0.015	<0.015	0.015	0.015	-	-
			S-3100-PR		<0.026	<0.026	0.026	0.026	-	-
			TFA		<0.070	0.29	0.084	0.10	0.053	<0.070–0.354

[1] n = number of independent trials.

[2] For computation, values <LOQ are assumed to be at the LOQ (0.005 ppm for epyrifenacil and S-3100-CA, 0.006 ppm for S-3100-DA, 0.007 ppm for S-3100-DP-Me, and 0.013 ppm for S-3100-PR in grain; 0.010 ppm for epyrifenacil, 0.011 ppm for S-3100-CA, 0.012 ppm for S-3100-DA, 0.015 ppm for S 3100-DP-Me, and 0.026 ppm for S-3100-PR in forage, hay, and straw; and 0.070 ppm for TFA, as analyte, in all matrices).

[3] Residues of the metabolites were converted to epyrifenacil equivalents using molecular weight conversion factors: S-3100-CA (1.06), S-3100-DA (1.20), S-3100-DP-Me (1.47), and S-3100-PR (2.64). TFA residues reported as analyte (NOT converted to epyrifenacil equivalents).

Crop field trials and residue decline on canola	**PMRA No. 3309432**

Crop field trials were conducted in 2020 in Canada and the United States. Trials were conducted in North American growing regions 5 (3 trials), 7 (2 trials) and 14 (8 trials) for a total of 13 trials. A 55 g a.i./L emulsifiable concentrate (EC) formulation of epyrifenacil was applied as a single broadcast application at a rate of 20–21 g a.i./ha/application 2–4 days prior to planting of canola. An adjuvant (crop oil concentrate or methylated seed oil) was added to the spray mixture for each application. Samples of canola seed were harvested at normal crop maturity; at three trials, samples were allowed to dry for 6 or 13 days prior to collection. At two trials, additional samples were collected 9–11 and 4–6 days before and 9–10 days after target harvest to assess residue decline.

Crop	Total Application Rate (g a.i./ha)	PHI (days)	Analyte	Residue Levels [2,3] (ppm)						
				n[1]	LAFT	HAFT	Median	Mean	SDEV	Range of TFA residues in/on control samples
Canola seed	20–21	80–167	Epyrifenacil	13	<0.005	<0.005	0.005	0.005	-	-
			S-3100-CA		<0.005	<0.005	0.005	0.005	-	-
			S-3100-DA		<0.006	<0.006	0.006	0.006	-	-
			S-3100-DP-Me		<0.007	<0.007	0.007	0.007	-	-
			S-3100-PR		<0.013	<0.013	0.013	0.013	-	-
			TFA		<0.050	0.14	0.050	0.057	0.025	<0.050–0.127

[1]n = number of independent trials.
[2]For computation, values <LOQ are assumed to be at the LOQ (0.005 ppm for epyrifenacil and S 3100 CA, 0.006 ppm for S 3100 DA, 0.007 ppm for S-3100-DP-Me, and 0.013 ppm for S 3100 PR; and 0.050 ppm for TFA).
[3]Residues of the metabolites were converted to epyrifenacil equivalents using molecular weight conversion factors: S-3100-CA (1.06), S-3100-DA (1.20), S-3100-DP-Me (1.47), and S-3100-PR (2.64). TFA residues reported as analyte (NOT converted to epyrifenacil equivalents).

Processed food and feed - Soybean **PMRA No. 3309439**

Processing studies were conducted in one trial in NAFTA growing region 5 using a 55 g a.i./L emulsifiable concentrate (EC) formulation of epyrifenacil at 120 g a.i./ha (3 to 5-fold of maximum single seasonal use-rate) in/on crops. Adequate storage stability data are available on diverse crop types to support the storage intervals of the processed food and feed. Samples were analyzed using a validated analytical method.

Epyrifenacil, S-3100-CA, S-3100-DA, S-3100-DP-Me, S-3100-PR, and TFA residues were all <LOQ (<0.005 ppm for epyrifenacil and related metabolites (except TFA), <0.10 ppm for TFA) in soybean seed and all processed commodities. Processing factors could not be calculated for epyrifenacil, S-3100-CA, S-3100-DA, S-3100-DP-Me, S-3100-PR, and TFA in soybean seed processed fractions.

Processed food and feed – Field corn **PMRA No. 3309436**

Processing studies were conducted in one trial in NAFTA growing region 5 using a 55 g a.i./L emulsifiable concentrate (EC) formulation of epyrifenacil at 120 g a.i./ha (threefold of maximum single seasonal use-rate) in/on crops. Adequate storage stability data are available on diverse crop types to support the storage intervals of the processed food and feed. Samples were analyzed using a validated analytical method.

Except for TFA, epyrifenacil, S-3100-CA, S-3100-DA, S-3100-DP-Me, and S-3100-PR were all <LOQ (<0.005 ppm for epyrifenacil and related metabolites) in corn grain and all processed commodities. Processing factors could not be calculated for epyrifenacil, S-3100-CA, S-3100-DA, S-3100-DP-Me, and S-3100-PR corn grain processed fractions. Calculated processing factors for TFA are shown in the following rows.

TFA				
RAC	**Processed fractions**	**TFA residues[1] [Average] (ppm)**	**Processing factor[2] for TFA**	**TFA residues in control samples (ppm)**
Corn grain	Corn grain (RAC)	<0.050, <0.050 [<0.050]	-	<0.050
	Grits	<0.050, <0.050 [<0.050]	Not calculated	<0.050
	Meal	<0.050, <0.050 [<0.050]	Not calculated	<0.050
	Flour	<0.050, <0.050 [<0.050]	Not calculated	<0.050
	Starch	<0.050, 0.061 [<0.056]	>1.1×	<0.050
	Oil (dry-milled RBD)	<0.050, <0.050 [<0.050]	Not calculated	<0.050
	Oil (wet-milled RBD)	<0.050, <0.050 [<0.050]	Not calculated	<0.050

[1] The LOQ was 0.05 ppm for corn commodities.
[2] Processing Factor = [Average residue for analyte in the processed fraction] / [Average residue for analyte in/on the RAC].
Not calculated when residues were below the LOQ in/on the RAC and processed fraction.

Processed food and feed - Wheat	**PMRA No. 3309441**

Processing studies were conducted in one trial in NAFTA growing region 5 using a 55 g a.i./L emulsifiable concentrate (EC) formulation of epyrifenacil at 122 g a.i./ha (3 to 6-fold of maximum single seasonal use-rate) in/on crops. Adequate storage stability data are available on diverse crop types to support the storage intervals of the processed food and feed. Samples were analyzed using a validated analytical method.

Except for TFA, epyrifenacil, S-3100-CA, S-3100-DA, S-3100-DP-Me, and S-3100-PR were all <LOQ (<0.005 ppm for epyrifenacil and related metabolites) in wheat grain and all processed commodities. Processing factors could not be calculated for epyrifenacil, S-3100-CA, S-3100-DA, S-3100-DP-Me, and S-3100-PR wheat grain processed fractions. Calculated processing factors for TFA are shown in the following rows.

TFA				
RAC	**Processed fractions**	**TFA residues[1] [Average] (ppm)**	**Processing factor[2] for TFA**	**TFA residues in control samples (ppm)**
Wheat grain	Wheat grain (RAC)	0.086, 0.082 [0.084]	-	0.097
	Bran	0.086, 0.077 [0.082]	1×	0.079

	Flour	<0.070, <0.070 [<0.070]	<0.8×	0.085
	Middlings	0.081, 0.086 [0.084]	1×	0.075
	Shorts	<0.070, <0.070 [<0.070]	<0.8×	<0.07
	Germ	<0.070, <0.070 [<0.070]	<0.8×	0.078

[1] The LOQ was 0.07 ppm for wheat commodities.
[2] Processing Factor = [Average residue for analyte in the processed fraction] / [Average residue for analyte in/on the RAC].

Processed food and feed - Canola	**PMRA No. 3309432**

Processing studies were conducted in one trial in NAFTA growing region 7 using [a 55 g a.i./L emulsifiable concentrate (EC) formulation of epyrifenacil at 120 g a.i./ha (2.5 to 5.0 fold of maximum single seasonal use-rate) in/on crops. Adequate storage stability data are available on diverse crop types to support the storage intervals of the processed food and feed. Samples were analyzed using a validated analytical method.

Except for TFA, epyrifenacil, S-3100-CA, S-3100-DA, S-3100-DP-Me, and S-3100-PR were all <LOQ (<0.005 ppm for epyrifenacil and related metabolites) in canola seed and all processed commodities. Processing factors could not be calculated for epyrifenacil, S-3100-CA, S-3100-DA, S-3100-DP-Me, and S-3100-PR canola seed processed fractions. Calculated processing factors for TFA are shown in the following rows.

TFA

RAC	**Processed fractions**	**TFA residues[1] [Average] (ppm)**	**Processing factor[2] for TFA**	**TFA residues in control samples (ppm)**
Canola seed	Canola Seed (RAC)	0.065, 0.057 [0.061]	-	0.054
	Meal	0.074, 0.074 [0.074]	1.2×	0.076
	Oil	<0.050, <0.050 [<0.050]	<0.8×	<0.05

[1] The LOQ was 0.05 ppm for canola commodities.
[2] Processing Factor = [Average residue for analyte in the processed fraction] / [Average residue for analyte in/on the RAC].

Confined accumulation in rotational crops – Radish, kale and wheat	**PMRA No. 3309212**
Radiolabel positions	[phenyl-U-^{14}C]epyrifenacil (PH label; specific activity 4.2 MBq/mg), [pyridinyl-4(6)-^{14}C]epyrifenacil (PY label; specific activity 4.1 MBq/mg), and [pyrimidinyl-4-^{14}C]epyrifenacil (PMD label; specific activity 4.2 MBq/mg)
Treatment	
Test site	Grown outdoors in 3 ft × 5 ft (91 cm × 152 cm) boxes
Soil type	Sandy loam
Treatment	Bare soil was treated at 41.9–44.1 g a.i./ha, and aged for 30, 120 and 360 days. Note: For each radiolabel, one box was used for each crop for the 30- and 120-day PBIs; crops for the 360-day PBI were planted in the boxes for the 30-day PBI.

Formulation	Emulsifiable concentrate (EC) formulation of epyrifenacil			
Extraction procedures				
Matrices	**Extraction solvents**			
Homogenized samples	2× acetonitrile and 2× water			
PES	For 30-day PBI wheat straw samples from all labels and the 30-day PBI PMD-label wheat grain sample, PES were subjected to additional procedures to characterize residues. PES were sequentially extracted with: -HCl; -NaOH; -phosphate buffer (pH 7) plus NaCl; -α-amylase enzyme (in phosphate buffer, pH 7, plus NaCl); -protease enzyme (phosphate buffer, pH 7.5, plus $CaCl_2$); -NaOAc/EDTA (pH 4.5; straw only); -HCl in dioxane at reflux (straw only); -KOH (straw only; hydrolysate was neutralized with acetic acid); -sulfuric acid digestion (straw only; hydrolysate was neutralized with KOH).			
Matrices	**PHI (days)**	**phenyl-U-^{14}C TRR (ppm)[1]**	**pyridyl-4(6)-^{14}C TRR (ppm)[1]**	**pyrimidinyl-4-^{14}C TRR (ppm)[1]**
Radish tops	30	0.002	<0.001	0.042 (0.041)
	120	0.002	0.002	0.149 (0.144)
	360	0.001	<0.001	0.018 (0.019)
Radish root	30	0.003	0.002	0.008
	120	0.002	0.003	0.024 (0.027)
	360	0.001	<0.001	0.002
Immature kale	30	0.008	<0.001	0.020 (0.019)
	120	0.001	<0.001	0.081 (0.090)
	360	0.002	<0.001	0.013 (0.014)
Mature kale	30	0.009	0.002	0.073 (0.061)
	120	0.001	<0.001	0.101 (0.102)
	360	<0.002	<0.002	0.025 (0.020)
Wheat forage	30	0.005	0.003	0.045 (0.045)
	120	0.004	0.001	0.088 (0.101)
	360	0.003	0.001	0.020 (0.018)

Wheat hay	30	0.034 (0.037)	0.025 (0.019)	0.127 (0.142)
	120	0.009	0.004	0.096 (0.096)
	360	0.008	0.010 (0.010)	0.066 (0.063)
Wheat grain	30	0.010 (0.010)	0.007	0.042 (0.044)
	120	0.001	<0.001	0.024 (0.026)
	360	0.002	0.004	0.016 (0.015)
Wheat straw	30	0.094 (0.097)	0.042 (0.042)	0.300 (0.314)
	120	0.022 (0.021)	0.011 (0.011)	0.130 (0.128)
	360	0.019 (0.020)	0.020 (0.017)	0.138 (0.090)

[1] Residues in all matrices were initially determined by combustion/LSC. For samples subjected to extraction and analysis, residues were also determined by summing extractable and non-extractable radioactivity; these values are presented in parentheses. Summed TRR values were used for all further determinations.

Summary of major[1] identified metabolites in rotated crops

Plantback intervals (PBI)	**1st Rotation (30 days)**			**2nd Rotation (120 days)**			**3rd Rotation (360 days)**		
Radiolabel position	**phenyl-U-^{14}C**	**pyridyl-4(6)-^{14}C**	**pyrimidinyl-4-^{14}C**	**phenyl-U-^{14}C**	**pyridyl-4(6)-^{14}C**	**pyrimidinyl-4-^{14}C**	**phenyl-U-^{14}C**	**pyridyl-4(6)-^{14}C**	**pyrimidinyl-4-^{14}C**
Metabolites identified	**Major Metabolites**								
Wheat forage	-	-	-	-	-	TFA	-	-	-
Wheat hay	-	-	TFA	-	-	TFA	-	-	-
Wheat grain	-	-	-	-	-	-	-	-	-
Wheat straw	S-3100-CA	S-3100-CA	TFA	-	-	TFA	-	-	TFA
Radish root	-	-	-	-	-	-	-	-	-
Radish tops	-	-	S-3100-PR	-	-	TFA	-	-	S-3100-PR
Immature kale	-	-	S-3100-PR	-	-	TFA	-	-	S-3100-PR
Mature kale	-	-	S-3100-PR	-	-	TFA	-	-	S-3100-PR

[1] Major Metabolites are identified as >10% TRR and >0.005 ppm for food commodities and >0.01 ppm for feed commodities for epyrifenacil and related metabolites (except TFA); or >0.05 ppm for TFA.

Confined accumulation in rotational crops – Radish, kale, and wheat	**PMRA No. 3309213**
Radiolabel positions	[phenyl-U-^{14}C]epyrifenacil (PH label; specific activity 4.2 MBq/mg), [pyridinyl-4(6)-^{14}C]epyrifenacil (PY label; specific activity 4.1 MBq/mg), and [pyrimidinyl-4-^{14}C]epyrifenacil (PMD label; specific activity 4.2 MBq/mg)

Treatment				
Test site	Grown outdoors in 3 ft × 5 ft (91 cm × 152 cm) boxes			
Soil type	Sandy loam			
Treatment	Bare soil was treated at 126–131 g a.i./ha, and aged for 30, 120 and 360 days. Note: For each radiolabel, one box was used for each crop for the 30- and 120-day PBIs; crops for the 360-day PBI were planted in the boxes for the 30-day PBI.			
Formulation	Emulsifiable concentrate (EC) formulation of epyrifenacil			
Extraction procedures				
Matrices	**Extraction solvents**			
Homogenized samples	2× acetonitrile and 2× water			
PES	For 30-day PBI wheat grain samples and wheat straw samples from all PBIs, PES were subjected to additional procedures to characterize residues. PES were sequentially extracted with: -HCl; -NaOH; -phosphate buffer (pH 7) plus NaCl; -α-amylase enzyme (in phosphate buffer, pH 7, plus NaCl); -protease enzyme (phosphate buffer, pH 7.5, plus $CaCl_2$); -NaOAc/EDTA (pH 4.5; straw only); -HCl in dioxane at reflux (straw only); -KOH (straw only; hydrolysate was neutralized with acetic acid); -sulfuric acid digestion (straw only; hydrolysate was neutralized with KOH).			
Matrices	**PHI (days)**	**phenyl-U-^{14}C**	**pyridyl-4(6)-^{14}C**	**pyrimidinyl-4-^{14}C**
		TRR (ppm)[1]	**TRR (ppm)[1]**	**TRR (ppm)[1]**
Radish tops	30	0.013 (0.013)	0.006	0.129 (0.126)
	120	0.008	0.010 (0.008)	0.344 (0.349)
	360	0.005	0.001	0.070 (0.055)
Radish root	30	0.010 (0.015)	0.005	0.022 (0.024)
	120	0.005	0.010 (0.010)	0.057 (0.058)

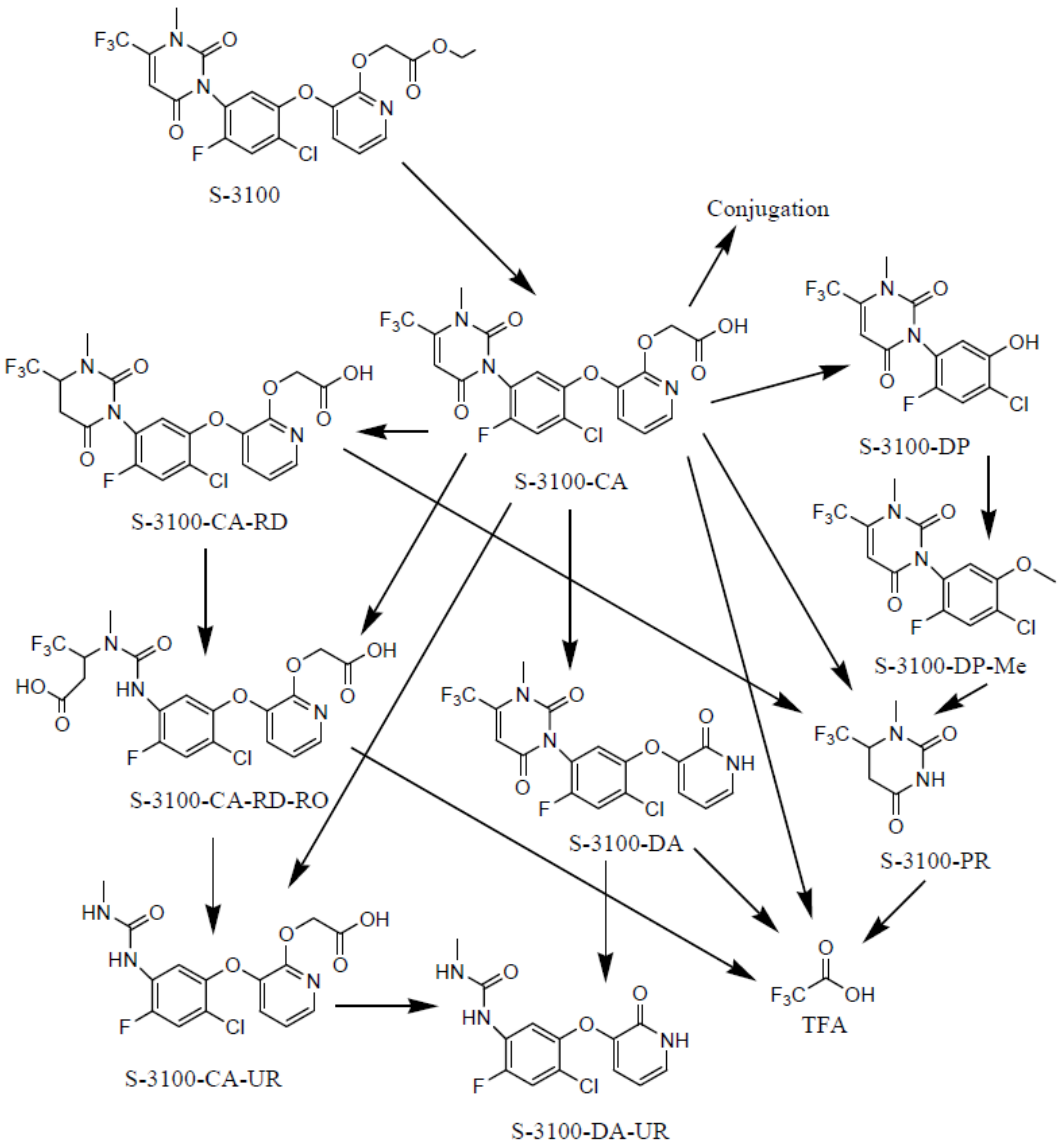
	360	0.004	0.002	0.008
Immature kale	30	0.075 (0.074)	0.004	0.200 (0.202)
	120	0.003	0.002	0.313 (0.335)
	360	0.006	<0.001	0.062 (0.053)
Mature kale	30	0.035 (0.029)	0.006	0.200 (0.178)
	120	0.004	0.002	0.343 (0.344)
	360	0.006	<0.001	0.068 (0.067)
Wheat forage	30	0.017 (0.016)	0.008	0.115 (0.112)
	120	0.007	0.004	0.200 (0.220)
	360	0.007	0.003	0.056 (0.050)
Wheat hay	30	0.127 (0.137)	0.084 (0.089)	0.536 (0.634)
	120	0.020 (0.014)	0.016 (0.012)	0.298 (0.290)
	360	0.033 (0.027)	0.017 (0.013)	0.118 (0.116)
Wheat grain	30	0.025 (0.036)	0.030 (0.042)	0.088 (0.124)
	120	0.002	0.001	0.097 (0.076)
	360	0.009	0.003	0.043 (0.065)
Wheat straw	30	0.270 (0.293)	0.142 (0.166)	0.898 (1.024)
	120	0.058 (0.059)	0.031 (0.032)	0.505 (0.547)
	360	0.082 (0.073)	0.038 (0.030)	0.356 (0.291)

[1] Residues in all matrices were initially determined by combustion/LSC. For samples subjected to extraction and analysis, residues were also determined by summing extractable and nonextractable radioactivity; these values are presented in parentheses. Summed TRR values were used for all further determinations.

Summary of major[1] identified metabolites in rotated crops									
Plantback intervals (PBI)	**1ST Rotation (30 days)**			**2nd Rotation (120 days)**			**3rd Rotation (360 days)**		
Radiolabel position	**phenyl-U-^{14}C**	**pyridyl-4(6)-^{14}C**	**pyrimidinyl-4-^{14}C**	**phenyl-U-^{14}C**	**pyridyl-4(6)-^{14}C**	**pyrimidinyl-4-^{14}C**	**phenyl-U-^{14}C**	**pyridyl-4(6)-^{14}C**	**pyrimidinyl-4-^{14}C**
Metabolites identified	**Major Metabolites**								
Wheat forage	-	-	TFA, S-3100-PR	-	-	TFA	-	-	-
Wheat hay	-	S-3100-CA	TFA	-	-	TFA	-	-	TFA, S-3100-PR
Wheat grain	S-3100-CA	S-3100-CA, S-3100-CA-UR	TFA	-	-	TFA	-	-	TFA
Wheat straw	S-3100-CA	S-3100-CA, S-3100-CA-UR	TFA, S-3100-PR	-	-	TFA	-	-	TFA
Radish root	S-3100-CA	-	TFA	-	-	TFA	-	-	-
Radish tops	S-3100-DP-Me	-	TFA, S-3100-PR	-	-	TFA	-	-	S-3100-PR
Immature kale	S-3100-CA, S-3100-CA-Gln	-	S-3100-CA, S-3100-CA-Gln, S-3100-PR	-	-	TFA	-	-	S-3100-PR
Mature kale	S-3100-DP-Me, S-3100-CA	-	TFA, S-3100-PR	-	-	TFA	-	-	TFA, S-3100-PR

[1] Major metabolites are identified as >10% TRR and >0.005 ppm for food commodities and >0.01 ppm for feed commodities for epyrifenacil and related metabolites (except TFA); or >0.05 ppm for TFA.

Proposed metabolic scheme in rotational crops



S-3100 = epyrifenacil

Residue data in field rotational crops									PMRA No. 3309215
Three trials (two each for radish, lettuce and wheat) were conducted during the 2019-2021 growing seasons in North American growing regions 2, 5, and 10. One broadcast application was made to bare soil with a 55 g a.i./L emulsifiable concentrate (EC) formulation of epyrifenacil at a rate of 39–41 g a.i./ha. Adjuvants were used at all trial sites. Adequate storage stability data are available on diverse commodity categories to support the storage intervals of the rotational crop field trials. Samples were analyzed using a validated analytical method.									
Commodity	**Total Application rate (g a.i./ha)**	**PBI (days)**	**Residue levels[2,3,4] (ppm)**						
			n[1]	**LAFT**	**HAFT**	**Median**	**Mean**	**SDEV**	**Range of TFA residues in/on control samples**
Epyrifenacil									
Lettuce	40–41	60	2	<0.005	<0.005	0.005	0.005	-	-
		117–119	2	<0.005	<0.005	0.005	0.005	-	-
		270–271	2	<0.005	<0.005	0.005	0.005	-	-
		362–365	2	<0.005	<0.005	0.005	0.005	-	-
Radish root	40–41	60	2	<0.005	<0.005	0.005	0.005	-	-
		117–119	2	<0.005	<0.005	0.005	0.005	-	-
		270–271	2	<0.005	<0.005	0.005	0.005	-	-
		362–365	2	<0.005	<0.005	0.005	0.005	-	-
Radish tops		60	2	<0.010	<0.010	0.010	0.010	-	-
		117–119	2	<0.010	<0.010	0.010	0.010	-	-
		270–271	2	<0.010	<0.010	0.010	0.010	-	-
		362–365	2	<0.010	<0.010	0.010	0.010	-	-
Wheat forage	39–41	30	2	<0.010	<0.010	0.010	0.010	-	-
		119	2	<0.010	<0.010	0.010	0.010	-	-
		267–270	2	<0.010	<0.010	0.010	0.010	-	-
		364–365	2	<0.010	<0.010	0.010	0.010	-	-
Wheat hay		30	2	<0.010	<0.010	0.010	0.010	-	-
		119	2	<0.010	<0.010	0.010	0.010	-	-
		267–270	2	<0.010	<0.010	0.010	0.010	-	-
		364–365	2	<0.010	<0.010	0.010	0.010	-	-
Wheat grain		30	2	<0.005	<0.005	0.005	0.005	-	-

		119	2	<0.005	<0.005	0.005	0.005	-	-
		267–270	2	<0.005	<0.005	0.005	0.005	-	-
		364–365	2	<0.005	<0.005	0.005	0.005	-	-
Wheat straw		30	2	<0.010	<0.010	0.010	0.010	-	-
		119	2	<0.010	<0.010	0.010	0.010	-	-
		267–270	2	<0.010	<0.010	0.010	0.010	-	-
		364–365	2	<0.010	<0.010	0.010	0.010	-	-
TFA									
Lettuce	40–41	60	2	<0.050	<0.050	<0.050	<0.050	-	<0.050
		117–119	2	<0.050	<0.050	<0.050	<0.050	-	<0.050
		270–271	2	<0.050	<0.050	<0.050	<0.050	-	<0.050
		362–365	2	<0.050	<0.050	<0.050	<0.050	-	<0.050
Radish root	40–41	60	2	<0.050	<0.068	0.059	0.059	-	<0.050
		117–119	2	<0.050	<0.050	<0.050	<0.050	-	<0.050
		270–271	2	<0.050	<0.050	<0.050	<0.050	-	<0.050
		362–365	2	<0.050	0.11	0.082	0.082	-	<0.050
Radish tops		60	2	<0.050	0.31	0.18	0.18	-	<0.050–0.0631
		117–119	2	<0.050	0.13	0.088	0.088	-	<0.050–0.1368
		270–271	2	<0.050	<0.056	0.053	0.053	-	<0.050–0.1530
		362–365	2	<0.050	0.46	0.26	0.26	-	<0.050–0.1279
Wheat forage	39–41	30	2	<0.070	<0.070	<0.070	<0.070	-	<0.070–0.0704
		119	2	<0.070	<0.070	<0.070	<0.070	-	<0.070
		267–270	2	<0.070	<0.070	<0.070	<0.070	-	<0.070
		364–365	2	<0.070	<0.070	<0.070	<0.070	-	<0.070–0.109
Wheat hay		30	2	<0.070	<0.070	<0.070	<0.070	-	0.0766–0.1715
		119	2	<0.070	<0.075	0.072	0.072	-	0.0729–0.227
		267–270	2	<0.074	0.093	0.083	0.083	-	<0.070
		364–365	2	<0.070	<0.070	<0.070	<0.070	-	0.074–0.2215
Wheat grain		30	2	<0.070	<0.070	<0.070	<0.070	-	0.0876–0.1983
		119	2	<0.070	<0.070	<0.070	<0.070	-	<0.070
		267–270	2	<0.070	0.11	0.090	0.090	-	<0.070–0.192
		364–365	2	<0.070	<0.070	<0.070	<0.070	-	<0.070–0.2231

Wheat straw		30	2	<0.070	<0.070	<0.070	<0.070	-	<0.070
		119	2	<0.070	0.074	0.072	0.072	-	<0.070–0.1635
		267–270	2	<0.070	0.10	0.086	0.086	-	<0.070–0.640
		364–365	2	<0.070	<0.070	<0.070	<0.070	-	<0.070–0.156

[1] n = number of independent field trials.
[2] Values based on per-trial averages. For computation, values <LOQ are assumed to be at the LOQ (**Epyrifenacil:** 0.050 ppm for lettuce, radish root, and wheat grain matrices and 0.010 ppm for radish tops and wheat forage, hay, and straw matrices; **TFA:** 0.050 ppm for lettuce and radish matrices and 0.070 ppm for wheat matrices).
[3] TFA residues reported as analyte (NOT converted to epyrifenacil equivalents).
[4] Only Epyrifenacil and TFA are presented in this table. All other measured metabolites (S-3100-CA, S-3100-DA, S-3100-DP-Me, and S-3100-PR) were <LOQ (<0.005 ppm for lettuce, radish root, and wheat grain, and <0.010 ppm for radish tops and wheat forage, hay, and straw when reported as analyte (NOT converted to epyrifenacil equivalents)).

Based on the results of the field accumulation study, a plantback interval of 30 days is required for small grains crops and 60 days for all other non-labeled crops. Labeled crops (in other words, primary crops registered for use with epyrifenacil) may be replanted anytime.

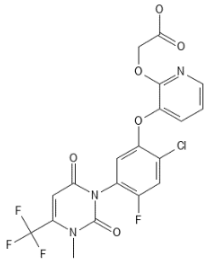
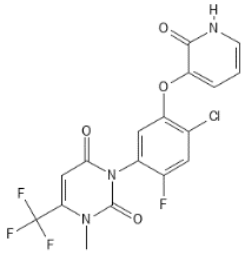
Table 13 Food residute chemistry overview of metabolism studies and risk assessment

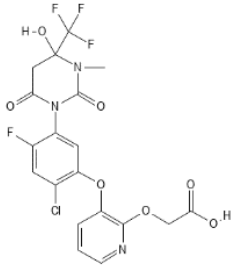
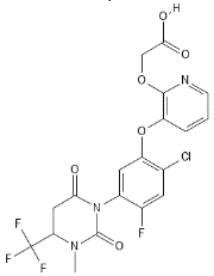
Plant studies	
Residue definition for enforcement **Primary crops: Canola, Corn, and Soybean** **Rotational crops: Radish, kale, and wheat**	Epyrifenacil
Residue definition for risk assessment **Primary crops: Canola, Corn, and Soybean** **Rotational crops: Radish, kale, and wheat**	Epyrifenacil
Metabolic profile in diverse crops	The nature of the residue has been determined for epyrifenacil in pulses and oilseeds (canola, soybean) and cereal/grass crops (field corn) for preplant/preemergent and fall burndown applications.[1]
Animal studies	
Animals	**Ruminant and poultry**
Residue definition for enforcement	Epyrifenacil
Residue definition for risk assessment	Epyrifenacil
Metabolic profile in animals (goat, hen, rat)	Yes - goat, hen and rat show similar metabolic profiles.
Fat soluble residue	Yes[2]

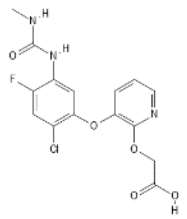
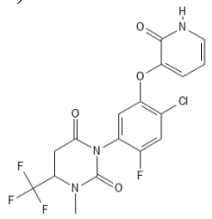
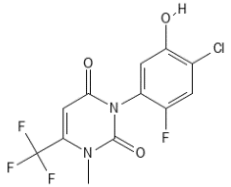
[1] The residue definition for plants may need to be revised if new uses are added in the future.
[2] Octanol/water partition coefficient log(K_{ow}) is 3.42.

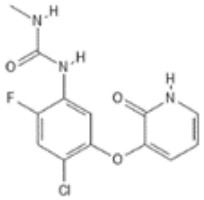
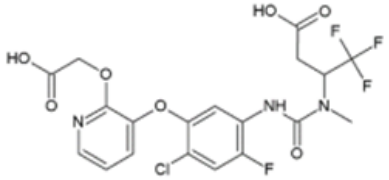
Dietary risk from food and drinking water			
Basic acute dietary exposure analysis, 95th percentile **ARfD = 0.02 mg/kg bw** **Estimated acute drinking water concentration = 0.0976 ppm**	**Population**	**Estimated risk % of acute reference dose (ARfD)**	
		Food alone	**Food and drinking water**
	Females 13–49 years	0.8	29.8
Basic chronic (non-cancer and cancer) dietary exposure analysis **ADI = 0.01 mg/kg bw/day** **Estimated chronic drinking water concentration = 0.112 ppm**	**Population**	**Estimated risk % of acceptable daily intake (ADI)**	
		Food alone	**Food and drinking water**
	General Population	1.1	20.8
	All infants (<1 year old)	1.6	75.3
	Children 1–2 years	5.2	32.4
	Children 3–5 years	3.2	25.3
	Children 6–12 years	1.9	18.3
	Youth 13–19 years	1.0	14.9
	Adults 20–49 years	0.7	20.3
	Adults 50+ years	0.6	19.7
	Females 13–49 years	0.7	20.0

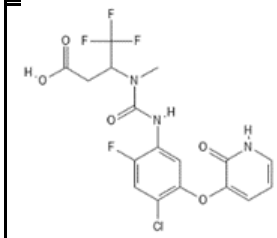
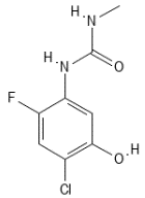
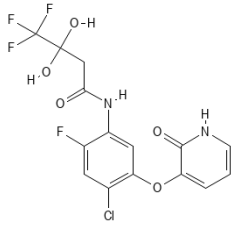
Table 14 Summary of the major transformation products of epyrifenacil in the environmental fate laboratory studies

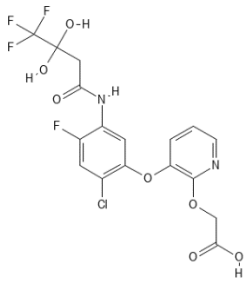
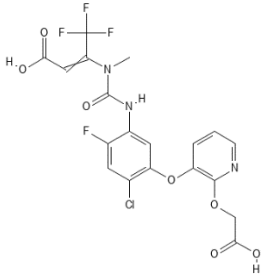
Major transformation product (TP)[1]	Maximum mean concentration reached in the environmental fate laboratory studies[2]
Major TP 1: S-3100-CA **IUPAC Name:** 2-[3-[2-chloro-4-fluoro-5-[3-methyl-2,6-dioxo-4-(trifluoromethyl)pyrimidin-1-yl]phenoxy]pyridin-2-yl]oxyacetic acid(3-{2-chloro-4-fluoro-5-[1,2,3,6-tetrahydro-3-methyl2,6-dioxo-4-(trifluoromethyl)pyrimidin-1-yl] phenoxy}pyridin-2-yloxy)acetic acid  $C_{19}H_{12}ClF_4N_3O_6$ Molecular weight (MW): 489.77 g/mol	Hydrolysis: **40.3% AR**[3] Phototransformation on soil: N/A Aqueous phototransformation: **28.1% AR**[3] **(irradiated); 94.1% AR (dark)** Aerobic biotransformation in soil: **93.7% AR** Anaerobic biotransformation in soil: **88.2% AR** Aerobic aquatic biotransformation: **94.5% AR**[3] Anaerobic aquatic biotransformation: **97.6% AR**
Major TP 2: S-3100-DA **IUPAC Name**: 3-[4-chloro-2-fluoro-5-[(2-oxo-1H-pyridin-3-yl)oxy]phenyl]-1-methyl-6-(trifluoromethyl)pyrimidine-2,4-dione  $C_{17}H_{10}ClF_4N_3O_4$ MW 431.73 g/mol	Hydrolysis: Not detected Phototransformation on soil: N/A Aqueous phototransformation: Not included in the chemical analysis Aerobic biotransformation in soil: **28.2% AR** Anaerobic biotransformation in soil: ~1% AR Aerobic aquatic biotransformation: **24.6% AR**[3] Anaerobic aquatic biotransformation: **27.3% AR**

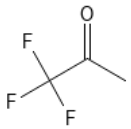
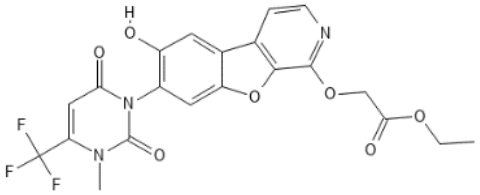
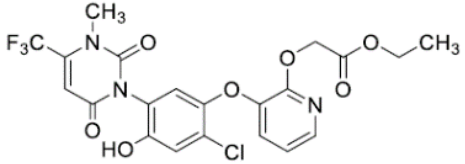
Major transformation product (TP)[1]	Maximum mean concentration reached in the environmental fate laboratory studies[2]
Major TP 3: 4"-OH-S-3100-CA **IUPAC Name**: (3-{2-chloro-4-fluoro-5-[1,2,3,4,5,6-hexahydro-4-hydroxy-3-methyl-2,6-dioxo-4-(trifluoromethyl)pyrimidin-1-yl]phenoxy}pyridine-2-yloxy)acetic acid  $C_{19}H_{14}ClF_4N_3O_7$ MW 507.79 g/mol	Hydrolysis: **14.6% AR**[4] Phototransformation on dry soil: N/A Aqueous phototransformation: Not included in the chemical analysis Aerobic biotransformation in soil: **23.1% AR** Anaerobic biotransformation in soil: <1 % AR Aerobic aquatic biotransformation: 5.00% AR Anaerobic aquatic biotransformation: 1.7% AR[5]
Major TP 4: S-3100-CA-RD **IUPAC Name:** (3-{2-chloro-4-fluoro-5-[1,2,3,4,5,6-hexahydro-3-methyl-2,6-dioxo-4-(trifluoromethyl)pyrimidin-1-yl]phenoxy}pyridine-2-yloxy)acetic acid  $C_{19}H_{14}ClF_4N_3O_6$ MW 491.79 g/mol	Hydrolysis: Not detected Phototransformation on dry soil: N/A Aqueous phototransformation : Not included in the chemical analysis Aerobic biotransformation in soil: **42.3% AR** Anaerobic biotransformation in soil: Not detected Aerobic aquatic biotransformation: **16.1% AR**[4] Anaerobic aquatic biotransformation: **13.1% AR**[3]
Major TP 5: S-3100-CA-UR **IUPAC Name:** {3-[2-chloro-4-fluoro-5-(3-methylureido)phenoxy] pyridin-2-yloxy}acetic acid	Hydrolysis: **61.4% AR**[4] Phototransformation on soil : N/A Aqueous phototransformation : Not included in the chemical analysis Aerobic biotransformation in soil: **21.4% AR**

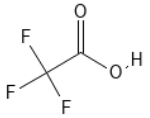
Major transformation product (TP)[1]	Maximum mean concentration reached in the environmental fate laboratory studies[2]
 $C_{15}H_{13}ClFN_3O_5$ MW 369.74 g/mol	Anaerobic biotransformation in soil: **61.9% AR** Aerobic aquatic biotransformation: **48.2% AR** Anaerobic aquatic biotransformation: **66.4% AR**[5]
Major TP 6: S-3100-DA-RD IUPAC Name: 3-[4-chloro-5-(1,2-dihydro-2-oxpyridin-3-yloxy)-2-fluorophenyl]-1,2,3,4,5,6-hexahydro-1-methyl-6-(trifluoromethyl)pyrimidine-2,4-dione  $C_{17}H_{12}ClF_4N_3O_4$ MW 433.75 g/mol	Hydrolysis: Not detected Phototransformation on soil : N/A Aqueous phototransformation : Not included in the chemical analysis Aerobic biotransformation in soil: **53.7% AR** Anaerobic biotransformation in soil: 1.9% AR Aerobic aquatic biotransformation: **27.9% AR** Anaerobic aquatic biotransformation: 3.55% AR[4]
Major TP 7: S-3100-DP **IUPAC Name:** 3-(4-chloro-2-fluoro-5-hydroxyphenyl)-1-methyl-6-(trifluoromethyl)pyrimidine2,4(1H,3H)-dione  $C_{12}H_7ClF_4N_2O_3$ MW 338.65 g/mol	Hydrolysis: Not included in the chemical analysis Phototransformation on dry soil: N/A Aqueous phototransformation : Not measured above the limit of quantitation Aerobic biotransformation in soil: **10.5% AR** Anaerobic biotransformation in soil: <1% AR Aerobic aquatic biotransformation**: 9.61% AR (10.7% AR in one replicate)** Anaerobic aquatic biotransformation: <1% AR

Major transformation product (TP)[1]	Maximum mean concentration reached in the environmental fate laboratory studies[2]
Major TP 8: S-3100-DA-UR **IUPAC Name:** 1-[4-chloro-2-fluoro-5-[(2-oxo-1H-pyridin-3-yl)oxy]phenyl]-3-methyl-urea  $C_{13}H_{11}ClFN_3O_3$ MW: 311.7 g/mol	Hydrolysis: Not included in the chemical analysis Phototransformation on soil: N/A Aqueous phototransformation: Not included in the chemical analysis Aerobic biotransformation in soil: 4.95% AR Anaerobic biotransformation in soil: 1.2% AR Aerobic aquatic biotransformation: **49.3% AR** Anaerobic aquatic biotransformation: **55.7% AR**[4]
Major TP 9: S-3100-CA-RD-RO **IUPAC Name:** 3-{[(5-{[2-(carboxymethoxy)pyridin-3-yl]oxy}-4- chloro-2-fluorophenyl)carbamoyl](methyl)amino}- 4,4,4-trifluorobutanoic acid  $C_{19}H_{16}ClF_4N_3O_7$ MW: 509.80 g/mol	Hydrolysis: Not included in the chemical analysis Phototransformation on soil: N/A Aqueous phototransformation: Not included in the chemical analysis Aerobic biotransformation in soil: Not included in the chemical analysis Anaerobic biotransformation in soil: **8.33% AR (max. 10.2% in one replicate)** Aerobic aquatic biotransformation: Not included in the chemical analysis Anaerobic aquatic biotransformation: 4.59% AR[3]
Major TP 10: S-3100-DA-RD-RO **IUPAC Name:** 3-(3-(4-chloro-2-fluoro-5-((2-oxo-1,2-dihydropyridin-3-yl)oxy)phenyl)-1-methylureido)-4,4,4-trifluorobutanoic acid	Hydrolysis: Not included in the chemical analysis Phototransformation on soil: N/A Aqueous phototransformation: Not included in the chemical analysis Aerobic biotransformation in soil: Not included in the chemical analysis Anaerobic biotransformation in soil: Not included in the chemical analysis

Major transformation product (TP)[1]	Maximum mean concentration reached in the environmental fate laboratory studies[2]
 $C_{17}H_{14}ClF_4N_3O_5$ MW: 451.76 g/mol	Aerobic aquatic biotransformation: Not included in the chemical analysis Anaerobic aquatic biotransformation: **16.2% AR**[4]
Major TP 11: S-3100-DP-UR **IUPAC Name:** 1-(4-chloro-2-fluoro-5-hydroxyphenyl)-3-methylurea  $C_8H_8ClFN_2O_2$ MW: 218.62 g/mol	Hydrolysis: Not included in the chemical analysis Phototransformation on soil: N/A Aqueous phototransformation: Not included in the chemical analysis Aerobic biotransformation in soil: Not included in the chemical analysis Anaerobic biotransformation in soil: Not included in the chemical analysis Aerobic aquatic biotransformation: Not included in the chemical analysis Anaerobic aquatic biotransformation: **23.5% AR**[4]
Major TP 12: S-3100-DA-RO1 **IUPAC Name:** not provided  $C_{15}H_{11}ClF_4N_2O_5$ MW: 410.71 g/mol	Hydrolysis: Not included in the chemical analysis Phototransformation on soil: N/A Aqueous phototransformation: Not included in the chemical analysis Aerobic biotransformation in soil: Not included in the chemical analysis Anaerobic biotransformation in soil: Not included in the chemical analysis Aerobic aquatic biotransformation: Not included in the chemical analysis Anaerobic aquatic biotransformation: **10.6% AR**[4]

Major transformation product (TP)[1]	Maximum mean concentration reached in the environmental fate laboratory studies[2]
Major TP 13: S-3100-CA-RO1 **IUPAC Name:** {3-[2-chloro-4-fluoro-5-(4,4,4-trifluoro-3,3-dihydroxy-butanamido)phenoxy]pyridin-2-yloxy}acetic acid  $C_{17}H_{13}ClF_4N_2O_7$ MW: 468.75 g/mol	Hydrolysis: **16.8% AR**[4] Phototransformation on soil: N/A Aqueous phototransformation: Not included in the chemical analysis Aerobic biotransformation in soil: Not included in the chemical analysis Anaerobic biotransformation in soil: **13.5% AR** Aerobic aquatic biotransformation: Not included in the chemical analysis Anaerobic aquatic biotransformation: Not included in the chemical analysis
Major TP 14: S-3100-CA-RO2 **IUPAC Name:** (E)-3-(3-(5-((2-(carboxymethoxy)pyridin-3-yl)oxy)-4-chloro-2-fluorophenyl)-1-methylureido)-4,4,4-trifluorobut-2-enoic acid  $C_{19}H_{14}ClF_4N_3O_7$ MW: 507.79 g/mol	Hydrolysis: **14.6% AR**[3] Phototransformation on soil: N/A Aqueous phototransformation: Not included in the chemical analysis Aerobic biotransformation in soil: Not included in the chemical analysis Anaerobic biotransformation in soil: Not included in the chemical analysis Aerobic aquatic biotransformation: Not included in the chemical analysis Anaerobic aquatic biotransformation: Not included in the chemical analysis
Major TP 15: 1,1,1-trifluoroacetone **IUPAC Name:** 1,1,1-trifluoropropan-2-one	Hydrolysis: **58.9% AR**[3] Phototransformation on soil: N/A Aqueous phototransformation: Not included in the chemical analysis

Major transformation product (TP)[1]	Maximum mean concentration reached in the environmental fate laboratory studies[2]
 $C_3H_3F_3O$ MW: 112.05 g/mol	Aerobic biotransformation in soil: Not included in the chemical analysis Anaerobic biotransformation in soil: **12.1% AR** Aerobic aquatic biotransformation: **11.2% AR** Anaerobic aquatic biotransformation: **26.9% AR**[3]
Major TP 16: S-3100-BFP **IUPAC Name:** ethyl 2-((6-hydroxy-7-(3-methyl-2,6-dioxo-4-(trifluoromethyl)-3,6-dihydropyrimidin-1(2H)-yl)benzofuro[2,3-c]pyridin-1-yl)oxy)acetate  $C_{21}H_{16}F_3N_3O_7$ MW: 479.37 g/mol	Hydrolysis: Not included in the chemical analysis Phototransformation on soil : N/A Aqueous phototransformation: **19.2% AR** (irradiated); not detected (dark) Aerobic biotransformation in soil: Not included in the chemical analysis Anaerobic biotransformation in soil: Not included in the chemical analysis Aerobic aquatic biotransformation: Not included in the chemical analysis Anaerobic aquatic biotransformation: Not included in the chemical analysis
Major TP 17: 4'-OH-S-3100 **IUPAC Name:** ethyl 2-((3-(2-chloro-4-hydroxy-5-(3-methyl-2,6-dioxo-4-(trifluoromethyl)-3,6-dihydropyrimidin-1(2H)-yl)phenoxy)pyridin-2-yl)oxy)acetate  $C_{21}H_{17}ClF_3N_3O_7$ MW: 515.83 g/mol	Hydrolysis: Not included in the chemical analysis Phototransformation on soil : N/A Aqueous phototransformation: **12.0% AR (irradiated)**; not detected (dark) Aerobic biotransformation in soil: Not included in the chemical analysis Anaerobic biotransformation in soil: Not included in the chemical analysis Aerobic aquatic biotransformation: Not detected Anaerobic aquatic biotransformation: Not included in the chemical analysis

Major transformation product (TP)[1]	Maximum mean concentration reached in the environmental fate laboratory studies[2]
Major TP 18: Trifluoroacetic acid (TFA) **IUPAC Name:** 2,2,2-trifluoroacetic acid  $C_2HF_3O_2$ MW: 114.02 g/mol	Hydrolysis: Not included in the chemical analysis Phototransformation on soil: N/A Aqueous phototransformation: Not included in the chemical analysis Aerobic biotransformation in soil: Not included in the chemical analysis Anaerobic biotransformation in soil: Not included in the chemical analysis Aerobic aquatic biotransformation: **27.7% AR** Anaerobic aquatic biotransformation: **29.9% AR**[3]

>10% bolded

N/A – Not applicable, because this is not a significant transformation pathway for epyrifenacil

(1) The environmental fate studies used ^{14}C-epyrifenacil, with radiolabels on the phenyl, pyridyl and pyrimidinyl rings of the molecule.

(2) The maximum mean concentration of data from all available radiolabels is presented, unless otherwise indicated. When differences in test conditions or sampling intervals made averaging the radiolabels inappropriate, the mean of a single radiolabel is presented.

(3) Mean of the pyrimidinyl-labelled samples presented.

(4) Mean of the phenyl-labelled samples presented.

(5) Mean of the pyridyl-labelled samples presented.

Table 15 Fate and behaviour of epyrifenacil and its transformation products in the environment

Property	Test substance	Medium/Test conditions	Value	Kinetic Model	Major transformation products[1]	Comments	PMRA No.
Abiotic transformation							
Hydrolysis	Epyrifenacil (phenyl and pyrimidinyl rings ^{14}C-labelled)	pH 4, 50°C	Stable	N/A	S-3100-CA S-3100-CA-UR 4"-OH-S-3100-CA S-3100-CA-RO1 S-3100-CA-RO2	Hydrolysis of epyrifenacil is temperature- and pH-dependent. It is an important route of dissipation under alkaline conditions but less so under	3308407 3308408
		pH 7, 15°C	t_R/DT_{50} = 141 d	SFO			
		pH 7, 25°C	t_R/DT_{50} = 46.4 d	SFO			
		pH 7, 50°C	t_R/DT_{50} = 1.8 d	SFO			
		pH 9, 15°C	t_R/DT_{50} = 0.65 d	SFO			
		pH 9, 25°C	t_R/DT_{50} = 0.28 d	SFO			

Property	Test substance	Medium/Test conditions	Value	Kinetic Model	Major transformation products[1]	Comments	PMRA No.
		pH 9, 50°C	t_R/DT_{50} = 0.02 d	SFO	1,1,1-trifluoroacetone	neutral and acidic conditions.	
	S-3100-CA (TP) (pyridyl ring ^{14}C-labelled)	pH 7, 25°C	t_R/DT_{50} = 214 d	SFO	S-3100-CA-UR	Hydrolysis is not expected to be an important route of dissipation for these TPs.	3308409
	S-3100-DA (TP) (phenyl ring ^{14}C-labelled)	pH 7, 25°C	t_R/DT_{50} = 143 d	SFO	S-3100-DA-UR		3308410
Phototransformation on soil	Epyrifenacil (all 3 rings ^{14}C-labelled)	Phototransformation on soil is a negligible process for epyrifenacil.					3308411
Phototransformation in water	Epyrifenacil (all 3 rings ^{14}C-labelled)	Aqueous pH 5 buffer solution, 25°C, irradiated	t_R/DT_{50} (summer sunlight equivalent at 40°N latitude) = 7.9 days	SFO	S-3100-BFP 4'-OH-S-3100 CO_2	Phototransformation in water can be a route of dissipation near the surface in water bodies exposed to sunlight.	3308412 3308413 3308414
Phototransformation in air	N/A – volatilization of epyrifenacil and its major TPs in the field is expected to be negligible.						
Biotransformation							
Biotransformation in aerobic soil (20°C)	Epyrifenacil	DU Barnes (loam, pH 5.1, 3.2% organic carbon (OC))	**Epyrifenacil** t_R = 0.79 days DT_{50} = 0.4 days	IORE	S-3100-CA S-3100-DA S-3100-CA-RD	Epyrifenacil is non-persistent in these soils while S-3100-CA is slightly persistent to persistent. S-	3308416

Property	Test substance	Medium/Test conditions	Value	Kinetic Model	Major transformation products[1]	Comments	PMRA No.
	(phenyl ring ^{14}C-labelled)		**S-3100-CA (TP)** t_R = 358 days DT_{50} = 276 days	DFOP	4"-OH-S-3100-CA	3100-CA-RD is persistent in the PD Lihen soil; its highest concentrations in the other soils were measured at the end of the studies. Sufficient data were not available to calculate degradation kinetics for the other major TPs.	
		IF Fayette (silt loam, pH 6.9, 2.3% OC)	**Epyrifenacil** t_R = 0.22 days DT_{50} = 0.11 days **S-3100-CA (TP)** t_R = 234 days DT_{50} = 47.7 days	IORE IORE	S-3100-CA S-3100-DA-RD S-3100-CA-RD S-3100-CA-UR		
		PD Lihen (loamy sand, pH 5.7, 0.57% OC)	**Epyrifenacil** t_R = 0.33 days DT_{50} = 0.19 days **S-3100-CA (TP)** t_R = 98.2 days DT_{50} = 37.5 days **S-3100-CA-RD (TP)** t_R/DT_{50}= 471 days	IORE IORE SFO	S-3100-CA S-3100-DA S-3100-DA-RD S-3100-CA-RD 4"-OH-S-3100-CA S-3100-DP		
	Epyrifenacil (all 3 rings ^{14}C-labelled)	MSL Gardena (sandy loam, pH 6.2–6.4, 2.2–3.1% OC)	**Epyrifenacil** t_R = 0.25 days DT_{50} = 0.14 days **S-3100-CA (TP)** t_R = 164 days DT_{50} = 56.4 days	IORE IORE	S-3100-CA S-3100-DA S-3100-DA-RD S-3100-CA-RD S-3100-CA-UR 4"-OH-S-3100-CA		3308416 3308417 3308418

Property	Test substance	Medium/Test conditions	Value	Kinetic Model	Major transformation products[1]	Comments	PMRA No.
	Epyrifenacil (phenyl and pyridyl rings ^{14}C-labelled)	Argissolo (clay, pH 5.6, 0.62% OC)	**Epyrifenacil** t_R = 0.12 days DT_{50} = 0.07 days **S-3100-CA** t_R = 180 days DT_{50} = 135 days	IORE DFOP	S-3100-CA S-3100-CA-RD S-3100-CA-UR	These are Brazilian soils which may not be relevant to Canada. As such, the results are for qualitative use only and supplement those from the American soils. Epyrifenacil is non-persistent in the tested soils. S-3100-CA is slightly persistent to moderately persistent in these soils. Sufficient data were not available to calculate degradation kinetics for the other major TPs.	3308419
		Gleissolo (sand, pH 5.0, 0.86% OC)	**Epyrifenacil** t_R = 1.1 days DT_{50} = 0.23 days **S-3100-CA** t_R/DT_{50} = 88.9 days	IORE SFO	S-3100-CA S-3100-CA-RD S-3100-CA-UR 4"-OH-S-3100-CA		
		Neossolo (clay, pH 4.0, 1.3% OC)	**Epyrifenacil** t_R = 0.24 days DT_{50} = 0.02 days **S-3100-CA** t_R/DT_{50} = 21.2 days	IORE SFO	S-3100-CA S-3100-DA-RD S-3100-CA-RD		
	Epyrifenacil (all 3 rings ^{14}C-labelled)	Latossolo (sandy loam, pH 4.9, 1.9% OC)	**Epyrifenacil** t_R = 0.83 days DT_{50} = 0.16 days **S-3100-CA** t_R/DT_{50} = 66.0 days	IORE SFO	S-3100-CA S-3100-DA S-3100-CA-RD S-3100-CA-UR 4"-OH-S-3100-CA		
	S-3100-CA (TP; pyridyl ring ^{14}C-labelled)	Illinois 1 (silty clay loam, pH 5.4, 3.2% OC)	t_R/DT_{50} = 18.4 days	SFO	S-3100-DA-RD S-3100-CA-RD 4"-OH-S-3100-CA	S-3100-CA is slightly to moderately persistent in the tested soils.	3308422

Property	Test substance	Medium/Test conditions	Value	Kinetic Model	Major transformation products[1]	Comments	PMRA No.
		Illinois 2 (silty clay, pH 6.0, 3.1% OC)	t_R = 101 days DT_{50} = 70 days	DFOP	S-3100-CA-RD 4"-OH-S-3100-CA S-3100-DA		
		Iowa-Fayette (silt loam, pH 6.7, 2.6% OC)	t_R = 79.9 days DT_{50} = 29.3 days	DFOP	S-3100-CA-RD S-3100-CA-UR		
		JJ-SL-PF (sandy loam, pH 4.7, 1.1% OC)	t_R = 108 days DT_{50} = 51.8 days	DFOP	S-3100-CA-RD 4"-OH-S-3100-CA S-3100-CA-UR S-3100-DA		
		MSL (sandy clay loam, pH 6.0, 3.2% OC)	t_R/DT_{50} = 33.5 days	SFO	S-3100-CA-RD 4"-OH-S-3100-CA		
	S-3100-DA (TP; phenyl ring ^{14}C labelled)	DU-L Barnes (sandy clay loam, pH 5.7, 3.0% OC)	t_R = 835 days DT_{50} = 663 days	DFOP	None	S-3100-DA is moderately persistent to persistent in the tested soils. The rate of transformation may have been reduced due to decreasing microbial activity during the test.	3308420
		PD Lihen (loamy sand, pH 6.5, 0.68% OC)	t_R = 3659 days DT_{50} = 1515 days	DFOP	S-3100-DA-RD		
		Iowa-Fayette (silt loam, pH 7.2, 2.4% OC)	t_R = 106 days DT_{50} = 58.5 days	DFOP	S-3100-DA-RD S-3100-DP		
	4"-OH-S-3100-CA (TP, pyridyl ring ^{14}C labelled)	Illinois 2 (silty clay, pH 6.0, 3.1% OC)	t_R/DT_{50} = 4.2 days	SFO	S-3100-CA-UR	4"-OH-S-3100-CA is non-persistent in the tested soils.	3308421
		Iowa-Fayette (silt loam, pH 6.7, 2.6% OC)	t_R/DT_{50} = 1.7 days	SFO	S-3100-CA-UR S-3100-DA-UR		

Property	Test substance	Medium/Test conditions	Value	Kinetic Model	Major transformation products[1]	Comments	PMRA No.
		JJ-SL-PF (sandy loam, US, pH 4.7, 1.1% OC)	Not calculated due to high variability between replicates and poor model fit		S-3100-CA-UR		
	S-3100-CA-RD (TP, pyridyl ring ^{14}C labelled)	Illinois 1 (silt loam, pH 5.2, 1.9% OC)	t_R = 231 days DT_{50} = 185 days	DFOP	S-3100-DA-RD	S-3100-CA-RD is slightly persistent to persistent in the tested soils.	3308425
		Iowa-Fayette (silt loam, pH 6.8, 2.8% OC)	t_R = 28.4 days DT_{50} = 24.5 days	IORE	S-3100-DA-RD CO_2		
		MSL (sandy clay loam, pH 6.1, 2.7% OC)	t_R = 150 days DT_{50} = 82.7 days	DFOP	S-3100-DA-RD		
	S-3100-CA-UR (TP, pyridyl ring ^{14}C labelled)	Illinois 1 (silt loam, pH 5.2, 1.9% OC)	t_R = 1147 days DT_{50}= 943 days	DFOP	S-3100-DA-UR	S-3100-CA-UR is persistent in the tested soils.	3308424
		Iowa-Fayette (silt loam, pH 6.8, 2.8% OC)	t_R = 776 days DT_{50} = 578 days	DFOP	S-3100-DA-UR		
		MSL (sandy clay loam, pH 6.1, 2.7% OC)	t_R = 8710 days DT_{50} = 6207 days	DFOP	S-3100-DA-UR		
	S-3100-DA-RD (TP, pyridyl ring ^{14}C labelled)	Illinois 1 (silt loam, pH 5.2, 1.9% OC)	t_R/DT_{50}: 481 days	SFO	None	S-3100-DA-RD is persistent in the tested soils.	3308423
		Iowa-Fayette (silt loam, pH 6.8, 2.8% OC)	t_R = 398 days DT_{50} = 357 days	DFOP	None		

Property	Test substance	Medium/Test conditions	Value	Kinetic Model	Major transformation products[1]	Comments	PMRA No.
		MSL (sandy clay loam, pH 6.1, 2.7% OC)	t_R = 832 days DT_{50} = 718 days	DFOP	None		
	S-3100-DP (TP, phenyl ring ^{14}C labelled)	New York (sandy loam, pH 6.1, 2.0% OC)	t_R = 90.0 days DT_{50} = 15.1 days	IORE	Several major TPs were observed in the study but were not identified because S-3100-DP was measured at 10.5% AR in only one epyrifenacil-treated soil and was measured at <2% AR in the other six tested soils. Significant environmental exposure to the TPs of S-3100-DP is not expected.	S-3100-DP is non-persistent to moderately persistent in the tested soils.	3308426
		Norfolk (sandy loam, pH 6.0, 0.63% OC)	t_R = 120 days DT_{50} = 48.2 days	DFOP			
		Washington (sandy loam, pH 7.0, 1.0% OC)	t_R = 15.3 days DT_{50} = 7.2 days	IORE			
Biotransformation in anaerobic soil (20°C; total system)	Epyrifenacil (phenyl ring ^{14}C labelled)	Illinois 2 (silty clay, US, pH 6.0, 3.1% OC)	**Epyrifenacil** t_R = 0.36 days DT_{50} = 0.04 days **S-3100-CA** t_R/DT_{50} = 48.9 days	IORE SFO	S-3100-CA S-3100-CA-UR S-3100-CA-RO1	Epyrifenacil is non-persistent in the tested anaerobic soils while S-3100-CA is slightly to moderately persistent. Sufficient data to calculate the rate of dissipation for	3308427
		Iowa-Fayette (silt loam, pH 6.7, 2.6% OC)	**Epyrifenacil** t_R = 0.18 days DT_{50} = 0.02 days	IORE	S-3100-CA S-3100-CA-UR S-3100-CA-RO1		

Property	Test substance	Medium/Test conditions	Value	Kinetic Model	Major transformation products[1]	Comments	PMRA No.
			S-3100-CA t_R/DT_{50} = 30.5 days	SFO		the other major TPs are not available.	
		JJ-SL-PF (sandy loam, pH 4.7, 1.1% OC)	**Epyrifenacil** t_R = 1.23 days DT_{50} = 0.07 days **S-3100-CA** t_R/DT_{50} = 30.5 days	IORE SFO	S-3100-CA S-3100-CA-UR S-3100-CA-RO1		
	Epyrifenacil (all 3 rings ^{14}C labelled)	MSL (sandy clay loam, pH 6.0, 3.2% OC)	**Epyrifenacil** t_R = 0.20 days DT_{50} = 0.02 days **S-3100-CA** t_R/DT_{50} = 48.2 days	IORE SFO	S-3100-CA S-3100-CA-UR S-3100-CA-RD-RO S-3100-CA-RO1 1,1,1-trifluoroacetone		3308428
Biotransformation in aerobic water sediment (20°C; total system)	Epyrifenacil (all 3 rings ^{14}C labelled)	Goose River (water: pH at initiation = 7.2-8.4; sediment: loam, pH (0.01 M $CaCl_2$) = 7.8-8.0, 3.1-4.5% OC)	**Epyrifenacil** t_R/DT_{50} = 1.7 to 2.5 days **S-3100-CA** t_R = 27.9 to 39.7 days DT_{50} = 23.2 to 39.7 days **S-3100-CA-UR** t_R/DT_{50} = 141 to 185 days	SFO SFO and IORE SFO	S-3100-CA S-3100-CA-UR S-3100-DA-RD S-3100-DA S-3100-DA-UR TFA 1,1,1-trifluoroacetone Unidentified TP3 CO_2	Epyrifenacil is non-persistent in the tested aerobic systems while S-3100-CA is slightly to moderately persistent and S-3100-CA-UR is to persistent. Degradation kinetics were calculated separately for each radiolabel due to variations in the test systems.	3309611 3309612 3309613

Property	Test substance	Medium/Test conditions	Value	Kinetic Model	Major transformation products[1]	Comments	PMRA No.
		Weweantic River (water: pH at initiation = 6.01-6.5; Sediment: sand, pH (0.01 M $CaCl_2$) = 5.1-5.2, 0.83-0.91% OC)	**Epyrifenacil** t_R/DT_{50} = 2.8 to 3.2 days **S-3100-CA** t_R = 186 to 351 days DT_{50} = 58.3 to 120 days **S-3100-CA-UR** t_R/DT_{50} = 258 to 292 days	SFO DFOP SFO	S-3100-CA S-3100-CA-UR S-3100-DA-RD S-3100-DA S-3100-DA-UR S-3100-CA-RD TFA S-3100-DP		
Biotransformation in anaerobic water-sediment (20°C, total system)	Epyrifenacil (all 3 rings ^{14}C labelled)	Taunton River (water: pH 7.0-7,2; sediment: silt loam, pH (0.01 M $CaCl_2$) = 4.9–5.4, 3.2–3.6% OC)	**Epyrifenacil** t_R/DT_{50} = 4.0 days **S-3100-CA** t_R/DT_{50} = 47.7 days	SFO SFO	S-3100-CA S-3100-DA-RO1 TFA 1,1,1-trifluoroacetone S-3100-CA-UR S-3100-DA-UR S-3100-DA S-3100-DA-RD-RO Unidentified TP3	Epyrifenacil is non-persistent in the tested anaerobic systems while S-3100-CA is non-persistent to moderately persistent.	3309614 3309615
		Golden Lake (water: pH 8.3 – 8.71; sediment: loamy sand, pH (0.01 M $CaCl_2$) = 7.5 - 8.1,	**Epyrifenacil** t_R = 1.5 days DT_{50} = 0.98 days **S-3100-CA** t_R/DT_{50} = 11.6 days	IORE SFO	S-3100-CA S-3100-CA-RD S-3100-DA-RO1 TFA 1,1,1-trifluoroacetone S-3100-CA-UR		

Property	Test substance	Medium/Test conditions	Value	Kinetic Model	Major transformation products[1]	Comments	PMRA No.
		0.76 -0.94% OC)			S-3100-DA-UR S-3100-DP-UR Unknown C (tautomerisation of S-3100-DA-UR/S-3100-DP-UR) CO_2		
Mobility							
Adsorption/ desorption	Epyrifenacil	DU loam, US (pH 5.6, 3.2% OC)	K_F: 6.6 L/kg K_{FOC}: 207 L/kg 1/n: 0.94 K_d: 7.3 L/kg K_{OC}: 229 L/kg	N/A	N/A	Moderate mobility	3309617
		IF silt loam, US (pH 7.2, 2.3% OC)	K_F: 3.4 L/kg K_{FOC}: 147 L/kg 1/n: 0.92 K_d: 4.2 L/kg K_{OC}: 184 L/kg	N/A	N/A	Moderate mobility	
		MSL sandy loam, US (pH 6.8, 2.2% OC)	K_F: 3.6 L/kg K_{FOC}: 165 L/kg 1/n: 0.88 K_d: 5.3 L/kg K_{OC}: 241 L/kg	N/A	N/A	Moderate mobility	
		MT Clay, US (pH 8.0, 0.87% OC)	K_F: 2.0 L/kg K_{FOC}: 225 L/kg 1/n: 0.98 K_d: 1.9 L/kg K_{OC}: 224 L/kg	N/A	N/A	Moderate mobility	

Property	Test substance	Medium/Test conditions	Value	Kinetic Model	Major transformation products[1]	Comments	PMRA No.
		PD loamy sand, US (pH 6.3, 0.57% OC)	K_F: 1.3 L/kg K_{FOC}: 234 L/kg 1/n: 0.95 K_d: 1.4 L/kg K_{OC}: 254 L/kg	N/A	N/A	High mobility	
		Taunton River loam sediment, US (pH 5.9, 5.6% OC)	K_F: 22.9 L/kg K_{FOC}: 408 L/kg 1/n: 0.97 K_d: 24 L/kg K_{OC}: 428 L/kg	N/A	N/A	Moderate mobility	
		Argissolo clay, Brazil (pH 6.0, 0.62% OC)	K_F: 1.3 L/kg K_{FOC}: 208 L/kg 1/n: 0.94 K_d: 1.4 L/kg K_{OC}: 224 L/kg	N/A	N/A	These are tropical soils that may not be relevant to Canada. The results from these soils are for qualitative use only and supplement those from American soils reported above. Epyrifenacil has moderate to high mobility in soil.	3309618
		Gleissolo sand, Brazil (pH 5.6, 0.86% OC)	K_F: 3.4 L/kg K_{FOC}: 401 L/kg 1/n: 0.96 K_d: 3.6 L/kg K_{OC}: 416 L/kg	N/A	N/A		
		Neossolo clay, Brazil (pH 4.4, 1.3% OC)	K_F: 1.7 L/kg K_{FOC}: 129 L/kg 1/n: 0.95 K_d: 1.8 L/kg K_{OC}: 135 L/kg	N/A	N/A		
		Latossolo sandy loam, Brazil (pH pH 5.4, 1.9% OC)	K_F: 4.7 L/kg K_{FOC}: 248 L/kg 1/n: 0.96 K_d: 5.0 L/kg K_{OC}: 261 L/kg	N/A	N/A		

Property	Test substance	Medium/Test conditions	Value	Kinetic Model	Major transformation products[1]	Comments	PMRA No.
	S-3100-CA (TP)	DU loam, US (pH 5.6, 3.2% OC)	K_F: 2.4 L/kg K_{FOC}: 74 L/kg 1/n: 0.93 K_d: 2.5 L/kg K_{OC}: 78 L/kg	N/A	N/A	High mobility	3309616
		IF silt loam, US (pH 7.2, 2.3% OC)	K_F: 0.87 L/kg K_{FOC}: 38 L/kg 1/n: 0.90 K_d: 0.94 L/kg K_{OC}: 41 L/kg	N/A	N/A	Very high mobility	
		MSL sandy loam, US (pH 6.8, 2.2% OC)	K_F: 1.2 L/kg K_{FOC}: 55 L/kg 1/n: 0.91 K_d: 1.3 L/kg K_{OC}: 59 L/kg	N/A	N/A	High mobility	
		MT Clay, US (pH 8.0, 0.87% OC)	K_F: 0.2 L/kg K_{FOC}: 23 L/kg 1/n: 0.95 K_d: 0.21 L/kg K_{OC}: 24 L/kg	N/A	N/A	Very high mobility	
		PD loamy sand, US (pH 6.3, 0.57% OC)	K_F: 0.3 L/kg K_{FOC}: 53 L/kg 1/n: 0.93 K_d: 0.31 L/kg K_{OC}: 55 L/kg	N/A	N/A	High mobility	
		Taunton River loam sediment, US (pH 5.9, 5.6% OC)	K_F: 7.1 L/kg K_{FOC}: 127 L/kg 1/n: 0.94 K_d: 7.6 L/kg K_{OC}: 135 L/kg	N/A	N/A	High mobility	

Property	Test substance	Medium/Test conditions	Value	Kinetic Model	Major transformation products[1]	Comments	PMRA No.
	S-3100-DA (TP)	Barnes DU-L sandy clay loam, US (pH 5.7, 3.0% OC)	K_F: 4.5 L/kg K_{FOC}: 152 L/kg 1/n: 0.86 K_d: 5.1 L/kg K_{OC}: 169 L/kg	N/A	N/A	Moderate mobility	3309625
		Fayette IF silt loam, US (pH 7.2, 2.4% OC)	K_F: 2.2 L/kg K_{FOC}: 90 L/kg 1/n: 0.87 K_d: 2.4 L/kg K_{OC}: 101 L/kg	N/A	N/A	High mobility	
		Gardena (MSL-PF) sandy clay loam, US (pH 6.7, 2.3% OC)	K_F: 3.4 L/kg K_{FOC}: 148 L/kg 1/n: 0.86 K_d: 3.8 L/kg K_{OC}: 163 L/kg	N/A	N/A	Moderate mobility	
		Marias (MT) Clay, US (pH 8.1, 0.93% OC)	K_F: 0.72 L/kg K_{FOC}: 77 L/kg 1/n: 0.93 K_d: 0.74 L/kg K_{OC}: 80 L/kg	N/A	N/A	High mobility	
		Lihen (PD) loamy sand, US (pH 6.5, 0.68% OC)	K_F: 1.0 L/kg K_{FOC}: 153 L/kg 1/n: 0.92 K_d: 1.1 L/kg K_{OC}: 164 L/kg	N/A	N/A	Moderate mobility	
	4"-OH-S-3100-CA (TP)	Barnes (DU-L) sandy clay loam, US (pH 5.7, 3.0% OC)	K_F: 2.8 L/kg K_{FOC}: 94 L/kg 1/n: 0.91 K_d: 3.1 L/kg K_{OC}: 102 L/kg	N/A	N/A	High mobility	3309627

Property	Test substance	Medium/Test conditions	Value	Kinetic Model	Major transformation products[1]	Comments	PMRA No.
		Lihen (PD) loamy sand, US (pH 6.5, 0.68% OC)	K_F: 0.52 L/kg K_{FOC}: 76 L/kg 1/n: 0.96 K_d: 0.52 L/kg K_{OC}: 76 L/kg	N/A	N/A	High mobility	
	S-3100-CA-RD (TP)	Illinois silt loam, US (pH 5.7, 1.9% OC)	K_F: 1.1 L/kg K_{FOC}: 56 L/kg 1/n: 0.82 K_d: 1.2 L/kg K_{OC}: 66 L/kg	N/A	N/A	High mobility	3309620
		Iowa-Fayette silt loam, US (pH 7.1, 2.8% OC)	K_F: 1.1 L/kg K_{FOC}: 40 L/kg 1/n: 0.88 K_d: 1.3 L/kg K_{OC}: 45 L/kg	N/A	N/A	Very high mobility	
		M-SL-PF sandy clay loam, US (pH 6.6, 2.7% OC)	K_F: 1.6 L/kg K_{FOC}: 61 L/kg 1/n: 0.87 K_d: 1.9 L/kg K_{OC}: 71 L/kg	N/A	N/A	High mobility	
	S-3100-CA-UR (TP)	Illinois silt loam, US (pH 5.7, 1.9% OC)	K_F: 4.0 L/kg K_{FOC}: 209 L/kg 1/n: 0.86 K_d: 4.9 L/kg K_{OC}: 259 L/kg	N/A	N/A	Moderate mobility	3309622
		Iowa-Fayette silt loam, US (pH 7.1, 2.8% OC)	K_F: 3.2 L/kg K_{FOC}: 116 L/kg 1/n: 0.84 K_d: 4.1 L/kg K_{OC}: 146 L/kg	N/A	N/A	High mobility	

Property	Test substance	Medium/Test conditions	Value	Kinetic Model	Major transformation products[1]	Comments	PMRA No.
		M-SL-PF sandy clay loam, US (pH 6.6, 2.7% OC)	K_F: 6.5 L/kg K_{FOC}: 242 L/kg 1/n: 0.83 K_d: 8.0 L/kg K_{OC}: 297 L/kg	N/A	N/A	Moderate mobility	
	S-3100-DA-RD (TP)	Illinois silt loam, US (pH 5.7, 1.9% OC)	K_F: 2.9 L/kg K_{FOC}: 152 L/kg 1/n: 0.88 K_d: 3.2 L/kg K_{OC}: 165 L/kg	N/A	N/A	Moderate mobility	3309623
		Iowa-Fayette silt loam, US (pH 7.1, 2.8% OC)	K_F: 3.6 L/kg K_{FOC}: 130 L/kg 1/n: 0.88 K_d: 4.3 L/kg K_{OC}: 152 L/kg	N/A	N/A	Moderate mobility	
		M-SL-PF sandy clay loam, US (pH 6.6, 2.7% OC)	K_F: 5.3 L/kg K_{FOC}: 195 L/kg 1/n: 0.86 K_d: 6.1 L/kg K_{OC}: 226 L/kg	N/A	N/A	Moderate mobility	
	S-3100-DP (TP)	New York sandy loam, US (pH 6.6, 2.0% OC)	K_F: 1.1 L/kg K_{FOC}: 56 L/kg 1/n: 0.94 K_d: 1.1 L/kg K_{OC}: 57 L/kg	N/A	N/A	High mobility	3309624
		Norfolk sandy loam, US (pH 6.4, 0.63% OC)	K_F: 0.52 L/kg K_{FOC}: 82 L/kg 1/n: 0.87 K_d: 0.57 L/kg K_{OC}: 91 L/kg	N/A	N/A	High mobility	

Property	Test substance	Medium/Test conditions	Value	Kinetic Model	Major transformation products[1]	Comments	PMRA No.
		Washington sandy loam, US (pH 7.5, 1.0% OC)	K_F: 0.57 L/kg K_{FOC}: 57 L/kg 1/n: 0.86 K_d: 0.62 L/kg K_{OC}: 62 L/kg	N/A	N/A	High mobility	
Soil leaching	A soil column leaching study for epyrifenacil on Brazilian soils was submitted but not reviewed because tropical soils may not be relevant to Canada. An acceptable adsorption/desorption study on soils relevant to Canada was submitted and satisfies the data requirement.						
Volatilization	Not required based on the low vapour pressure (1.3×10^{-13} Pa) and Henry's law constant (1.72×10^{-11} Pa m^3 mole) of epyrifenacil.						
Field studies							
Terrestrial field dissipation (bare soil sites)	End-use product: V-10456 0.46 EC (55.1 g a.i./L)	Ontario sandy loam, pH 6.7. Three applications of 40.4 g a.i./ha at 14-day intervals	**Epyrifenacil** Insufficient data to calculate kinetics due to rapid dissipation **S-3100-CA** DT_{50} = 18.1 days **S-3100-CA-RD** DT_{50} = 69.3 days **S-3100-DA-RD** DT_{50} = 402 days	N/A SFO IORE SFO	S-3100-CA S-3100-CA-RD S-3100-DA-RD	Epyrifenacil is non-persistent under field conditions while S-3100-CA is non-persistent to slightly persistent, S-3100-CA-RD is moderately persistent to persistent and S-3100-DA-RD is persistent. Insufficient data were available to calculate the dissipation kinetics of S-3100-DA. No leaching of epyrifenacil or transformation products below the 0–15-cm soil layer was observed.	3309379 3309423
		North Dakota clay, pH 7.8, Three applications of	**Epyrifenacil** Insufficient data to calculate kinetics due to rapid dissipation	N/A	S-3100-CA S-3100-CA-RD S-3100-DA-RD S-3100-DA		

Property	Test substance	Medium/Test conditions	Value	Kinetic Model	Major transformation products[1]	Comments	PMRA No.
		40.4 g a.i./ha at 14-day intervals	**S-3100-CA** DT_{50} = 13.0 days **S-3100-CA-RD** DT_{50} = 193 days **S-3100-DA-RD** DT_{50} = 511 days	DFOP SFO SFO			
Aquatic field dissipation	An aquatic field dissipation study was not submitted and is not required.						
Bioconcentration / bioaccumulation							
Fish bioconcentration	Epyrifenacil	Whole fish, 4.0 µg a.i./L (low dose)	BCF_{KGL} (based on TRR) = 45.89 L/kg	N/A	Epyrifenacil was metabolized in fish during the exposure phase to form S-3100-CA and S-3100-DA	Epyrifenacil residues are not expected to bioaccumulate in fish. >99% of epyrifenacil residues (as TRR) were depurated by Day 3.	3308477
		Whole fish, 40 µg a.i./L (high dose)	BCF_{KGL} (based on TRR) = 112.07 L/kg	N/A			
BCF_{KGL} = kinetic bioconcentration factor corrected for growth and lipid content; TRR = total radioactive residues; DFOP = double first order in parallel; IORE = indeterminate order rate equation; SFO = single first order; t_R = representative half-life (for modelling purposes); N/A = not applicable;							

Table 16 Estimated environmental concentrations for the risk assessment

Substance	EEC[1, 2]	Method of calculation	Notes
Soil: Screening level risk assessment			
Epyrifenacil	80.0 g a.i./ha	Epyrifenacil transforms rapidly into more persistent major TPs for which toxicity data are not available. To provide a conservative estimate of exposure meant to cover exposure to the TPs, EECs in soil were calculated assuming direct application of the maximum	EECs in g a.i./ha were used to evaluate risks to non-target

Substance	EEC[1, 2]		Method of calculation	Notes
			yearly application rate to soil with no dissipation occurring between applications (in other words, 80 g a.i./ha, based on two applications of 40 g a.i./ha).	terrestrial plants (seedling emergence). EECs in mg/kg dw soil were used to evaluate risks to earthworms.
	0.036 mg a.i./kg dw soil		The maximum cumulative application rate was assumed to be evenly distributed in the 0–15-cm depth of the soil, which has a bulk density of 1.5 g/cm^3.	
Soil: Refined risk assessment – Spray drift				
Epyrifenacil	4.8 g a.i./ha		The screening level soil EEC was adjusted to account for 6% spray drift deposition of medium sized spray droplets 1-metre downwind of the point of application (field sprayer).	EECs were used in the spray drift assessment to evaluate risks to non-target terrestrial plants (seedling emergence).
	18.4 g a.i./ha		The screening level soil EEC was adjusted to account for 23% spray drift deposition of medium sized spray droplets 1-metre downwind of the point of application (aerial application to agricultural crops).	
	48.0 g a.i./ha		The screening level soil EEC was adjusted to account for 60% spray drift deposition of medium sized spray droplets 1-metre downwind of the point of application (aerial application to non-crop areas).	
Water: Screening level risk assessment				
Water depth:	**15 cm**	**80 cm**		
Epyrifenacil	80 g a.i./ha		As with the soil EECs, the water EECs were calculated using the maximum application rate to water, with no dissipation.	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.
	0.053 mg a.i./L	0.01 mg a.i./L	EECs for epyrifenacil in surface water were calculated considering a direct overspray to a one-hectare wetland with depths of 15 and 80 cm at the above maximum cumulative application rate to water.	
S-3100-CA	0.050 mg/L	0.009 mg/L	EECs for the major TPs in surface water were calculated based on a direct overspray of the maximum application rate (2 × 40 g a.i./ha) assuming 100% transformation of the parent to each TP	
S-3100-DA	0.044 mg/L	0.008 mg/L		
S-3100-CA-RD	0.051 mg/L	0.009 mg/L		

Substance	EEC[1, 2]		Method of calculation	Notes
S-3100-DA-RD	0.045 mg/L	0.008 mg/L	on a molar basis. No dissipation of the parent or TP between applications was considered.	
S-3100-CA-UR	0.038 mg/L	0.007 mg/L		
4”-OH-S-3100-DA-UR	0.052 mg/L	0.010 mg/L		
S-3100-DP	0.035 mg/L	0.007 mg/L		
S-3100-DA-UR	0.032 mg/L	0.006 mg/L		
TFA	0.012 mg/L	0.002 mg/L		
Water: Refined risk assessment – Spray drift to freshwater				
Water depth:	**15 cm**	**80 cm**		
Epyrifenacil	0.003 mg a.i./L	0.0006 mg a.i./L	The screening level surface water EECs were adjusted to account for 6% spray drift deposition of medium sized spray droplets 1-metre downwind of the point of application (field sprayer).	Used in the spray drift risk assessment for freshwater organisms
S-3100-CA	0.003 mg a.i./L	0.0006 mg a.i./L		
S-3100-DA	0.0027 mg/L	0.0005 mg/L		
S-3100-DP	0.0021 mg/L	0.0004 mg/L		
Epyrifenacil	0.012 mg a.i./L	0.002 mg a.i./L	The screening level surface water EECs were adjusted to account for 23% spray drift deposition of medium sized spray droplets 1-metre downwind of the point of application (aerial application to agricultural crops).	
S-3100-CA	0.012 mg a.i./L	0.002 mg a.i./L		
S-3100-DA	0.010 mg/L	0.002 mg/L		
S-3100-DP	0.008 mg/L	0.002 mg/L		
Epyrifenacil	0.032 mg a.i./L	0.006 mg a.i./L	The screening level surface water EECs were adjusted to account for 60% spray drift deposition of medium sized spray droplets 1-	
S-3100-CA	0.030 mg/L	0.006 mg/L		

Substance	EEC[1, 2]		Method of calculation	Notes
S-3100-DA	0.027 mg/L	0.005 mg/L	metre downwind of the point of application (aerial application to non-crop areas).	
S-3100-DP	0.021 mg/L	0.004 mg/L		
Water: Refined risk assessment – Spray drift to estuarine/marine environments				
Water depth:	**15 cm**	**80 cm**		
Epyrifenacil	N/A	0.0003 mg a.i./L	The screening level surface water EEC was adjusted to account for (1) a single application of 40 g a.i./ha, and; (2) 6% spray drift deposition of medium sized spray droplets 1-metre downwind of the point of application (field spray application).	Used in the spray drift risk assessment for estuarine/marine organisms
		0.0012 mg a.i./L	The screening level surface water EEC was adjusted to account for (1) a single application of 40 g a.i./ha, and; (2) 23% spray drift deposition of medium sized spray droplets 1-metre downwind of the point of application (aerial application to agricultural crops).	
		0.003 mg a.i./L	The screening level surface water EEC was adjusted to account for (1) a single application of 40 g a.i./ha, and; (2) 60% spray drift deposition of medium sized spray droplets 1-metre downwind of the point of application (aerial application to non-crop areas).	
Plant surfaces: Screening level risk assessment				
Epyrifenacil	55.2 g a.i./ha		Maximum cumulative application rate of epyrifenacil to plant surfaces considering 2 × 40 g a.i./ha with a 14-day re-application interval and a default foliar half-life of 10 days.	Used to evaluate risks to beneficial arthropods and non-target terrestrial plants (vegetative vigour).
Plant surfaces: Refined risk assessment – Spray drift				
Epyrifenacil	3.31 g a.i./ha		The screening level EEC on plant surfaces was adjusted to account for 6% spray drift deposition of medium sized spray droplets 1-metre downwind of the point of application (field sprayer).	Used in the spray drift risk assessment for non-target terrestrial plants.
	12.7 g a.i./ha		The screening level surface water EECs were adjusted to account for 23% spray drift deposition of medium sized spray droplets 1-	

Substance	EEC[1, 2]	Method of calculation	Notes
		metre downwind of the point of application (aerial application to agricultural crops).	
	33.1 g a.i./ha	The screening level surface water EECs were adjusted to account for 60% spray drift deposition of medium sized spray droplets 1-metre downwind of the point of application (aerial application to non-crop areas).	
Screening Level EECs for Bees (Oral exposure to pollen and/or nectar, or via direct contact)			
Epyrifenacil	1.14 µg a.i./bee (adult)	Oral exposure estimate for bees = maximum single application rate (0.04 kg a.i./ha) × adjustment factor • Adult adjustment factor of 28.62 µg a.i./bee per kg a.i./ha was calculated as the food consumption of 0.292 g/bee per day × 98 µg a.i./g per kg a.i./ha (default tall grass residues). • Larvae adjustment factor of 12.15 µg a.i./bee per kg a.i./ha was calculated as the food consumption of 0.124 g/bee per day × 98 µg a.i./g per kg a.i./ha (default tall grass residues).	Used to evaluate risks to pollinators (bees).
	0.49 µg a.i./bee (larvae)		
	0.10 µg a.i./bee (adult)	Estimated contact exposure (µg a.i./bee) = 2.4 µg a.i./bee/1 kg a.i./ha × maximum single application rate (0.04 kg a.i./ha)	

(1) See Appendix I, Table 19 for the EECs in food items for birds and mammals. The EECs for birds and mammals were calculated based on 2 × 40 g a.i./ha with a 14-day re-application interval and a default foliar half-life of 10 days.
(2) See Appendix I, Tables 24 and 25 for EECs in surface water from runoff used in the refined aquatic risk assessment.

Table 17 Toxicity endpoints for epyrifenacil, its transformation products and end-use products to non-target organisms

Organism	Exposure	Test substance	Endpoint	Degree of toxicity[1] and/or comments	PMRA No.
Invertebrates					
Earthworm, *Eisenia andrei*	56-d Chronic	Epyrifenacil	NOEC = 484 mg a.i./kg dry soil	No classification	3308449
Honey bee, *Apis mellifera*	48-h Acute contact, adults	Epyrifenacil	LD_{50} > 100 µg a.i./bee	Practically non-toxic	3308450
	48-h Acute oral, adults	Epyrifenacil	LD_{50} > 20 µg a.i./bee	Practically non-toxic	3308451
	Larval (single exposure)	Epyrifenacil	LD_{50} = 23.98 µg a.i./larva	No classification	3308453
	4-d Larval (repeat exposure)	Epyrifenacil	NOED = 3.25 µg a.i./bee	No classification	3308452
	10-d Chronic oral, adults	Epyrifenacil	NOEDD = 19 µg a.i./bee/d	No classification	3308454
Predatory mite, *Typhlodromus pyri*	7-d Glass plates	V-10456 0.46 EC (end-use product, 5.21% epyrifenacil)	LR_{50} > 120 g a.i./ha	No classification 18% control-corrected mortality at 120 g a.i./ha, the highest rate tested.	3308455
Parasitoid wasp, *Aphidius rhopalosiphi*	48-h Glass plates	V-10456 0.46 EC (end-use product, 5.21% epyrifenacil)	LR_{50} > 120 g a.i./ha	No classification 12.5% control-corrected mortality at 120 g a.i./ha, the highest rate tested.	3308456
Birds					
Northern bobwhite,	Acute oral	Epyrifenacil	LD_{50} > 2250 mg a.i./kg bw	Practically non-toxic	3308478

Organism	Exposure	Test substance	Endpoint	Degree of toxicity[1] and/or comments	PMRA No.
Colinus virginianus				0% mortality at 2250 mg a.i./kg bw, the highest dose tested.	
	5-d Dietary	Epyrifenacil	LC_{50} > 5620 mg a.i./kg diet LD_{50} > 1370 mg a.i./kg bw/d	Practically non-toxic 0% mortality at 5620 mg a.i./kg diet, the highest concentration tested.	3308481
	10-week Reproduction, pilot study	Epyrifenacil	NOEC = 5000 mg a.i./kg diet NOEL = 421 mg a.i./kg bw/d	No classification. Acceptable for qualitative use only. No treatment-related effects at the highest concentration tested.	3308484
	22-week Reproduction	Epyrifenacil	NOEC = 1000 mg a.i./kg diet NOEL = 95.7 mg a.i./kg bw/d	No classification No treatment-related effects at the highest concentration tested.	3308483
Mallard, *Anas platyrhynchos*	Acute oral	Epyrifenacil	LD_{50} > 2250 mg a.i./kg bw	Practically non-toxic. 0% mortality at 2250 mg a.i./kg bw, the highest dose tested.	3308479
	5-d Dietary	Epyrifenacil	LC_{50} > 5620 mg a.i./kg diet	Practically non-toxic. 0% mortality at	3308482

Organism	Exposure	Test substance	Endpoint	Degree of toxicity[1] and/or comments	PMRA No.
			LD_{50} > 2409 mg a.i./kg bw/d	5620 mg a.i.kg diet, the highest concentration tested.	
	10-week Reproduction, pilot study	Epyrifenacil	NOEC = 1000 mg a.i./kg diet NOED = 141 mg a.i./kg bw/d	No classification. Acceptable for qualitative use only.	3308486
	21-week Reproduction	Epyrifenacil	NOEC = 1000 mg a.i./kg diet NOED = 138 mg a.i./kg bw/d	No classification. No treatment-related effects up to 1000 mg a.i./kg diet, the highest concentration tested.	3308485
Zebra finch, *Taeniopygia guttata*	Acute oral	Epyrifenacil	LD_{50} > 2250 mg a.i./kg bw	Practically non-toxic. 0% mortality at 2250 mg a.i./kg bw, the highest dose tested.	3308480
Mammals					
Rat	Acute oral	Epyrifenacil	LD_{50} > 2000 mg a.i./kg bw	Practically non-toxic	3308309
		S-3100 0.46 EC Herbicide (end-use product, 5.34 - 5.43% epyrifenacil)	LD_{50} > 2000 mg end-use product/kg bw (> 107 or 109 mg a.i./kg bw)	Practically non-toxic	3307091
		V-10488 0.94 SE Herbicide (end-use product, 1.08% epyrifenacil, 4.96%	LD_{50} > 5000 mg end-use product/kg bw (> [54 mg epyrifenacil + 248 mg pyroxasulfone	Practically non-toxic	3307132

Organism	Exposure	Test substance	Endpoint	Degree of toxicity[1] and/or comments	PMRA No.
		pyroxasulfone, 4.77% flumioxazin)	+ 204 mg flumioxazin]/kg bw)		
	Two-generation Reproduction, exposure through the diet	Epyrifenacil	NOAEL = 6.61 and 7.70 mg a.i./kg bw/d for males and females, respectively.	No classification. Endpoints based on increased mortality and decreased body weight, body weight gain and food consumption in the F1 generation.	3308329
Vascular plants					
Non-target terrestrial plants	14-d Seedling emergence (tomato)	V-10456 0.46 EC (end-use product, 5.21% epyrifenacil)	ER_{25} (emergence) = 5 g a.i./ha	No classification	3308512
	14-d Seedling emergence (all ten tested species)	V-10488 0.94 SE (end-use product, 1.11% epyrifenacil, 4.91% pyroxasulfone, 4.7% flumioxazin)	ER_{25} > 120 g end-use product/ha (> [1.33 g epyrifenacil + 5.89 g pyroxaxulfone + 5.64 g flumioxazin]/ha	No classification. No treatment related effects observed at 120 g end-use product/ha, the highest concentration tested.	3462634
	21-d Vegetative vigour (tomato)	V-10456 0.46 EC (end-use product, 5.21% epyrifenacil)	ER_{25} (shoot dry weight) = 0.34 g a.i./ha	No classification	3308511
		V-10488 0.94 SE (End-use product, 1.11% epyrifenacil,	ER_{25} (shoot dry weight) = 2.7 g end-use product/ha	No classification	3462635

Organism	Exposure	Test substance	Endpoint	Degree of toxicity[1] and/or comments	PMRA No.
		4.91% pyroxasulfone, 4.7% flumioxazin)	(0.03 g epyrifenacil + 0.13 g pyroxasulfone + 0.13 g flumioxazin)/ha		
Freshwater species					
Water flea, *Daphnia magna*	48-h Acute, static-renewal	Epyrifenacil	EC_{50} > 3.2 mg a.i./L	Practically non-toxic up to 3.2 mg a.i./L, the highest concentration tested. 0% immobilization was observed.	3308457
	48-h Acute, static	S-3100-CA (TP)	EC_{50} > 48 mg/L	Practically non-toxic up to 48 mg/L, the highest concentration tested. 0% immobilization was observed.	3308458
	48-h Acute, static	Sodium trifluoroacetate (NaTFA)[2]	EC_{50} > 1008 mg/L	Practically non-toxic up to 1008 mg/L, the highest concentration tested. 0% immobilization was observed.	3648595, 3014765[3]
	21-d Chronic, static-renewal	Epyrifenacil	NOEC = 0.037 mg a.i./L	No classification	3308459
Midge, *Chironomus dilutes*	10-d, Spiked sediment, renewal of overlying water	Epyrifenacil	NOEC = 0.037 mg a.i./L (pore water)	No classification	3308460

Organism	Exposure	Test substance	Endpoint	Degree of toxicity[1] and/or comments	PMRA No.
Amphipod, *Hyalella azteca*	10-d, Spiked sediment, renewal of overlying water	Epyrifenacil	NOEC = 1.7 mg a.i./L (pore water)	No classification	3308461
Rainbow trout, *Oncorhynchus mykiss*	96-h Acute, static renewal	Epyrifenacil	LC_{50} > 2.7 mg a.i./L	Practically non-toxic up to 2.7 mg/L, the highest concentration tested. No treatment-related effects were observed.	3308469
Bluegill sunfish, *Lepomis macrochirus*	96-h Acute, flow-through	Epyrifenacil	LC_{50} = 2.7 mg a.i./L	Moderately toxic	3308470
	96-h Acute, static-renewal	S-3100-CA (TP)	LC_{50} > 50 mg/L	Practically non-toxic up to 50 mg/L, the highest concentration tested. No treatment-related effects were observed.	3308471
Zebrafish, *Danio rerio*	96-h Acute, static	Sodium trifluoroacetate (NaTFA)[2]	LC_{50} > 1008 mg/L	Practically non-toxic at 1008 mg/L, the highest concentration tested (limit test). No mortality was observed.	3648595, 3014765[3]
Fathead minnow, *Pimephales promelas*	96-h Acute, flow-through	Epyrifenacil	LC_{50} > 3.5 mg a.i./L	Practically non-toxic up to 3.5 mg a.i./L, the highest concentration tested. No	3308472

Organism	Exposure	Test substance	Endpoint	Degree of toxicity[1] and/or comments	PMRA No.
				treatment-related effects were observed.	
	32-d Early life-stage, flow-through	Epyrifenacil	NOEC = 0.0029 mg a.i./L	No classification	3308475
	Early life-stage, adjusted for UV-light enhanced conditions	Epyrifenacil	NOEC = 0.00104 mg a.i./L	No classification Calculated using the molar equivalency approach and results from the early life-stage study (PMRA No. 3308475).	3308476
Amphibians	96h-Acute (bluegill sunfish surrogate)	Epyrifenacil	LC_{50} = 2.7 mg a.i./L	Moderately toxic	3308470
	Chronic (fathead minnow surrogate)	Epyrifenacil	NOEC = 0.00104 mg a.i./L	No classification	3308476
Green alga, *Raphidocelis subcapitata*	96-h Acute, static	Epyrifenacil	EC_{50} (yield) = 0.00086 mg a.i./L	Very highly toxic	3308488
	96-h Acute, static	S-3100-CA (TP)	72-h EC_{50} (yield) = 0.0078 mg/L	Very highly toxic	3308491
	96-h Acute, static	S-3100-DA (TP)	EC_{50} (yield and area under the growth curve) = 0.0015 mg/L	Very highly toxic	3308497
	96-h Acute, static	S-3100-DA-RD (TP)	EC_{50} (all parameters) > 0.47 mg/L	Practically non-toxic up to 0.47 mg/L, the highest	3308531

Organism	Exposure	Test substance	Endpoint	Degree of toxicity[1] and/or comments	PMRA No.
				concentration tested. 1% to 11.4% inhibition observed at 0.47 mg/L.	
	96-h Acute, static	S-3100-CA-RD (TP)	72-h EC_{50} (yield) = 0.71 mg/L	Highly toxic	3308496
	96-h Acute, static	S-3100-CA-UR (TP)	EC_{50} (all parameters) > 1 mg/L	Practically non-toxic up to 1 mg/L, the highest concentration tested. -8% to 7.3% inhibition was observed at 1 mg/L.	3308492
	96-h Acute, static	4"-OH-S-3100-CA (TP)	EC_{50} (yield) = 0.11 mg/L	Highly toxic	3308494
	96-h Acute, static	S-3100-DP (TP)	72-h EC_{50} (yield and area under the growth curve) = 0.0012 mg/L	Very highly toxic	3308495
	96-h Acute, static	S-3100-DA-UR (TP)	EC_{50} (all parameters) > 0.97 mg/L	Practically non-toxic up to 0.97 mg/L, the highest concentration tested. 2% to 11% inhibition was observed at 0.97 mg/L.	3308524
	72-h Acute, static	Sodium trifluoroacetate (NaTFA)[2]	EC_{50} (area under the growth curve) = 4.19 mg/L	Moderately toxic	3014765[3]
	72-h Acute, static	Sodium trifluoroacetate (NaTFA)[2]	EC_{50} (all parameters) > 1.2 mg/L	Practically non-toxic up 1.2 mg/L, the	3014765[3]

Organism	Exposure	Test substance	Endpoint	Degree of toxicity[1] and/or comments	PMRA No.
				highest concentration tested. 6.1 to 29% inhibition was observed at 1.2 mg/L.	
Diatom, *Navicula pelliculosa*	96-h Acute, static	Epyrifenacil	72-h EC_{50} (yield) = 0.00052 mg a.i./L	Very highly toxic	3308490
	96-h Acute, static	S-3100-CA (TP)	EC_{50} (all parameters) > 0.92 mg/L	Practically non-toxic up to 0.92 mg/L, the highest concentration tested. 15% to 44% inhibition was observed at 0.92 mg/L.	3308530
	96-h Acute, static	S-3100-DA (TP)	EC_{50} (yield) = 0.099 mg/L	Very highly toxic	3308529
	96-h Acute, static	S-3100-DA-RD (TP)	EC_{50} (all parameters) > 0.88 mg/L	Practically non-toxic up to 0.88 mg/L, the highest concentration tested. -8% to 24.3% inhibition was observed at 0.88 mg/L.	3308527
	96-h Acute, static	S-3100-CA-RD (TP)	EC_{50} (all parameters) > 0.90 mg/L	Practically non-toxic up to 0.90 mg/L, the highest concentration tested. -18% to 8.7% inhibition was observed at 0.90 mg/L.	3308532

Organism	Exposure	Test substance	Endpoint	Degree of toxicity[1] and/or comments	PMRA No.
	96-h Acute, static	S-3100-CA-UR (TP)	EC_{50} (all parameters) > 0.97 mg/L	Practically non-toxic up to 0.97 mg/L, the highest concentration tested. 2% to 5.6% inhibition was observed at 0.97 mg/L.	3308493
	96-h Acute, static	4"-OH-S-3100-CA (TP)	EC_{50} (all parameters) > 0.16 mg/L	Practically non-toxic up to 0.16 mg/L, the highest concentration tested. -9% to 11.9% inhibition was observed at 0.16 mg/L.	3308526
	96-h Acute, static	S-3100-DP (TP)	72-h EC_{50} (yield) = 0.028 mg/L	Very highly toxic	3308528
	96-h Acute, static	S-3100-DA-UR (TP)	EC_{50} (yield) = 0.069 mg/L	Very highly toxic	3308525
Cyanobacterium, *Anabaena flos-aquae*	96-h Acute, static	Epyrifenacil	EC_{50} (all response variables) > 2.9 mg a.i./L	Practically non-toxic up to 2.9 mg/L, the highest concentration tested. -3% to -15% inhibition was observed at 2.9 mg a.i./L.	3308489
Duckweed, *Lemna gibba*	7-d Static-renewal	Epyrifenacil	EC_{50} (yield, based on dry weight) = 0.0022 mg a.i./L	Very highly toxic	3308513
	7-d, Static	Sodium trifluoroacetate (NaTFA)[2]	EC_{50} = 769 mg TFA/L	Practically non-toxic	3014765[3]

Organism	Exposure	Test substance	Endpoint	Degree of toxicity[1] and/or comments	PMRA No.
Watermilfoil, *Myriophyllum sibiricum*	14-d	TFA	EC_{50} (root length) = 340 mg/L	Practically non-toxic	3014765 3648597
Eurasian watermilfoil, *Myriophyllum spicatum*	14-d	TFA	EC_{50} (root length) = 222.1 mg/L	Practically non-toxic	3014765 3648597
Marine/estuarine species					
Mysid shrimp, *Americamysis bahia*	96-h Acute, flow-through	Epyrifenacil	LC_{50} = 0.38 mg a.i./L	Highly toxic	3308462
	28-d Chronic, flow-through	Epyrifenacil	NOEC = 0.0021 mg a.i./L	No classification	3308465
Amphipod, *Leptocheirus plumulosus*	10-d Spiked sediment, renewal of overlying water	Epyrifenacil	NOEC = 0.034 mg a.i./L (pore water)	No classification	3308464
Eastern oyster, *Crassostrea virginica*	96-h Acute, flow-through	Epyrifenacil	EC_{50} > 1.1 mg a.i./L	Practically non-toxic up to 1.1 mg a.i./L, the highest concentration tested. No treatment-related effects were observed.	3308463
Sheepshead minnow, *Cyprinodon variegatus*	96-h Acute, flow-through	Epyrifenacil	LC_{50} > 3.4 mg a.i./L	Practically non-toxic up to 3.4 mg a.i./L, the highest concentration tested. No treatment-related effects were observed.	3308473
	34-d Early life-stage, flow-	Epyrifenacil	NOEC = 0.009 mg a.i./L	No classification	3308474

Organism	Exposure	Test substance	Endpoint	Degree of toxicity(1) and/or comments	PMRA No.
	through; exposure from 6 d pre-hatch to 28 d post-hatch				
	Early life-stage, adjusted for UV-light enhanced conditions	Epyrifenacil	NOEC = 0.00104 mg a.i./L	No classification Calculated using the molar equivalency approach and results from early life-stage study (PMRA No. 3308474)	3308476
Diatom, *Skeletonema costatum*	96-h Static	Epyrifenacil	EC_{50} (yield) = 0.0004702 mg a.i./L	Very highly toxic	3308510

(1) USEPA classification, where applicable.
(2) Endpoints from this study have been converted from mg NaTFA/L to mg TFA/L.
(3) Endpoints from this study were published in PRVD2021-01 *Flufenacet and Its Associated End-use Products*.

Table 18 Screening level risk assessment for non-target species (Excluding birds and mammals)

Organism	Exposure	Test substance	EEC	Endpoint value	UF	Effects metric	RQ[(1)]	LOC	LOC Exceeded?
Terrestrial organisms									
Invertebrates									
Earthworm, *Eisenia Andrei*	56-d Chronic	Epyrifenacil	0.036 mg/kg dw soil	484 mg/kg dw soil	1	484 mg/kg dw soil	0.0001	1	No
Honey bee, *Apis mellifera* L.	48-h Contact	Epyrifenacil	0.096 µg a.i./bee	>100 µg a.i./bee	1	>100 µg a.i./bee	<0.0010	0.4	No
	48-h Oral	Epyrifenacil	1.15 µg a.i./bee	>20 µg a.i./bee	1	>20 µg a.i./bee	<0.057	0.4	No
	Larval (single exposure)	Epyrifenacil	0.486 µg a.i./larva	23.98 µg a.i./larva	1	24.0 µg a.i./larva	0.020	0.4	No
	4-d Larval (repeated exposure)	Epyrifenacil	0.486 µg a.i./bee/d	3.25 µg a.i./bee/d	1	3.25 µg a.i./bee/d	0.15	0.4	No
	10-d Chronic Oral	Epyrifenacil	1.15 µg a.i./bee/d	19 µg a.i./bee/d	1	19 µg a.i./bee/d	0.060	1	No
Predatory arthropod, *Typhlodromus pyri*	7-d Glass plate	V-10456 0.46 EC (end-use product, 5.21% epyrifenacil)	55.2 g a.i./ha	>120 g a.i./ha	1	>120 g a.i./ha	<0.46	2	No
Parasitic arthropod, *Aphidius rhopalopsiphi*	7-d Glass plate	V-10456 0.46 EC (end-use product, 5.21% epyrifenacil	55.2 g a.i./ha	>120 g a.i./ha	1	>120 g a.i./ha	<0.46	2	No

Organism	Exposure	Test substance	EEC	Endpoint value	UF	Effects metric	RQ[(1)]	LOC	LOC Exceeded?
Vascular plants									
Non-target terrestrial plants	Seedling emergence (tomato, emergence)	V-10456 0.46 EC (end-use product, 5.21% epyrifenacil	80.0 g a.i./ha	5 g a.i./ha	1	5 g a.i./ha	**16**	1	**Yes**
	Seedling emergence (all 10 test species)	V-10448 SE (end-use product, 4.91% epyrifenacil, 4.70% flumioxazin)	80.0 g a.i./ha	1.33 g a.i./ha	1	1.33 g a.i./ha	**60**	1	**Yes**
	Vegetative vigour (tomato, dry shoot weight)	V-10456 0.46 EC (end-use product, 5.21% epyrifenacil	55.16 g a.i./ha	0.34 g a.i./ha	1	0.34 g a.i./ha	**162**	1	**Yes**
	Vegetative vigour (tomato, dry shoot weight)	V-10448 SE (end-use product, 4.91% epyrifenacil, 4.70% flumioxazin)	55.16 g a.i./ha	0.03 g a.i./ha	1	0.03 g a.i./ha	**1839**	1	**Yes**
Freshwater organisms									
Daphnia magna	48-h Acute	Epyrifenacil	0.010 mg a.i./L	>3.2 mg a.i./L	2	>1.60 mg a.i./L	<0.006	1	No
	48-h Acute	S-3100-CA (TP)	0.009 mg/L	>48 mg/L	2	>24.0 mg/L	<0.0004	1	No

Organism	Exposure	Test substance	EEC	Endpoint value	UF	Effects metric	RQ[(1)]	LOC	LOC Exceeded?
	48-h Acute	Sodium trifluoroacetate (NaTFA)	0.002 mg TFA/L	>1008 mg TFA/L	2	>504 mg TFA/L	<0.000004	1	No
	21-d Chronic	Epyrifenacil	0.010 mg a.i./L	0.037 mg a.i./L	1	0.037 mg a.i./L	0.27	1	No
Midge, *Chironomus dilutes*	10-d Spiked sediment, renewal of overlying water	Epyrifenacil	0.010 mg a.i./L	0.037 mg a.i./L	1	0.037 mg a.i./L	0.27	1	No
Amphipod, *Hyalella Azteca*	10-d Spiked sediment, renewal of overlying water	Epyrifenacil	0.010 mg a.i./L	1.7 mg a.i./L	1	1.7 mg a.i./L	0.006	1	No
Rainbow trout, *Oncorhynchus mykiss*	96-h Acute	Epyrifenacil	0.010 mg a.i./L	>2.7 mg a.i./L	10	>0.27 mg a.i./L	<0.037	1	No
Bluegill sunfish, *Lepomis macrochirus*	96-h Acute	Epyrifenacil	0.010 mg a.i./L	2.7 mg a.i./L	10	0.27 mg a.i./L	0.037	1	No
		S-3100-CA	0.009 mg/L	>50 mg/L	10	>5.000 mg/L	<0.002	1	No
Zebrafish, *Dario rerio*	96-h Acute	Sodium trifluoroacetate (NaTFA)	0.002 mg TFA/L	>1008 mg TFA/L	10	>100.8 mg TFA/L	<0.00002	1	No
Fathead minnow,	96-h Acute	Epyrifenacil	0.010 mg a.i./L	>3.5 mg a.i..L	10	>0.35 mg a.i./L	<0.029	1	No

Organism	Exposure	Test substance	EEC	Endpoint value	UF	Effects metric	RQ[(1)]	LOC	LOC Exceeded?
Pimephales promelas	32-d Early life stage	Epyrifenacil	0.010 mg a.i./L	0.0029 mg a.i./L	1	0.003 mg a.i./L	**3.5**	1	**Yes**
	32-d Early life stage, adjusted for UV-light enhanced conditions	Epyrifenacil	0.010 mg a.i./L	0.001 mg a.i./L	1	0.001 mg a.i./L	**9.6**	1	**Yes**
Amphibians	96-h Acute (bluegill sunfish surrogate)	Epyrifenacil	0.053 mg a.i./L	2.7 mg a.i./L	10	0.270 mg a.i./L	0.20	1	No
	Chronic (fathead minnow surrogate)		0.053 mg a.i./L	0.00104 mg a.i../L	1	0.001 mg a.i./L	**51**	1	**Yes**
Freshwater algae, *Rhaphidocelis subcapitata*	96-h Acute	Epyrifenacil	0.010 mg/L	0.00086 mg/L	2	0.0004 mg/L	**23**	1	**Yes**
		S-3100-CA	0.0095 mg/L	0.0078 mg/L	2	0.004 mg/L	**2.4**	1	**Yes**
		S-3100-DA	0.0083 mg/L	0.0015 mg/L	2	0.001 mg/L	**11**	1	**Yes**
		S-3100-DA-RD	0.0084 mg/L	>0.47 mg/L	2	>0.235 mg/L	<0.036	1	No
		S-3100-CA-RD	0.0095 mg/L	0.71 mg/L	2	0.355 mg/L	0.027	1	No
		S-3100-CA-UR	0.0071 mg/L	>1 mg/L	2	>0.500 mg/L	<0.014	1	No
		4"-OH-S-3100-CA	0.010 mg/L	0.11 mg/L	2	0.055 mg/L	0.18	1	No

Organism	Exposure	Test substance	EEC	Endpoint value	UF	Effects metric	RQ[(1)]	LOC	LOC Exceeded?
		S-3100-DP	0.007 mg/L	0.0012 mg/L	2	0.001 mg/L	**11**	1	**Yes**
		S-31000-DA-UR	0.006 mg/L	>0.97 mg/L	2	>0.485 mg/L	<0.012	1	No
	72-h Acute	Sodium trifluoroacetate (NaTFA)	0.002 mg TFA/L	4.19 mg TFA/L	2	2.095 mg TFA/L	0.001	1	No
			0.002 mg TFA/L	>1.2 mg TFA/L	2	0.060 mg TFA/L	0.004	1	No
Freshwater diatom, *Navicula pelliculosa*	96-h Acute	Epyrifenacil	0.010 mg a.i./L	0.00052 mg a.i./L	2	0.0003 mg/L	**39**	1	**Yes**
		S-3100-CA	0.009 mg/L	>0.92 mg/L	2	>0.460 mg/L	<0.021	1	No
		S-3100-DA	0.0083 mg/L	0.099 mg/L	2	0.050 mg/L	0.17	1	No
		S-3100-DA-RD	0.0084 mg/L	>0.88 mg/L	2	>0.440 mg/L	<0.022	1	No
		S-3100-CA-RD	0.0095 mg/L	>0.9 mg/L	2	>0.450 mg/L	<0.021	1	No
		S-3100-CA-UR	0.007 mg/L	>0.97 mg/L	2	>0.485 mg/L	<0.015	1	No
		4"-OH-S-3100-CA	0.01 mg/L	>0.16 mg/L	2	>0.080 mg/L	<0.12	1	No
		S-3100-DP	0.007 mg/L	0.028 mg/L	2	0.014 mg/L	0.47	1	No
		S-3100-DA-UR	0.006 mg/L	0.069 mg/L	2	0.035 mg/L	0.17	1	No
Freshwater algae, *Anabaena flos-aquae*	96-h Acute	Epyrifenacil	0.010 mg a.i./L	>2.9 mg a.i./L	2	>1.450 mg a.i./L	<0.007	1	No
Duckweed, *Lemna gibba*	7-d Static renewal	Epyrifenacil	0.010 mg a.i./L	1.4 mg a.i./L	2	0.700 mg a.i./L	0.014	1	No

Organism	Exposure	Test substance	EEC	Endpoint value	UF	Effects metric	RQ[(1)]	LOC	LOC Exceeded?
	7-d Static	Sodium trifluoroacetate (NaTFA)	0.002 mg TFA/L	769 mg TFA/L	2	384.5 mg/L	0.00001	1	No
Watermilfoil, *Myriophyllum sibiricum*	14-d	TFA	0.002 mg TFA/L	340 mg/L	2	170 mg/L	0.00002	1	No
Eurasian watermilfoil, *Myriophyllum spicatum*	14-d	TFA	0.002 mg TFA/L	222.1 mg/L	2	110.6 mg/L	0.053	1	No
Marine organisms									
Saltwater mysid, *Americamysis bahia*	96-h Acute	Epyrifenacil	0.010 mg a.i./L	0.38 mg a.i./L	2	0.19 mg a.i./L	0.053	1	No
	28-day Chronic	Epyrifenacil	0.010 mg a.i./L	0.0021 mg a.i./L	1	0.0021 mg a.i./L	**4.8**	1	**Yes**
Amphipod, *Leptocheirus plumulosus*	10-d Sediment	Epyrifenacil	0.010 mg a.i./L	0.034 mg a.i./L	1	0.034 mg a.i./L	0.30	1	No
Eastern oyster, *Crassostrea virginica*	96-h Acute	Epyrifenacil	0.010 mg a.i./L	>1.1 mg a.i./L	2	>0.55 mg a.i./L	<0.018	1	No
Sheepshead minnow, *Cyprinodon variegatus*	96-h Acute	Epyrifenacil	0.010 mg a.i./L	>3.4 mg a.i./L	10	>0.34 mg a.i./L	<0.029	1	No
	34-d Early life stage	Epyrifenacil	0.010 mg a.i./L	0.009 mg a.i./L	1	0.009 mg a.i./L	**1.1**	1	**Yes**
	34-d Early life stage adjusted	Epyrifenacil	0.010 mg a.i./L	0.00104 mg a.i./L	1	0.00104 mg a.i./L	**9.6**	1	**Yes**

Organism	Exposure	Test substance	EEC	Endpoint value	UF	Effects metric	RQ(1)	LOC	LOC Exceeded?
	for UV light								
Marine diatom, *Skeletonema costatum*	96-h Acute	Epyrifenacil	0.010 mg a.i./L	0.0004702 mg a.i./L	2	0.0002351 mg a.i./L	**43**	1	**Yes**

Bold: RQ exceeds LOC
(1) RQs were calculated using Microsoft Excel. Values in this table have been rounded for presentation which may result in minor discrepancies in RQs calculated based on the values presented in this table.

Table 19 Screening level risk assessment for birds and mammals

Organism	Effects metric (mg a.i./kg bw/d)(1)	Feeding guild (food item)	EDE (mg a.i./kg bw)(2)	RQ(3)	LOC	LOC exceeded ?
Small bird (0.02 kg)						
Acute	>225	Insectivore	4.49	<0.02	1	No
Reproduction	95.7	Insectivore	4.49	0.05	1	No
Medium sized bird (0.1 kg)						
Acute	>225	Insectivore	3.50	<0.02	1	No
Reproduction	95.7	Insectivore	3.50	0.04	1	No
Large sized bird (1 kg)						
Acute	>225	Herbivore (short grass)	2.26	<0.02	1	No
Reproduction	95.70	Herbivore (short grass)	2.26	0.02	1	No
Small mammal (0.015 kg)						
Acute	> 200	Insectivore	2.58	<0.01	1	No
Reproduction	6.61	Insectivore	2.58	0.39	1	No

Organism	Effects metric (mg a.i./kg bw/d)(1)	Feeding guild (food item)	EDE (mg a.i./kg bw)(2)	RQ(3)	LOC	LOC exceeded ?
Medium sized mammal (0.035 kg)						
Acute	> 200	Herbivore (short grass)	5.01	<0.03	1	No
Reproduction	6.61	Herbivore (short grass)	5.01	0.76	1	No
Large sized mammal (1 kg)						
Acute	> 200	Insectivore	2.68	<0.10	1	No
Reproduction	6.61	Insectivore	2.68	0.40	1	No

(1) To calculate the effects metric, uncertainty factors of 10 and 1 were applied to the acute oral (LD_{50}) and reproduction (NOED) endpoints, respectively.

(2) EDE = Estimated dietary exposure; is calculated using the following formula: (FIR/bw) × EEC, where:

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

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

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

For mammals, the "all mammals" equation was used: FIR (g dry weight/day) = 0.235 (bw in g) $^{0.822}$

EEC: Concentration of pesticide on food item based on Hoerger and Kenaga (1972) and Kenaga (1973) and modified according to Fletcher et al. (1994). At the screening level, relevant food items representing the most conservative EEC for each feeding guild are used.

The EECs for birds and mammals were calculated based on 2 × 40 g a.i./ha with a 14-day re-application interval and a default foliar half-life of 10 days.

(3) RQs were calculated using Microsoft Excel. Values in this table have been rounded for presentation which may result in minor discrepancies in RQs calculated based on the values presented in this table.

Table 20 Refined risk assessment for non-target terrestrial plants

Organism	Exposure	Test substance	EEC	Endpoint value	UF	Effects metric	RQ[(1)]	LOC	LOC exceeded?
6% Spray drift (Field sprayer, medium spray droplet)									
Non-target terrestrial plants	Seedling emergence (tomato, emergence)	V-10456 0.46 EC (end-use product, 5.21% epyrifenacil)	4.80 g a.i./ha	5 g a.i./ha	1	5 g a.i./ha	**1.0**	1	**Yes**
	Seedling emergence (all 10 test species)	V-10448 SE (end-use product, 4.91% epyrifenacil, 4.70% flumioxazin)	4.80 g a.i./ha	1.33 g a.i./ha	1	1.33 g a.i./ha	**3.6**	2	**Yes**
	Vegetative vigour (tomato, dry shoot weight)	V-10456 0.46 EC (end-use product, 5.21% epyrifenacil)	3.31 g a.i./ha	0.34 g a.i./ha	1	0.34 g a.i./ha	**9.7**	1	**Yes**
	Vegetative vigour (tomato, dry shoot weight)	V-10448 SE (end-use product, 4.91% epyrifenacil, 4.70% flumioxazin)	3.31 g a.i./ha	0.03 g a.i./ha	1	0.015 g a.i./ha	**110**	2	**Yes**

Organism	Exposure	Test substance	EEC	Endpoint value	UF	Effects metric	RQ[1]	LOC	LOC exceeded?
23% Spray drift (Aerial application to agricultural crops, medium spray droplet)									
Non-target terrestrial plants	Seedling emergence (tomato, emergence)	V-10456 0.46 EC (end-use product, 5.21% epyrifenacil)	18.4 g a.i./ha	5 g a.i./ha	1	5 g a.i./ha	**3.7**	1	**Yes**
	Seedling emergence (all 10 test species)	V-10448 SE (end-use product, 4.91% epyrifenacil, 4.70% flumioxazin)	18.4 g a.i./ha	1.33 g a.i./ha	1	1.33 g a.i./ha	**14**	1	**Yes**
	Vegetative vigour (tomato, dry shoot weight)	V-10456 0.46 EC (end-use product, 5.21% epyrifenacil)	12.7 g a.i./ha	0.34 g a.i./ha	1	0.34 g a.i./ha	**37**	1	**Yes**
	Vegetative vigour (tomato, dry shoot weight)	V-10448 SE (end-use product, 4.91% epyrifenacil, 4.70% flumioxazin)	12.7 g a.i./ha	0.03 g a.i./ha	1	0.015 g a.i./ha	**423**	1	**Yes**

Organism	Exposure	Test substance	EEC	Endpoint value	UF	Effects metric	RQ(1)	LOC	LOC exceeded?
60% Spray drift (Aerial application to non-crop areas, medium spray droplet)									
Non-target terrestrial plants	Seedling emergence (tomato, emergence)	V-10456 0.46 EC (end-use product, 5.21% epyrifenacil)	48.0 g a.i./ha	5 g a.i./ha	1	5 g a.i./ha	**9.6**	1	**Yes**
	Seedling emergence (all 10 test species)	V-10448 SE (end-use product, 4.91% epyrifenacil, 4.70% flumioxazin)	48.0 g a.i./ha	1.33 g a.i./ha	1	1.33 g a.i./ha	**36**	1	**Yes**
	Vegetative vigour (tomato, dry shoot weight)	V-10456 0.46 EC (end-use product, 5.21% epyrifenacil)	33.1 g a.i./ha	0.34 g a.i./ha	1	0.34 g a.i./ha	**97**	1	**Yes**
	Vegetative vigour (tomato, dry shoot weight)	V-10448 SE (end-use product, 4.91% epyrifenacil, 4.70% flumioxazin)	33.1 g a.i./ha	0.03 g a.i./ha	1	0.015 g a.i./ha	**1103**	1	**Yes**

Bold: RQ exceeds LOC

(1) RQs were calculated using Microsoft Excel. Values in this table have been rounded for presentation which may result in minor discrepancies in RQs calculated based on the values presented in this table.

Table 21 Refined risk assessment for aquatic organisms exposed to spray drift

Organism	Exposure	Test substance	EEC	Endpoint value	UF	Effects metric	RQ[(1)]	LOC	LOC exceeded?
Freshwater organisms: 6% Spray drift (Field sprayer, medium spray droplet)									
Fathead minnow, *Pimephales promelas*	32-d Early life stage, adjusted for UV-light enhanced conditions	Epyrifenacil	0.0006 mg a.i./L	0.001 mg a.i./L	1	0.001 mg a.i./L	0.001	1	No
Amphibians	Chronic (fathead minnow surrogate)	Epyrifenacil	0.0032 mg a.i./L	0.00104 mg a.i../L	1	0.001 mg a.i./L	**3.1**	1	**Yes**
Freshwater algae, *Rhaphidocelis subcapitata*	96-h Acute	Epyrifenacil	0.0006 mg a.i./L	0.00086 mg/L	2	0.0004 mg/L	**1.4**	1	**Yes**
		S-3100-CA	0.0006 mg/L	0.0078 mg/L	2	0.004 mg/L	0.15	1	No
		S-3100-DA	0.0005 mg/L	0.0015 mg/L	2	0.001 mg/L	0.67	1	No
		S-3100-DP	0.0004 mg/L	0.0012 mg/L	2	0.001 mg/L	0.65	1	No
Freshwater diatom, *Navicula pelliculosa*	96-h Acute	Epyrifenacil	0.0006 mg a.i./L	0.00052 mg a.i./L	2	0.0003 mg/L	**2.3**	1	**Yes**
Estuarine/marine organisms: 6% Spray drift (Field sprayer, medium spray droplet)									
Marine diatom, *Skeletonema costatum*	96-h Acute	Epyrifenacil	0.0003 mg a.i./L	0.0004702 mg a.i./L	2	0.0002351 mg a.i./L	**1.3**	1	**Yes**

Organism	Exposure	Test substance	EEC	Endpoint value	UF	Effects metric	RQ[(1)]	LOC	LOC exceeded?
Freshwater organisms: 23% Spray drift (Aerial application to agricultural crops, medium spray droplet)									
Fathead minnow, *Pimephales promelas*	32-d Early life stage, adjusted for UV-light enhanced conditions	Epyrifenacil	0.0023 mg a.i./L	0.001 mg a.i./L	1	0.001 mg a.i./L	**2.2**	1	**Yes**
Amphibians	Chronic (fathead minnow surrogate)	Epyrifenacil	0.012 mg a.i./L	0.00104 mg a.i../L	1	0.001 mg a.i./L	**12**	1	**Yes**
Freshwater algae, *Rhaphidocelis subcapitata*	96-h Acute	Epyrifenacil	0.0023 mg a.i./L	0.00086 mg/L	2	0.0004 mg/L	**5.3**	1	**Yes**
		S-3100-CA	0.0022 mg/L	0.0078 mg/L	2	0.004 mg/L	0.56	1	No
		S-3100-DA	0.0019 mg/L	0.0015 mg/L	2	0.001 mg/L	**2.6**	1	**Yes**
		S-3100-DP	0.0015 mg/L	0.0012 mg/L	2	0.001 mg/L	**2.5**	1	**Yes**
Freshwater diatom, *Navicula pelliculosa*	96-h Acute	Epyrifenacil	0.0023 mg a.i./L	0.00052 mg a.i./L	2	0.0003 mg/L	**8.8**	1	**Yes**
Estuarine/marine organisms: 23% Spray drift (Aerial application to agricultural crops, medium spray droplet)									
Marine diatom, *Skeletonema costatum*	96-h Acute	Epyrifenacil	0.0011 mg a.i./L	0.00047 mg a.i./L	2	0.00024 mg a.i./L	**4.9**	1	**Yes**
Freshwater organisms: 60% Spray drift (Aerial application to non-crop areas, medium spray droplet)									
Fathead minnow, *Pimephales promelas*	32-d Early life stage, adjusted for UV-light	Epyrifenacil	0.006 mg a.i./L	0.001 mg a.i./L	1	0.001 mg a.i./L	**5.7**	1	**Yes**

Organism	Exposure	Test substance	EEC	Endpoint value	UF	Effects metric	RQ(1)	LOC	LOC exceeded?
	enhanced conditions								
Amphibians	Chronic (fathead minnow surrogate)	Epyrifenacil	0.032 mg a.i./L	0.00104 mg a.i../L	1	0.001 mg a.i./L	**31**	1	**Yes**
Freshwater algae, *Rhaphidocelis subcapitata*	96-h Acute	Epyrifenacil	0.006 mg a.i./L	0.00086 mg/L	2	0.0004 mg/L	**14**	1	**Yes**
		S-3100-CA	0.006 mg/L	0.0078 mg/L	2	0.004 mg/L	**1.5**	1	**Yes**
		S-3100-DA	0.005 mg/L	0.0015 mg/L	2	0.001 mg/L	**6.7**	1	**Yes**
		S-3100-DP	0.004 mg/L	0.0012 mg/L	2	0.001 mg/L	**6.5**	1	**Yes**
Freshwater diatom, *Navicula pelliculosa*	96-h Acute	Epyrifenacil	0.0023 mg a.i./L	0.00052 mg a.i./L	2	0.0003 mg/L	**23**	1	**Yes**
Estuarine/marine organisms: 23% Spray drift (Aerial application)									
Marine diatom, *Skeletonema costatum*	96-h Acute	Epyrifenacil	0.003 mg a.i./L	0.00047 mg a.i./L	2	0.00024 mg a.i./L	**13**	1	**Yes**

Bold: RQ exceeds LOC

(1) RQs were calculated using Microsoft Excel. Values in this table have been rounded for presentation which may result in minor discrepancies in RQs calculated based on the values presented in this table.

Table 22 Fate inputs for modelling EECs from runoff of the combined residue of epyrifenacil, S-3100-CA, S-3100-DA and S-3100-DP to surface water

Parameter	Value	Details
K_{oc} (L/kg)	40.6	The 20th percentile of six values for the transformation product, S-3100-CA, which has the lowest K_{oc} among all compounds included in the residue definition.
Water column metabolism half-life (day) at 20°C	376.6	Aerobic aquatic whole system half-life. Data for two water/sediment systems are available. The longest half-life was used for modelling (the longest half-life from pyrimidinyl-labelled samples).
Benthic metabolism half-life (day) at 20°C	72.1	Anaerobic aquatic whole system half-life. Data for two water/sediment systems are available. The longest half-life was used for modelling (the longest half-life from phenyl-labelled samples).
Aqueous photolysis half-life (day) at 40°N	Stable	The aqueous phototransformation studies for epyrifenacil included reference standards for a limited number of TPs. At the end of the three studies, the total "unidentified products" ranged from 55.6 to 74% AR. The unidentified products may contain some of the TPs included in the residue definition. As such, the half-life of the combined residue was assumed to be stable.
Hydrolysis half-life (day) at 25°C (pH 7)	Stable	Only two TPs included in the residue definition, S-3100-CA and S-3100-DA, were identified in the hydrolysis of epyrifenacil studies. The concentrations of both compounds were increasing at the end of the studies. The hydrolysis half-life for the combined residue was assumed to be stable because insufficient data on the hydrolysis the TPs included in the residue definition were not available.
Soil half-life (day) at 20°C	828.2	Three aerobic soil studies using three radiolabels (phenyl, pyridyl and pyrimidinyl rings of the molecule radiolabeled). The phenyl and pyrimidinyl labels tracked the production of all three TPs included in the residue definition (S-3100-CA, S-3100-DA and S-3100-DP). The data from pyridyl label are not used for runoff modelling because it could not track the formation of S-3100-DP. The value presented is the 90% upper confidence bound on the mean of four soils.

Table 23 Estimated environmental concentration (in µg/L) of combined residues of epyrifenacil and transformation products S-3100-CA, S-3100-DA and S-3100-DP through runoff into a 1-ha water body of 15-cm depth

Crop	Use pattern (g a.i./ha)	Region	Water column EEC (µg/L)					
			Peak	24-hr	96-hr	21-d	60-d	90-d
Wheat, Spring	1 × 40	BC	0.4[1]	0.4[1]	0.4[1]	**0.4**[1]	0.3[1]	0.3[1]
		MB	3.1	3.0	3.0	2.7	2.5	2.3
		SK	3.3	3.3	3.2	2.9	2.4	2.2
		AB	3.6	3.5	3.5	3.2	2.9	2.7
		ON	7.8	7.7	7.6	7.0	6.3	5.8
		QC	11.4	11.3	11.2	10.5	9.4	8.8
		PEI	15.9	15.8	15.5	14.0	12.2	11.7
Wheat, Winter	1 × 40	BC	2.1	2.1	2.1	**1.9**	1.9	1.7
		MB	6.8	6.8	6.7	6.1	5.3	5.1
		SK	4.2	4.2	4.2	4.0	4.1	4.3
		AB	4.8	4.8	4.8	4.8	4.1	3.7
		ON	11.0	10.9	10.7	9.7	9.7	9.1
		QC	12.1	12.1	12.0	11.4	10.6	10.1
		PEI	18.2	18.2	18.2	17.2	14.5	13.4
Summer Fallow	2 × 20 (30-day interval)	BC	0.7[1]	0.7[1]	0.7[1]	**0.7**[1]	0.7[1]	0.7[1]
		MB	5.7	5.7	5.5	5.1	4.5	4.1
		SK	3.8	3.8	3.8	3.8	3.8	3.8
		AB	4.0	4.0	3.9	3.6	3.2	3.1
		ON	7.8	7.8	7.6	6.9	6.1	5.7
		QC	6.4	6.4	6.3	5.8	5.0	4.8
		PEI	8.3	8.3	8.3	8.3	7.3	7.0
Corn, field	1 × 40	BC	0.4[1]	0.4[1]	0.4[1]	**0.4**[1]	0.3[1]	0.3[1]
		ON	7.8	7.7	7.6	7.0	6.3	5.8
		QC	11.4	11.3	11.2	10.5	9.4	8.8
		PEI	15.9	15.8	15.5	14.0	12.2	11.7
Canola	1 × 20	MB	15.3	15.2	14.9	13.7	12.4	11.6
		SK	16.6	16.5	16.1	14.5	12.0	11.0

Crop	Use pattern (g a.i./ha)	Region	Water column EEC (µg/L)					
			Peak	24-hr	96-hr	21-d	60-d	90-d
		AB	17.8	17.6	17.3	15.9	14.3	13.3
Bare ground non-crop and IVM	2 × 40 (14-day interval)	BC	3.1	3.1	3.1	3.2	3.3	3.1
		MB	12.6	12.5	12.2	11.2	10.0	9.5
		SK	8.2	8.1	7.9	7.2	7.0	7.3
		AB	8.3	8.3	8.3	7.9	7.0	6.7
		ON	18.8	18.6	18.2	16.9	15.4	15.9
		QC	20.2	20.2	20.2	19.8	20.0	18.8
		PEI	30.6	30.4	30.0	**28.2**	24.2	23.4
Bolded were used as EECs in the runoff risk assessment (Appendix I, Table 25) [1] RQs are below the LOC.								

Table 24 Estimated environmental concentration (in µg/L) of combined residues of epyrifenacil and transformation products S-3100-CA, S-3100-DA and S-3100-DP through runoff into a 1-ha water body of 80-cm depth

Crop	Use pattern (g a.i./ha)	Region	Water column EEC (µg/L)					
			Peak	24-hr	96-hr	21-d	60-d	90-d
Wheat, Spring	1 × 40	BC	0.1[1]	0.1[1]	0.1[1]	0.1[1]	0.1[1]	0.1[1]
		MB	1.0	1.0	1.0	1.0	1.0	1.0
		SK	0.9	0.9	0.9	0.9	0.8	0.8
		AB	1.0	1.0	1.0	1.0	1.0	1.0
		ON	2.1	2.1	2.0	2.0	2.0	1.9
		QC	3.5	3.4	3.4	3.4	3.3	3.2
		PEI	4.2	4.2	4.1	4.1	4.0	4.1
Wheat, Winter	1 × 40	BC	**0.6**	0.6	0.6	**0.6**	0.6	0.5
		MB	1.8	1.8	1.8	1.7	1.7	1.7
		SK	1.5	1.5	1.5	1.5	1.6	1.6
		AB	1.2	1.2	1.2	1.3	1.3	1.3
		ON	3.2	3.2	3.2	3.2	3.3	3.2
		QC	3.8	3.8	3.8	3.7	3.7	3.7
		PEI	5.9	5.9	5.9	5.8	5.6	5.7

Crop	Use pattern (g a.i./ha)	Region	Water column EEC (µg/L)					
			Peak	24-hr	96-hr	21-d	60-d	90-d
Summer Fallow	2 × 20 (30-day interval)	BC	**0.2**[1]	0.2[1]	0.2[1]	**0.2**[1]	0.2[1]	0.2[1]
		MB	1.9	1.9	1.9	1.8	1.8	1.7
		SK	1.3	1.3	1.2	1.2	1.2	1.3
		AB	1.1	1.1	1.1	1.1	1.1	1.1
		ON	2.3	2.3	2.3	2.2	2.1	2.1
		QC	2.0	2.0	2.0	2.0	2.0	2.0
		PEI	2.9	2.9	2.9	2.9	2.9	3.0
Corn, field	1 × 40	BC	0.1[1]	0.1[1]	0.1[1]	0.1[1]	0.1[1]	0.1[1]
		ON	2.1	2.1	2.0	2.0	2.0	1.9
		QC	3.5	3.4	3.4	3.4	3.3	3.2
		PEI	4.2	4.2	4.1	4.1	4.0	4.1
Canola	1 × 20	MB	5.1	5.1	5.1	5.1	4.9	4.8
		SK	4.4	4.4	4.4	4.3	4.1	4.1
		AB	4.8	4.8	4.8	4.8	4.9	4.9
Bare ground non-crop and IVM	2 × 40 (14-day interval)	BC	1.0	1.0	1.0	1.0	1.0	0.9
		MB	3.8	3.8	3.8	3.7	3.6	3.5
		SK	2.6	2.6	2.6	2.6	2.6	2.6
		AB	2.7	2.7	2.7	2.7	2.7	2.7
		ON	5.3	5.3	5.3	5.2	5.2	5.3
		QC	7.1	7.1	7.1	7.2	7.2	7.1
		PEI	9.2	9.2	9.1	**9.1**	8.9	8.9

Bolded values were used as EECs in the runoff risk assessment (Appendix I, Table 25)
[1] RQs are below the LOC.

Table 25 Refined risk assessment for aquatic organisms exposed to epyrifenacil residues in surface water from runoff

Organism	Exposure	Test substance	EEC	Endpoint value	UF	Effects metric	RQ[1]	LOC	LOC Exceeded?
Runoff – Second lowest exposure scenario (two applications of 20 g a.i./ha, with a 30-day interval, to summer fallow in British Columbia)									
Fathead minnow, *Pimephales promelas* [2]	32-d Early life stage, adjusted for UV-light enhanced conditions	Epyrifenacil	0.0002 mg a.i./L	0.0010 mg a.i./L	1	0.001 mg a.i./L	0.19	1	No
Amphibians	Chronic (fathead minnow surrogate)	Epyrifenacil	0.0007 mg a.i./L	0.0010 mg a.i./L	1	0.001 mg a.i./L	0.67	1	No
Saltwater mysid, *Americamysis bahia*	28-day Chronic	Epyrifenacil	0.0002 mg a.i./L	0.0021 mg a.i./L	1	0.0021 mg a.i./L	0.095	1	No
Marine diatom, *Skeletonema costatum* [3]	96-h Acute	Epyrifenacil	0.0002 mg a.i./L	0.00047 mg a.i./L	2	0.00024 mg a.i./L	0.85	1	No
Runoff – Third lowest exposure scenario (one application of 40 g a.i./ha to winter wheat in British Columbia)									
Fathead minnow, *Pimephales promelas* [2]	32-d Early life stage, adjusted for UV-light	Epyrifenacil	0.0006 mg a.i./L	0.0010 mg a.i./L	1	0.001 mg a.i./L	0.56	1	No

Organism	Exposure	Test substance	EEC	Endpoint value	UF	Effects metric	RQ[1]	LOC	LOC Exceeded?
	enhanced conditions								
Amphibians	Chronic (fathead minnow surrogate)	Epyrifenacil	0.0019 mg a.i./L	0.0010 mg a.i./L	1	0.001 mg a.i./L	**1.8**	1	**Yes**
Saltwater mysid, *Americamysis bahia*	28-day Chronic	Epyrifenacil	0.0006 mg a.i./L	0.0021 mg a.i./L	1	0.0021 mg a.i./L	0.29	1	No
Marine diatom, *Skeletonema costatum* [3]	96-h Acute	Epyrifenacil	0.0006 mg a.i./L	0.00047 mg a.i./L	2	0.00024 mg a.i./L	**2.6**	1	**Yes**
Runoff – Highest exposure scenario (2 applications of 40 g a.i./ha, with a 14-day interval, to bare ground in Prince Edward Island.									
Fathead minnow *Pimephales promelas* [2]	32-d Early life stage, adjusted for UV-light enhanced conditions	Epyrifenacil	0.0091 mg a.i./L	0.0010 mg a.i./L	1	0.001 mg a.i./L	**8.8**	1	**Yes**
Amphibians	Chronic (fathead minnow surrogate)	Epyrifenacil	0.028 mg a.i./L	0.0010 mg a.i./L	1	0.001 mg a.i./L	**27**	1	**Yes**

Organism	Exposure	Test substance	EEC	Endpoint value	UF	Effects metric	RQ(1)	LOC	LOC Exceeded?
Saltwater mysid, *Americamysis bahia*	28-day Chronic	Epyrifenacil	0.0091 mg a.i./L	0.0021 mg a.i./L	1	0.0021 mg a.i./L	**4.3**	1	**Yes**
Marine diatom, *Skeletonema costatum* (3)	96-h Acute	Epyrifenacil	0.0092 mg a.i./L	0.00047 mg a.i./L	2	0.00024 mg a.i./L	**39**	1	**Yes**

Bold: RQ exceeds LOC

(1) RQs were calculated using Microsoft Excel. Values in this table have been rounded for presentation which may result in minor discrepancies in RQs calculated based on the values presented in this table.

(2) The fathead minnow was used as a surrogate for risk to freshwater and marine fish.

(3) The marine diatom was used as a surrogate for risk to freshwater and marine algae.

Table 26a List of supported uses for S-3100 0.46 EC Herbicide

Items	Label claims that are supported
Region	National
Efficacy claims	Refer to Table 26b
Host crops/use sites	Canola: Apply at 182 mL/ha a minimum of 3-days prior to planting and 363 mL/ha at a minimum of 7-days prior to planting. One application per year.
	Field corn and wheat (spring and winter): Apply up to 726 mL/ha at a minimum of 1-day prior to planting. Maximum two applications with a 14-day interval per year. Maximum annual application rate is 726 mL/ha.
	Soybean: Apply up to 726 mL/ha pre-plant or 3-days after planting but prior to the crop emergence. Maximum two applications with a 14-day interval per year. Maximum annual application rate is 726 mL/ha.
	For use in fall burndown and fallow land programs: Apply at 181–363 mL/ha in combination with labelled herbicides. Maximum two applications with a 30-day interval per year. Maximum annual application rate is 726 mL/ha.
	To maintain bare ground non-crop areas and for IVM: Apply at up to 726 mL/ha. Maximum two applications with a 14-day interval per year. Maximum annual application rate is 1452 mL/ha.

Items	Label claims that are supported	
Tank mixtures	Field corn, soybean, and wheat: Dicamba, glyphosate, glufosinate, 2,4-D, Fierce EZ, Fierce MTZ, and Valtera.	
	Canola: Bromoxynil, glyphosate, and glufosinate.	
	To maintain bare ground non-crop areas and for IVM: 2,4-D Ester, Hyvar X-L Weed and Brush Killer, Krovar I DF, Telar XP, Telar Herbicide Toss-N-Go, Torpedo EZ, Payload, Vanquish, Banvel, Banvel II, Banvel Dry EG, Banvel VM, Banvel VM Pro, Banvel 483, Karmex XP, Karmex DF, Arsenal, Arsenal PowerLine, Tordon 22K, Tordon 101, and Garlon Ultra.	
Application method	Ground application in a minimum of 100 L/ha of water with a spray pressure of 240–410 kPa. If weed populations are moderate to heavy and/or weeds are approaching maximum label size and/or crop canopy is dense, use a minimum of 187 L/ha of water with a spray pressure of 275–345 kPa.	
	Aerial application in a minimum of 70 L/ha of water for burndown programs. Higher water volume applications result in more consistent performance.	
Adjuvant and nitrogen	COC or MSO (which contains at least 15% emulsifier and 80% oil) at 1.0% v/v or Carrier (mineral oil and surfactant blend) at 0.5% v/v. When required by the tank mix partner, use 0.25% NIS. Combination of COC and NIS have shown enhanced burndown activity.	
	A spray grade N source, either 2.25 to 2.8 kg/ha or 28–32% solution at 2.3 to 4.6 L/ha may also be added to the spray mixture.	
Rotational crops	181.5 mL/ha	Immediate plant-back: Field corn, soybean, and wheat (spring and winter). 3 days: Canola. 1 month: Barley, oats, alfalfa, sorghum. 2 months: Sugar beet, dry bean, chickpea, flax, lentil, field pea, potato.
	363 mL/ha	The same as the above except canola with a 7-day interval.
	726 mL/ha	Immediate plant-back: Wheat (spring and winter). 1 month: Barley, oats, field corn, and soybean. 2 months: Alfalfa, canola, dry bean, chickpea, field pea, flax, lentil, potato, and sorghum. 4 months: Sugar beet.
	For other crops, at all three rates	Successful soil bioassay must be performed prior to planting crops not listed above.
Rainfastness	One hour	

Table 26b Efficacy claims that are supported for S-3100 0.46 EC Herbicide

Common name	Application rates (mL/ha)		
	181.5 (10 g a.i./ha)	363 (20 g a.i./ha)	726 (40 g a.i./ha)
Broadleaf weeds			
Palmer amaranth	Suppression	Control	Control
Canada fleabane	-	Suppression	Suppression
Volunteer canola	Suppression	Control	Control
Common chickweed	-	Suppression	Control
Mouse-ear chickweed	-	Control	Control
Cleavers (catchweed bedstraw)	-	Control	Control
Common cocklebur	-	Control	Control
Dandelion	-	Control	Control
Kochia	Suppression	Control	Control
Common lamb's-quarters	Suppression	Control	Control
Black medick	-	Control	Control
Entireleaf morningglory	Suppression	Control	Control
Ivyleaf morningglory	Suppression	Control	Control
Pitted morningglory	Suppression	Control	Control
Powell (green) pigweed	-	Control	Control
Redroot pigweed	-	Control	Control
Smooth pigweed	-	Control	Control
Prickly lettuce	-	Control	Control
Common purslane	-	Control	Control
Common ragweed	-	Control	Control
Giant ragweed	-	Suppression	Control
Shepherd's-purse	-	Suppression	Control
Pale smartweed	-	Control	Control
Annual sow-thistle	-	Control	Control
Perennial sow-thistle	-	Suppression	Suppression
Canada thistle	-	Control	Control

Common name	Application rates (mL/ha)		
	181.5 (10 g a.i./ha)	363 (20 g a.i./ha)	726 (40 g a.i./ha)
Velvetleaf	Control	Control	Control
Common waterhemp	Suppression	Control	Control
Tall waterhemp	-	Control	Control
Wild mustard	-	Control	Control
Grassy weeds			
Common barnyardgrass	Suppression	Suppression	Control
Annual bluegrass	Suppression	Suppression	Suppression
Downy brome	-	Suppression	Suppression
Large crabgrass	Suppression	Control	Control
Giant foxtail	Control	Control	Control
Green foxtail	Control	Control	Control
Yellow foxtail	Control	Control	Control
Rhizome johnsongrass	-	Control	Control
Fall panicum	-	Suppression	Control
Italian ryegrass	-	Suppression	Suppression
Broadleaf signalgrass	Suppression	Suppression	Control
Wild oats	Suppression	Control	Control

Table 26c List of supported uses for V-10488 0.94 SE Herbicide

Items	Label claims that are supported
Region	National
Burndown claims	Refer to Table 26d
Residual efficacy claims	1.75–2.0 L/ha in cropland: Palmer amaranth, annual sowthistle, Canada fleabane, volunteer canola†, cleavers, common chickweed, dandelion, kochia, lamb's-quarters, Eastern black nightshade, hairy nightshade, Pennsylvania smartweed, green pigweed, redroot pigweed, common ragweed, Russian thistle†, velvetleaf, common waterhemp, wild buckwheat, wild mustard, barnyard grass, downy brome†, Japanese brome†, large crabgrass, foxtail barley†, green foxtail, and wild oats†.

Items	Label claims that are supported
	† Suppression only.
	3.5 L/ha in non-cropland: all weed listed above plus control of witchgrass.
Timing and crop/use sites	Soybean: Apply at 1.75–2.0 L/ha pre-plant or after planting but prior to the crop emergence. One application per year.
	Spring wheat: Apply 1.75 L/ha at a minimum of 30 days prior to planting. One application per year.
	For use in fall burndown and fallow land programs: Apply at 1.75–2.0 L/ha in combination with labelled herbicides in the fall.
	To maintain bare ground on-crop areas and for IVM: Apply at 1.75–3.5 L/ha. Do not apply more than 3.5 L/ha per application. Do not apply more than two applications and 3.5 L/ha per year.
Tank mixtures	Soybean: For burndown weed control - BlackHawk, glyphosate, Liberty 200 SN, and/or Select EC. For residual weed control - BroadStrike RC, FirstRate, Sencor, Pursuit, Prowl, and Classic.
	Wheat: For burndown weed control - glyphosate, 2,4-D, MCPA, BlackHawk, Conquer II, ThunderHawk, and GoldWing.
	TO maintain bare ground non-crop areas: 2,4-D Ester, Hyvar XL, Krovar, Telar, Vanquish, Banvel, Karmex, Arsenal, Tordon, and Garlon.
Application method	Ground application in a minimum of 100 L of water per hectare with a spray pressure of 240–410 kPa. If weed populations are moderate to heavy and/or weed are approaching max label size and/or crop canopy is dense, apply in a minimum of 187 L of water per hectare with a spray pressure of 275–345 kPa.
Additives	COC or MSO (which contains at least 15% emulsifier and 80% oil) at 1.0% v/v or Carrier (mineral oil and surfactant blend) at 0.5% v/v. When required by the tank mix partner, use 0.25% NIS. Combinations of COC and NIS have shown enhanced burndown activity.
	A spray grade N source, either 2.25 to 2.8 kg/ha or 28–32% solution at 2.3–4.6 L/ha may also be added to the spray mixture.

Items	Label claims that are supported
Rotational crops at 1.75 – 2.0 L/ha	Immediate plant-back: Soybean. 1 month: Field corn and wheat (spring and winter). 2 months: Chickpea and field pea. 6 months: Lentil. 11 months: Barley, oats, and alfalfa (1.75 L/ha). 12 months: Canola and alfalfa (>1.75 L/ha). For other crops: Successful soil bioassay must be performed prior to planting crops not listed above.
Rainfastness	One hour

Table 26d Burndown efficacy claims that are supported for V-10488 0.94 SE Herbicide

Common Name	1.75–2.0 L/ha (labelled crops)	3.5 L/ha (non-crop areas)
Broadleaf weeds		
Palmer amaranth	Control	Control
Annual sowthistle	Control	Control
Canada fleabane	Suppression	Suppression
Volunteer canola	Control	Control
Common chickweed	Control	Control
Mouse-ear chickweed	Control	Control
Cleavers (catchweed bedstraw)	Control	Control
Common cocklebur	Control	Control
Dandelion	Control	Control
Kochia	Control	Control
Common lamb's-quarters	Control	Control
Black medick	Control	Control
Entireleaf morningglory	Control	Control
Ivyleaf morningglory	Control	Control
Pitted morningglory	Control	Control

Common Name	1.75–2.0 L/ha (labelled crops)	3.5 L/ha (non-crop areas)
Green pigweed/Powell amaranth	Control	Control
Redroot pigweed	Control	Control
Smooth pigweed	Control	Control
Prickly lettuce	Control	Control
Common purslane	Control	Control
Common ragweed	Control	Control
Giant ragweed	Suppression	Control
Shepherd's-purse	Suppression	Control
Pale smartweed	Control	Control
Perennial sowthistle	Suppression	Suppression
Canada thistle	Control	Control
Velvetleaf	Control	Control
Common waterhemp	Control	Control
Tall waterhemp	Control	Control
Wild mustard	Control	Control
Grassy weeds		
Common barnyardgrass	Suppression	Control
Annual bluegrass	Suppression	Suppression
Downy brome	Suppression	Suppression
Large crabgrass	Control	Control
Giant foxtail	Control	Control
Green foxtail	Control	Control
Yellow foxtail	Control	Control
Rhizome johnsongrass	Control	Control
Fall panicum	Suppression	Control
Italian ryegrass	Suppression	Suppression
Broadleaf signalgrass	Suppression	Control
Wild oats	Control	Control

Table 27 Toxic Substances Management Policy (TSMP) considerations – Comparisons to TSMP Track 1 criteria

TSMP Track 1 criteria	TSMP Track 1 criterion value		Active ingredient endpoints	Transformation products endpoints
CEPA toxic or CEPA toxic equivalent[1]	Yes		Yes	Yes
Predominantly anthropogenic[2]	Yes		Yes	Yes
Persistence[3]	Soil	Half-life ≥ 182 days	No, the range of DT_{50} values in aerobic and anaerobic soils (n = 8) is 0.02–0.4 days	**S-3100-CA:** No for 11/12 available DT_{50} values. The range of DT_{50} values in aerobic (n = 4) and anaerobic soils (n = 3) treated with epyrifenacil, and aerobic soils treated with S-3100-CA (n = 5) is 18.4–276 days **S-3100-CA-RD:** Yes for 2/4 available DT_{50} values. The range of DT_{50} values in aerobic soil treated with epyrifenacil (n = 1), and aerobic soils treated with S-3100-CA-RD (n = 3) is 24.5–471 days **S-3100-DA:** Yes for 2/3 DT_{50} values. The range of DT_{50} values in aerobic soil treated with S-3100-DA is 58.5–1515 days **S-3100-CA-UR:** Yes, the range of DT_{50} values in aerobic soil treated with S-3100-CA-UR (n = 3) is 578–6207 days **S-3100-DA-RD:** Yes, the range of DT_{50} values in aerobic soil treated with S-3100-DA-RD (n = 3) is 357–718 days

TSMP Track 1 criteria	TSMP Track 1 criterion value		Active ingredient endpoints	Transformation products endpoints
				4"-OH-S-3100-CA: No, the range of DT_{50} values in aerobic soil treated with 4"-OH-S-3100-CA (n = 2) is 1.7–4.2 days **S-3100-DP:** No, the range of DT_{50} values in aerobic soil treated with S-3100-DP (n = 3) is 7.2–48.2 days **Other major TPs:** Not available
	Water	Half-life ≥ 182 days	No, the range of DT_{50} values in aerobic and anaerobic whole systems is 0.98–4 days	**S-3100-CA:** No, the range of aerobic and anaerobic DT_{50} values in whole systems treated with epyrifenacil (n = 4) is 11.6 to 93.3 days **S-3100-CA-UR:** Yes, the range of DT_{50} values in aerobic and anaerobic whole systems treated with epyrifenacil (n = 4) is 104–717 days **Other major TPs:** Not available
	Sediment	Half-life ≥ 365 days		
	Air	Half-life ≥ 2 days, or evidence of atmospheric transport to remote regions such as the Arctic	The AOPWIN (v. 1.92) model is not suited for predicting the atmospheric half-life of epyrifenacil given the large fraction expected to be sorbed to airborne particles.	**1,1,1-trifluoroacetone and TFA:** Yes, the AOPWIN (v. 1.92) predicted half-lives in the gas phase in the atmosphere are 715 and 20.6 days, respectively, based on the hydroxyl (OH) radical reaction (1.5×10^6 molecules OH/cm^3) during 12 hours of daylight. **Other major TPs:** The AOPWIN (v1.92) model is not suited for predicting the atmospheric half-life of the other major transformation products of epyrifenacil

TSMP Track 1 criteria	TSMP Track 1 criterion value	Active ingredient endpoints	Transformation products endpoints
			given the large fraction expected to be sorbed to airborne particles.
Bioaccumulation[4]	Log $K_{OW} \geq 5$	No, log K_{OW}: 3.42	**Major TPs:** No, all log K_{ow} values < 2.02
	BCF ≥ 5000	No, BCF_{KGL} (whole fish, TRR) = 45.89–112.07 L/kg, based on total residues of epyrifenacil and the TPs that formed in fish tissues (S-3100-CA and S-3100-DA).	
	BAF ≥ 5000	Not available	Not available
Is the chemical a TSMP Track 1 substance (all four criteria must be met)?		No, does not meet all of the TSMP Track 1 criteria.	No, do not meet all of the TSMP Track 1 criteria.

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

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

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

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

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

Epyrifenacil is an active ingredient that is concurrently being registered in Canada and the United States for use on soybean, field corn, wheat, and canola. In accordance with Table 1, the MRLs proposed in Canada for epyrifenacil on these four crops are the same as corresponding tolerances to be promulgated in the United States. American tolerances are not being established for animal commodities.

Once established, the American tolerances for epyrifenacil on crops will be listed in the Electronic Code of Federal Regulations, 40 CFR Part 180, by pesticide.

Currently, there are no Codex MRLs[11] listed for epyrifenacil in or on any commodity on the Codex Alimentarius Pesticide Index website. A listing of established Codex MRLs is available on the Codex Alimentarius Pesticide Index webpage, by pesticide or commodity.

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

Table 1 Comparison of proposed Canadian MRLs, American Tolerances and Codex MRLs (where different)

Food commodity	Proposed Canadian MRL	Proposed American Tolerance (ppm)	Codex MRL (ppm)
Dry soybean	0.005	0.005	Not established
Field corn	0.005	0.005	
Wheat	0.005	0.005	
Rapeseeds (canola)	0.005	0.005	
Eggs; fat, meat, and meat byproducts of cattle, goats, horses, hogs, sheep, and poultry; milk	0.01	None	

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

References

A. List of studies/Information submitted by registrant

1.0 Chemistry

PMRA Document Number	Reference
S-3100 Technical	
3307034	2020, Enforcement Analytical Methods of S-3100 Technical Grade, DACO: 2.13.1
3307035	2020, Enforcement Analytical Methods of S-3100 Technical Grade, DACO: 2.13.1 CBI
3307038	2021, 1st Amendment Report: S-3100 Technical Grade: Confirmation of Identity of Active Ingredient and Impurities, DACO: 2.13.2
3307040	2021, Characterization of Active Ingredient and Identification of Ingredients in S-3100 Technical Grade, DACO: 2.13.2
3307041	2021, Characterization of Active Ingredient and Identification of Ingredients in S-3100 Technical Grade, DACO: 2.13.2 CBI
3307043	2021, S-3100 Technical: Product Identity and Composition, Description of Materials Used to Produce the Product, Description of Production Process and Discussion on Formation of Impurities, DACO: 2.11.1,2.11.2, 2.11.3, 2.11.4, 2.13.2 CBI
3307044	2020, Batch Analysis of S-3100 Technical Grade, DACO: 2.13.3
3307045	2020, Batch Analysis of S-3100 Technical Grade, DACO: 2.13.3 CBI
3307046	2017, S-3100 PAI: Physico-Chemical Properties, DACO: 2.14.1, 2.14.12, 2.14.15,2.14.2,2.14.3,2.14.4,2.14.5,830.7000
3307047	2017, S-3100 - Determining the Partitioning Coefficient (n-Octanol/Water) by the Shake Flask Method Following OECD 107 and OCSPP 830.7550, DACO: 2.14.11
3307049	2020, Stability of S-3100 Technical Grade to Normal and Elevated Temperatures, Metals and Metal Ions, DACO: 2.14.13
3307050	2020, Storage Stability and Corrosion Characteristics of S-3100 Technical Grade, DACO: 2.14.14,2.16
3307051	2018, S-3100 TG: Physicochemical Properties, DACO: 2.14.1,2.14.15, 2.14.2, 2.14.3,2.14.6,2.14.8,2.16,830.7000
3307052	2017, S-3100 - Determination of the Water Solubility of a Test Substance Following OECD 105 and OCSPP 830.7840 Guidelines, DACO: 2.14.7
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3308322	2021, A GLP 28-Day Oral (Dietary) Study of 4"-OH-S-3100-CA in CD-1 Mice, DACO: 4.3.3
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3.0 Environment

PMRA Document Number	Reference
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3379298	2022, S-3100: Response to Comments in 75-Day Deficiency Letter Regarding the Physicochemical Properties of Major Transformation Products, DACO: 8.2.1
3308407	2017, [phenyl-14C] S-3100 - Determination of Abiotic Degradation by Hydrolysis, DACO: 8.2.3.2
3308408	2019, [pyrimidinyl-4-14C]S-3100 - Determination of Abiotic Degradation by Hydrolysis, DACO: 8.2.3.2
3308409	2021, [14C]S-3100-CA - Determination of Abiotic Degradation by Hydrolysis, DACO: 8.2.3.2
3308410	2021, [14C]S-3100-DA - Determination of Abiotic Degradation by Hydrolysis, DACO: 8.2.3.2
3308411	2020, V-10456: Photodegradation in/on Soil by Artificial Sunlight, DACO: 8.2.3.3.1
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3308415	2021, Stability of S-3100 in Air (Calculation by Atkinsons Method), DACO: 8.2.3.3.3
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3308418	2019, [Pyrimidinyl-4-14C]S-3100 - Aerobic Degradation in Soil, DACO: 8.2.3.4.2
3308419	2020, [14C]S-3100 - Aerobic Degradation in Four Brazilian Soils, DACO: 8.2.3.4.2
3308420	2021, Determination of Aerobic Metabolism of [phenyl-14C]S-3100-DA in Soil - Rate Study, DACO: 8.2.3.4.2
3308421	2021, [14C]4"-OH-S-3100-CA - Aerobic Degradation in Three Soils - Rate Study, DACO: 8.2.3.4.2
3308422	2021, [14C]S-3100-CA: - Aerobic Degradation in Five US Soils, DACO: 8.2.3.4.2
3308423	2021, [14C]S-3100-DA-RD: Aerobic Degradation in Three US Soils, DACO: 8.2.3.4.2
3308424	2021, [14C]S-3100-CA-UR: Aerobic Degradation in Three US Soils, DACO: 8.2.3.4.2
3308425	2021, [14C]S-3100-CA-RD: Aerobic Degradation in Three US Soils, DACO: 8.2.3.4.2
3308426	2021, [14C]S-3100-DP: Aerobic Degradation in Three Soils - Rate Study, DACO: 8.2.3.4.2
3308427	2021, [14C]S-3100 - Anaerobic Degradation in Three US Soils, DACO: 8.2.3.4.4
3308428	2021, [14C]S-3100 - Anaerobic Degradation in a US Soil, DACO: 8.2.3.4.4
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3309612	2019, [pyridyl-4(6)-14C]S-3100 - Aerobic Transformation in Aquatic Sediment Systems, DACO: 8.2.3.5.4
3309613	2019, [pyrimidinyl-4-14C]S-3100 - Aerobic Transformation in Aquatic Sediment Systems, DACO: 8.2.3.5.4
3309614	2021, [pyrimidinyl-4-14C]S-3100 - Anaerobic Transformation in Aquatic Sediment Systems, DACO: 8.2.3.5.6
3309615	2021, [14C] V-10456: Degradation under Anaerobic Aquatic Conditions, DACO: 8.2.3.5.6
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3309617	2017, [14C] S-3100 - Adsorption-Desorption on Five Soils and One Sediment using a Batch Equilibrium Method, DACO: 8.2.4.2
3309618	2019, [14C]S-3100 - Adsorption-Desorption on Four Brazilian Soils using a Batch Equilibrium Method, DACO: 8.2.4.2
3309620	2021, [pyridyl-4(6)-14C]S-3100-CA-RD: Adsorption on Three Soils using a Batch Equilibrium Method, DACO: 8.2.4.2
3309621	2021, [14C]S-3100: Adsorption Study on Volcanic Ash Soil, DACO: 8.2.4.2
3309622	2021, [pyridyl-4(6)-14C]S-3100-CA-UR: Adsorption on Three Soils using a Batch Equilibrium Method, DACO: 8.2.4.2

PMRA Document Number	Reference
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3309625	2021, S-3100-DA: Adsorption/Desorption (Batch Equilibrium), DACO: 8.2.4.2
3309626	2021, S-3100 CA: Adsorption Study on Volcanic Ash Soil, DACO: 8.2.4.2
3309627	2021, 4"-OH-S-3100-CA: Adsorption/Desorption (Batch Equilibrium), DACO: 8.2.4.2
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3309354	2021, V-10456: Freezer Storage Stability of V-10456 and Metabolites in Soil, DACO: 8.6
3308449	2020, V-10456: Effects on Reproduction and Growth of Earthworms *Eisenia andrei* in Artificial Soil, DACO: 9.2.3
3308450	2018, S-3100 TG: An Acute Contact Toxicity Study with the Honey Bee, DACO: 9.2.4.1
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3308452	2020, S-3100 TG: A Chronic Larval Toxicity Study With The Honey Bee (*Apis Mellifera*), DACO: 9.2.4.3
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3308454	2020, S-3100: 10-Day Oral Toxicity Test with the Adult Honey Bee (*Apis mellifera*), DACO: 9.2.4.4
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3308458	2020, Acute Immobilisation Study of S-3100-CA with *Daphnia magna*, DACO: 9.3.2
3308459	2019, S-3100 TG - Full Life-Cycle Toxicity Test with Water Fleas (*Daphnia magna*) Under Static-Renewal Conditions, DACO: 9.3.3
3308460	2020, V-10456 Technical: 10-Day Toxicity Test Exposing Midge (*Chironomus dilutus*) to a Test Substance Applied to Sediment Under Intermittent-Renewal Conditions, DACO: 9.3.4
3308461	2020, V-10456 Technical: 10-Day Toxicity Test Exposing Freshwater Amphipods (*Hyalella azteca*) to a Test Substance Applied to Sediment Under Intermittent-Renewal Conditions, DACO: 9.3.4
3308462	2019, V-10456 TG: Acute Toxicity Test with Mysids (*Americamysis bahia*) Under Flow-Through Conditions, DACO: 9.4.2
3308464	2021, V-10456 Technical: 10-Day Toxicity Test Exposing Estuarine Amphipods (*Leptocheirus plumulosus*) to a Test Substance Applied to Sediment Under Intermittent-Renewal Conditions, DACO: 9.4.2

PMRA Document Number	Reference
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3308470	2018, S-3100 TG - Acute Toxicity Test with Bluegill Sunfish (*Lepomis macrochirus*) Under Flow-Through Conditions, DACO: 9.5.2.2
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3308472	2018, S-3100 TG - Acute Toxicity Test with Fathead Minnow (*Pimephales promelas*) Under Flow-Through Conditions, DACO: 9.5.2.3
3308473	2019, V-10456 Technical: Acute Toxicity Test with Sheepshead Minnow (*Cyprinodon variegatus*) Under Flow-Through Conditions, DACO: 9.5.2.4
3308474	2020, V-10456: Early Life-Stage Toxicity Test with Sheepshead Minnow (*Cyprinodon variegatus*), DACO: 9.5.3.1
3308475	2018, S-3100 TG - Early Life-Stage Toxicity Test with Fathead Minnow (*Pimephales promelas*), DACO: 9.5.3.1
3308476	2021, S-3100: Request to Waive the Requirement for a uV Enhanced Fish Early Life Stage Toxicity Study, DACO: 9.5.3.1
3308477	2018, [phenyl-14C]S-3100 - Flow-Through Bioconcentration and Metabolism Study with Bluegill Sunfish (*Lepomis macrochirus*), DACO: 9.5.6
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3308484	2021, S-3100 TG: A Pilot Reproduction Study With The Northern Bobwhite, DACO: 9.6.3.1
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3308489	2019, V-10456: 96-Hour Toxicity Test with the Freshwater Cyanobacterium, *Anabaena flos-aquae*, DACO: 9.8.2
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3308492	2021, S-3100-CA-UR: Toxicity to the Freshwater Green Alga, *Raphidocelis subcapitata*, DACO: 9.8.2
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PMRA Document Number	Reference
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3308497	2021, S-3100-DA: Toxicity to the Freshwater Green Alga, *Raphidocelis subcapitata*, DACO: 9.8.2
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3308525	2021, S-3100-DA-UR: Toxicity to the Freshwater Diatom, *Navicula pelliculosa*, DACO: 9.8.2
3308526	2021, 4"-OH-S-3100-CA: Toxicity to the Freshwater Diatom, *Navicula pelliculosa*, DACO: 9.8.2
3308527	2021, S-3100-DA-RD: Toxicity to the Freshwater Diatom, *Navicula pelliculosa*, DACO: 9.8.2
3308528	2021, S-3100-DP: Toxicity to the Freshwater Diatom, *Navicula pelliculosa*, DACO: 9.8.2
3308529	2021, S-3100-DA: Toxicity to the Freshwater Diatom, *Navicula pelliculosa*, DACO: 9.8.2
3308530	2021, S-3100-CA: Toxicity to the Freshwater Diatom, *Navicula pelliculosa*, DACO: 9.8.2
3308531	2021, S-3100-DA-RD: Toxicity to the Freshwater Green Alga, *Raphidocelis subcapitata*, DACO: 9.8.2
3308532	2021, S-3100-CA-RD: Toxicity to the Freshwater Diatom, *Navicula pelliculosa*, DACO: 9.8.2
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3308512	2020, V-10456: Seedling Emergence Test, DACO: 9.8.4
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4.0 Value

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3307077	2021, S-3100 0.46 EC Herbicide: Annex IIA Tier II Summary, Efficacy and crop tolerance data and information on S-3100 0.46 EC Herbicide, containing epyrifenacil, for use on bare ground (non-crop), canola, corn (field), soybean, and wheat, DACO: 10.1, 10.2, 10.2.1, 10.2.2, 10.2.3.1, 10.2.3.3(B), 10.3.1, 10.3.2(A), 10.3.3, 10.4, 10.5.1, 10.5.2, 10.5.3, and 10.5.4.
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PMRA Document Number	Reference
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3307115	2021, V-10488 0.94 SE Herbicide: Annex IIA Tier II Summary, Efficacy and crop tolerance data and information on V-10488 0.94 SE Herbicide (containing epyrifenacil, flumioxazin, and pyroxasulfone) for use on bare ground (non-crop), soybean, and wheat, DACO: 10.1, 10.2.1, 10.2.2, 10.2.3.1, 10.2.3.3(B), 10.3, 10.3.1, 10.3.2(A), 10.3.3, 10.5.1, 10.5.2, and 10.5.3.

B. Additional information considered

i) Published information

1.0 Human and animal health

PMRA Document Number	Reference
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3435231	2016, Sources, fates, toxicity, and risks of trifluoroacetic acid and its salts: Relevance to substances regulated under the Montreal and Kyoto Protocols, Journal of Toxicology and Environmental Health, Part B, 19(7), 289-304, DACO: 11.1
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3435216	2021, Insufficient evidence for the existence of natural trifluoroacetic acid, Environmental Science: Processes & Impacts, 23(11), 1641-1649, DACO: 11.1
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2.0 Environment

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3648570	2016, US EPA Memorandum: Guidance on Light-Dependent Peroxidizing Herbicides, DACO: 9.9
3648595	1999, Environmental Toxicology and Chemistry, Vol. 18, No. 5, pp. 1053-1059, Toxicity of trifluoroacetate to aquatic organisms, DACO: 9.9
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