Proposed Registration Decision PRD2025-06

Cyclobutrifluram, A22011 Crop, A23156 Crop, VICTRATO and VICTRATO 2

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Overview

Proposed registration decision for cyclobutrifluram

Health Canada's Pest Management Regulatory Agency (PMRA), pursuant to subsection 28(1) of the *Pest Control Products Act*, is proposing registration for the sale and use of Cyclobutrifluram Technical, A22011 Crop, A23156 Crop, VICTRATO and VICTRATO 2, containing the technical grade active ingredient cyclobutrifluram, a nematicide and fungicide for use on romaine lettuce and as a soybean seed treatment.

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 cyclobutrifluram and A22011 Crop, A23156 Crop, VICTRATO and VICTRATO 2.

What does Health Canada consider when making a registration decision?

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

Before making a final registration decision on cyclobutrifluram, A22011 Crop, A23156 Crop, VICTRATO and VICTRATO 2, Health Canada's PMRA will consider any written comments received from the public directly related to the proposed decision in this consultation document.[3]

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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."

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

Health Canada will then publish a Registration Decision[4] on cyclobutrifluram, A22011 Crop, A23156 Crop, VICTRATO and VICTRATO 2, 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 cyclobutrifluram?

Cyclobutrifluram is a new conventional active ingredient for nematode and fungal disease management in Canada. As a nematicide, it works on contact and by systemic feeding activity on certain nematodes to disrupt ATP (adenosine triphosphate) production in nematode mitochondria. Cyclobutrifluram is also a systemic and selective fungicide that inhibits spore germination and mycelial growth of certain fungal pathogens.

Health considerations

Can approved uses of cyclobutrifluram affect human health?

A22011 Crop, A23156 Crop, VICTRATO, and VICTRATO 2, containing cyclobutrifluram, are unlikely to affect your health when used according to proposed label directions.

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

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

In laboratory animals, the technical grade active ingredient cyclobutrifluram was of low acute toxicity via the oral, dermal, and inhalation routes of exposure. It was not irritating to the eyes or skin and did not cause an allergic skin reaction.

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

The acute toxicity of end-use product A22011 Crop, containing cyclobutrifluram, was low via the oral, dermal and inhalation routes of exposure. It was minimally irritating to the eyes, and non-irritating to the skin. It did not cause an allergic skin reaction.

The acute toxicity of end-use product A23156 Crop, containing cyclobutrifluram, was low via the oral and inhalation routes of exposure and it was considered to be of low acute toxicity via the dermal route. A23156 Crop was slightly irritating to the skin. It was moderately irritating to the eyes and caused an allergic skin reaction; consequently, the signal word "WARNING" and hazard statements "EYE IRRITANT" and "POTENTIAL SKIN SENSITIZER" are required on the label.

The acute toxicity of end-use products VICTRATO and VICTRATO 2, containing cyclobutrifluram, was low via the oral, dermal and inhalation routes of exposure. VICTRATO and VICTRATO 2 were minimally irritating to the eyes and they did not cause an allergic skin reaction. VICTRATO and VICTRATO 2 were mildly irritating to the skin; consequently, the signal word and hazard statement "CAUTION – SKIN IRRITANT" are required on the label.

Registrant-supplied short- and long-term (lifetime) animal toxicity tests, as well as information from the published scientific literature, were assessed for the potential of cyclobutrifluram to cause neurotoxicity, immunotoxicity, chronic toxicity, cancer, reproductive and developmental toxicity, and various other potential human health hazards. The most sensitive endpoints for risk assessment were effects on body weight, sexual development and fertility, the lung and the thyroid. There was no evidence to suggest that cyclobutrifluram damaged genetic material. Cyclobutrifluram did, however, cause liver tumours in mice and thyroid tumours in rats. 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 A22011 Crop and A23156 Crop

Occupational risks are not of health concern when A22011 Crop and A23156 Crop are used according to the proposed label directions, which include protective measures.

Workers mixing, loading or applying A22011 Crop and A23156 Crop, and workers entering recently treated fields can be exposed to cyclobutrifluram residues through direct skin contact or through inhalation. Therefore, the labels specify that anyone mixing, loading and applying A22011 Crop and A23156 Crop and performing cleaning and repair activities must wear a long-sleeved shirt, long pants, chemical-resistant gloves, socks and shoes. In addition, when mixing and loading A23156 Crop and performing cleaning and repair activities, workers must wear protective eyewear (goggles or face shield). The labels also require that workers do not enter or be allowed into treated fields during the restricted-entry interval (REI) of 12 hours.

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 A22011 Crop and A23156 Crop are not of health concern when the end-use products are used according to the proposed label directions.

Occupational risks from handling VICTRATO and VICTRATO 2

Occupational risks are not of health concern when VICTRATO and VICTRATO 2 are used according to the proposed label directions, which include protective measures.

Workers treating soybean seed with VICTRATO and VICTRATO 2 in commercial facilities, by commercial mobile systems or on-farm, and workers planting treated soybean seed can come into direct contact with cyclobutrifluram residues on the skin and through inhalation.

The VICTRATO and VICTRATO 2 labels specify that workers mixing, loading, treating, and calibrating during commercial soybean seed treatment of soybean with open or closed transfer, must wear a long-sleeved shirt, long pants, chemical-resistant gloves, socks and shoes. For good hygiene practice, it is also recommended to wear a NIOSH-approved N95 (minimum) filtering facepiece respirator (dust mask) that is properly fit tested. For bagging/sewing/stacking, any other activities involving handling treated seeds, and cleaning and repairing, workers must wear a long-sleeved shirt, long pants, chemical-resistant gloves, shoes and socks, and a NIOSH-approved N95 (minimum) filtering facepiece respirator (dust mask) that is properly fit tested.

When handling and planting commercially treated seed, workers must wear a long-sleeved shirt, long pants, chemical-resistant gloves, socks, and shoes and a NIOSH-approved N95 (minimum) filtering facepiece respirator (dust mask) that is properly fit tested, and must use a closed-cab tractor when planting. Gloves and respirator are not required within a closed cab.

On-farm workers involved in mixing, loading, transferring (either through an open or closed transfer system), treating, and calibrating, must wear a long-sleeved shirt, long pants, chemical-resistant gloves, socks and shoes. In addition, when cleaning, repairing, handling and planting treated bulk or bagged seed, workers must wear a long-sleeved shirt, long pants, chemical-resistant gloves, socks and shoes and a NIOSH-approved N95 (minimum) filtering facepiece respirator (dust mask) that is properly fit tested, and must use a closed-cab tractor when planting. Gloves and respirator are not required within a closed cab.

Taking into consideration these label statements and the duration of exposure for handlers and workers, health risks to these individuals are not a concern.

Health risks in residential and other non-occupational environments

A22011 Crop, A23156 Crop, VICTRATO and VICTRATO 2 are not domestic class products and are not permitted for use in residential settings or other non-occupational environments.

Health risks to bystanders

Bystander risks are not of health concern when A22011 Crop, A23156 Crop, VICTRATO and VICTRATO 2 are used according to the proposed label directions and spray drift restrictions are observed.

A standard label statement to protect against drift during application is on the labels. Therefore, health risks to bystanders are not of concern when the end-use products are 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.

The basic acute aggregate dietary intake estimates (food plus drinking water) revealed that the general population, females aged 13–49 and infants less than one-year-old are expected to be exposed to less than 4% of the acute reference dose (ARfD). When the common metabolite trifluoroacetic acid (TFA) is included for rotational crops and drinking water, the highest exposure estimate is less than 4% of the ARfD (infants less than one-year old). Based on these estimates, the acute dietary risk from cyclobutrifluram is not of health concern.

The basic chronic aggregate dietary intake estimates (food plus drinking water) revealed that the general population and infants less than one-year old are expected to be exposed to less than 15% of the acceptable daily intake (ADI). When TFA is included for rotational crops and drinking water, the highest exposure estimate is less than 15% of the ADI (infants less than one-year old). Based on these estimates, the chronic dietary risk from cyclobutrifluram is 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 *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 cyclobutrifluram is used according to the supported label directions, MRLs are being proposed as a result of this assessment (refer to PMRL2025-19, *Cyclobutrifluram*).

MRLs for cyclobutrifluram determined from the acceptable residue trials conducted throughout the United States and Brazil, including growing regions representative of Canada, on Romaine lettuce and soybeans, can be found in the Science evaluation of this document.

Environmental considerations

What happens when cyclobutrifluram is introduced into the environment?

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

Cyclobutrifluram enters the environment when its end-use products A22011 Crop, A23156 Crop, VICTRATO, and VICTRATO 2 are used to control diseases in labelled crops or on treated seeds. Cyclobutrifluram breaks down in soil or water in the presence of light to form several major transformation products (SYN510275, CGA177291, EXC8199, SYN551241, SYN551231 and TFA) and one minor transformation product (SYN549104). Cyclobutrifluram is otherwise slow to break down in the environment in the absence of light.

Cyclobutrifluram and its transformation products may move through soil and reach groundwater. They may also move off the treatment area in runoff to reach surface water. Cyclobutrifluram is not expected to dissipate into air in significant quantities or to accumulate in the tissue of animals.

After a scientific review of the available information, the PMRA has concluded that the environmental risks from the proposed uses of cyclobutrifluram are acceptable when used according to label directions.

Value considerations

What is the value of A22011 Crop, A23156 Crop, VICTRATO, and VICTRATO 2?

Cyclobutrifluram is the active ingredient in A22011 Crop, A23156 Crop, VICTRATO, and VICTRATO 2. The registration of these products will provide Canadian growers with a new mode of action to manage important nematode infection and fungal diseases on the crops specified on these product labels.

A22011 Crop, A23156 Crop, VICTRATO, and VICTRATO 2 contain cyclobutrifluram as their sole active ingredient. A22011 Crop and A23156 Crop, applied as soil drench or banded spray applications, are effective against root-knot nematode in romaine lettuce. VICTRATO and VICTRATO 2, applied as seed treatments, are effective against soybean cyst nematode and early season *Fusarium* infection, the cause of sudden death syndrome in soybean.

Measures to minimize risk

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

The key risk-reduction measures being proposed on the label of Cyclobutrifluram Technical, A22011 Crop, A23156 Crop, VICTRATO and VICTRATO 2 to address the potential risks identified in this assessment are as follows.

Key risk-reduction measures

Human health

A22011 Crop and A23156 Crop

To reduce the potential exposure of workers to cyclobutrifluram through direct skin contact or inhalation of sprays, workers mixing, loading and applying A22011 Crop and A23156 Crop and performing cleaning and repair activities must wear a long-sleeved shirt, long pants, chemical-resistant gloves, socks and shoes. Additionally, workers must wear protective eyewear (goggles or face shield) when mixing, loading, cleaning or performing repair activities involving A23156 Crop. The labels also require that workers do not enter or be allowed entry into treated areas during the REI of 12 hours. Risks to workers are not of health concern when A22011 Crop and A23156 Crop are used according to the proposed label directions and restricted-entry intervals (REIs) are observed. Furthermore, a standard label statement to protect against drift during application is present on the labels.

VICTRATO and VICTRATO 2

To reduce the potential exposure of workers to cyclobutrifluram through direct skin contact or inhalation of sprays, the VICTRATO and VICTRATO 2 labels specify that workers mixing, loading, treating, calibrating in commercial soybean seed treating facilities with open or closed transfer system, must wear a long-sleeved shirt, long pants, chemical-resistant gloves, socks and shoes. For good hygiene practice, it is also recommended to wear a NIOSH-approved N95 (minimum) filtering facepiece respirator (dust mask) that is properly fit tested. For bagging/sewing/stacking, any other activities involving handling treated seeds, and cleaning and repairing, workers must wear a long-sleeved shirt, long pants, chemical-resistant gloves, shoes and socks, and a NIOSH-approved N95 (minimum) filtering facepiece respirator (dust mask) that is properly fit tested.

When handling and planting commercially treated seed, workers must wear a long-sleeved shirt, long pants, chemical-resistant gloves, socks, and shoes and a NIOSH-approved N95 (minimum) filtering facepiece respirator (dust mask) that is properly fit tested and must use closed-cab tractor when planting. Gloves and respirator are not required within a closed cab.

On-farm workers involved in mixing, loading, transferring (either through an open or closed transfer system), treating, calibrating, wear a long-sleeved shirt, long pants, chemical-resistant gloves, socks and shoes. In addition, when cleaning, repairing, handling and planting treated bulk or bagged seed, workers must wear a long-sleeved shirt, long pants, chemical-resistant gloves, socks and shoes and a NIOSH-approved N95 (minimum) filtering facepiece respirator (dust mask) that is properly fit tested and must use closed-cab tractor when planting. Gloves and respirator are not required within a closed cab. Furthermore, a standard label statement to protect against drift during application is present on the labels.

Environment

- Precautionary label statements to inform users of the toxicity of cyclobutrifluram to aquatic organisms.
- Best management practice label statements to instruct users to avoid using the end-use products in areas more conducive to leaching to groundwater (in other words, where the soils are permeable and particularly where the water table is shallow).
- Best management practice label statements to reduce runoff entering sensitive aquatic habitats.
- Best management practice label statements to inform users to clean up spilled seed when cyclobutrifluram is used as a seed treatment.

Next steps

Before making a final registration decision on cyclobutrifluram, A22011 Crop, A23156 Crop, VICTRATO and VICTRATO 2, Health Canada's PMRA will consider any written comments received from the public that are directly related to this proposed decision, such as comments directed to the science evaluation in response to this consultation document up to 30 days from the date of publication (12 September 2025) of this document. If more time is required to provide comments, a request for an extension of up to 15 days can be made before the end of the original 30-day consultation period. Please note that, to comply with Canada's international trade obligations, consultation on the proposed MRLs will also be conducted internationally via a notification to the World Trade Organization. Please forward all comments to PMRA Publications, through the Public Engagement Portal (Public Engagement Forms – Consultation Comment). Health Canada will then publish a Registration Decision, which will include its decision, the reasons for it, a summary of comments received on the proposed decision and Health Canada's response to these comments.

Other information

When Health Canada makes its registration decision, it will publish a Registration Decision on cyclobutrifluram, A22011 Crop, A23156 Crop, VICTRATO and VICTRATO 2 (based on the Science Evaluation of this consultation document). In addition, the test data referenced in this consultation document will be available for public inspection, upon application, in the PMRA's Reading Room. For more information or if you have questions, please contact the Pest Management Information Service.

Science evaluation

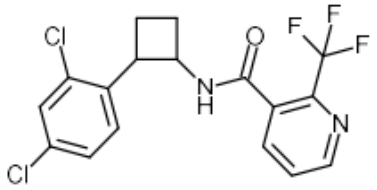
Cyclobutrifluram, A22011 Crop, A23156 Crop, VICTRATO and VICTRATO 2

1.0 The active ingredient, its properties and uses

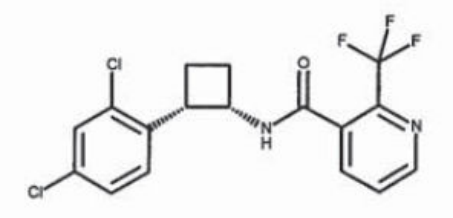
1.1 Identity of the active ingredient

Active substance	cyclobutrifluram
Function	nematicide, fungicide
Chemical name	
1. International Union of Pure and Applied Chemistry (IUPAC)	EN: mixture comprising 80–100% *N*-[(1*S*,2*S*)-2-(2,4-dichlorophenyl)cyclobutyl]-2-(trifluoromethyl)pyridine-3-carboxamide and 20–0% of the (1*R*,2*R*)-enantiomer
2. Chemical Abstracts Service (CAS)	*rel*-N-[(1*R*,2*R*)-2-(2,4-dichlorophenyl)cyclobutyl]-2-(trifluoromethyl)-3-pyridinecarboxamide
CAS number	mixture: 1460292-16-3 major (1*S*,2*S*)-enantiomer: 1644251-74-0 minor (1*R*,2*R*)-enantiomer: 2192196-56-6
Molecular formula	$C_{17}H_{13}Cl_2F_3N_2O$
Molecular weight	389.2 g/mol

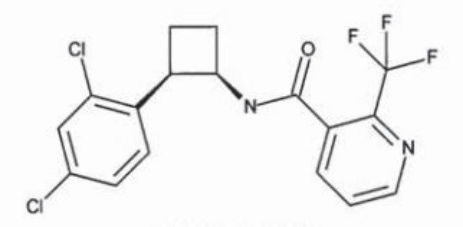
Structural formula Unspecified stereo bonds:



Major (1*S*,2*S*)-enantiomer:



Minor (1*R*,2*R*)-enantiomer:



Purity of the active ingredient 85%

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

Cyclobutrifluram technical

Property	Result
Colour and physical state	Grey solid
Odour	Odourless
Melting point for pure active ingredient (PAI)	125.4°C
Boiling point for PAI	Thermal decomposition begins at ~271°C; boiling point N/A
Density for technical grade active ingredient at 20°C	1.39 g/cm^3
Vapour pressure at 20°C	< 6.2 × 10^{-6} Pa
Ultraviolet (UV)-visible spectrum	λ_{max} = 225 nm
Solubility in water at 20°C	19 mg/L in pure water (TGAI) 33 mg/L in pure water (PAI)

Property	Result
Solubility in organic solvents at 20°C for PAI	Solvent — Solubility (g/L) acetone — >500 dichloromethane — 430 ethyl acetate — 390 n-hexane — 0.27 methanol — 420 n-octanol — 69 toluene — 53
n-Octanol-water partition coefficient (K_{ow})	log K_{ow} = 3.2
Dissociation constant (pK_a)	No dissociation was observed in the pH range of 2 to 12.
Stability (temperature, metal)	Stable at elevated temperature (54°C) and in contact with metals (aluminum and iron) and metal ions (aluminum acetate and iron (II) acetate).

End-use product—A22011 Crop

Property	Result
Colour	Beige
Odour	Sweetish
Physical state	Liquid
Formulation type	Suspension
Label concentration	Cyclobutrifluram 450 g/L
Container material and description	Plastic jug, 1–1000 L
Density	1.174 g/cm^3
pH of 1% dispersion in water	7.9
Oxidizing or reducing action	Compatible with water, 10% monoammonium phosphate, iron powder and sodium hypochlorite, in other words, does not exhibit oxidizing or reducing action.
Storage stability	Active content was shown to be stable at 54°C for 2 weeks in HDPE packaging.
Corrosion characteristics	Not corrosive to HDPE packaging
Explodability	Not explosive

End-use product—VICTRATO

Property	Result
Colour	Red
Odour	Slightly sweet
Physical state	Liquid

Property	Result
Formulation type	Suspension
Label concentration	Cyclobutrifluram 500 g/L
Container material and description	Plastic jug/tote, 1–1050 L
Density	1.203 g/cm^3
pH of 1% dispersion in water	6–8
Oxidizing or reducing action	Compatible with water, 10% monoammonium phosphate, and iron powder; slight incompatibility with sodium hypochlorite (oxidizing agent)
Storage stability	Active content was shown to be stable at 54°C for 2 weeks in HDPE packaging
Corrosion characteristics	Not corrosive to HDPE packaging
Explodability	Not explosive

End-use product—VICTRATO 2

Property	Result
Colour	Colourless
Odour	Slightly sweet
Physical state	Liquid
Formulation type	Suspension
Label concentration	Cyclobutrifluram 500 g/L
Container material and description	Plastic jug/tote, 1–1050 L
Density	1.203 g/cm^3
pH of 1% dispersion in water	7–9
Oxidizing or reducing action	Compatible with water, 10% monoammonium phosphate, and iron powder; slight incompatibility with sodium hypochlorite (oxidizing agent)
Storage stability	Active content was shown to be stable at 54°C for 2 weeks in HDPE packaging
Corrosion characteristics	Not corrosive to HDPE packaging
Explodability	Not explosive

End-use product—A23156 Crop

Property	Result
Colour	Beige
Odour	Weak soap-like
Physical state	Liquid

Property	Result
Formulation type	Suspension
Label concentration	Cyclobutrifluram 300 g/L
Container material and description	Plastic jug, 1–1000 L
Density	1.178 g/cm^3
pH of 1% dispersion in water	7.5
Oxidizing or reducing action	Compatible with water, 10% monoammonium phosphate (fire extinguishing agent) and iron powder (reducing agent). Not compatible with ~6% sodium hypochlorite (oxidizing agent)
Storage stability	Active content was shown to be stable at 54°C for 2 weeks in HDPE and fluorinated HDPE packaging
Corrosion characteristics	Not corrosive to HDPE or fluorinated HDPE packaging
Explodability	Not explosive

1.3 Directions for use

For the suppression of root-knot nematode on romaine lettuce, A22011 Crop or A23156 Crop may be applied once at planting through soil drench (including transplant water), low pressure drip, trickle or equivalent equipment, or soil-directed banded spray application using A22011 Crop at 222 mL product/ha or A23156 Crop at 333 mL product/ha, in accordance with label directions.

For the suppression or control of soybean cyst nematode and control of early season infection by *Fusarium virguliforme* (the cause of sudden death syndrome) on soybean, VICTRATO or VICTRATO 2 may be applied as a seed treatment at 50–100 mL product/100 kg seed. VICTRATO or VICTRATO 2 suppresses soybean cyst nematode at 50 mL product/100 kg seed, but controls at 100 mL product/100 kg seed. Both products may be mixed with listed fungicides or insecticides for protection of various soil- and seed-borne pathogens or insect pests in accordance with the label.

1.4 Mode of action

Cyclobutrifluram is a new conventional active ingredient for nematode and disease management in Canada. Cyclobutrifluram is classified in Group N-3 by the Insecticide Resistance Action Committee (IRAC) as it acts as a selective inhibitor of succinate dehydrogenase, killing the target nematodes on contact and by systemic feeding activity. As a fungicide, cyclobutrifluram is a succinate-dehydrogenase inhibitor (SDHI) fungicide, which belong to Group 7 fungicides by the Fungicide Resistance Action Committee (FRAC). It inhibits spore germination, mycelial growth, and sporulation of the fungus on the leaf surface.

2.0 Methods of analysis

2.1 Methods for analysis of the active ingredient

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

2.2 Method for formulation analysis

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

2.3 Methods for residue analysis

High performance liquid chromatography methods with tandem mass spectrometric detection (HPLC-MS/MS; QuEChERS method EN 15662:2018 in plant matrices and Method GRM076.10A or QuEChERS method EN 15662:2009 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. Extraction solvents used in the methods were similar to those used in the metabolism studies; thus, further demonstration of extraction efficiency with radiolabelled crops or animal matrices was not required for the enforcement method. Methods for residue analysis in plant and animal matrices are summarized in Appendix I, Table 2.

3.0 Impact on human and animal health

3.1 Hazard assessment

3.1.1 Toxicology summary

Cyclobutrifluram is a contact nematicide that belongs to the pyridine-3-carboxamide chemical class. The pesticidal mode of action (MOA) of cyclobutrifluram is through inhibition of mitochondrial complex II electron transport and succinate dehydrogenase inhibition.

A detailed review of the toxicology database for cyclobutrifluram was conducted. The database is complete, consisting of the full array of toxicity studies currently required for hazard assessment purposes. Additional studies included mechanistic studies to support a proposed MOA for liver tumours in mice as well as studies assessing the effects of cyclobutrifluram exposure on thyroid function in rats, and acute toxicity and genotoxicity studies for a metabolite of cyclobutrifluram. The required studies were carried out in accordance with currently accepted international testing protocols and Good Laboratory Practices. The human health risk assessment also considered any relevant information found in the published literature. The scientific quality of the data is acceptable and the database is considered adequate to characterize the potential health hazards associated with cyclobutrifluram.

The metabolism and toxicokinetics of cyclobutrifluram in the rat were investigated following oral administration of single low or high doses or repeated low doses of cyclobutrifluram radiolabelled at the phenyl or pyridinyl ring. Total absorption for both radiolabels was 97–99% of the administered dose (AD) at the low-dose level, and 52–75% of the AD at the high-dose level, based on the sum of radioactivity measured in bile, urine, cage wash, plasma, red blood cells and carcass. Following a single low dose, peak blood and plasma concentrations of radioactivity were observed at 0.5 and 2 hours post-dosing for the phenyl or pyridinyl label, respectively. For both radiolabels, the highest concentration of radioactivity was observed in the liver followed by the adrenal glands. Following a single high dose, the tissues with the highest concentration of radioactivity at 2 hours post-dosing were the liver and adrenal glands in both sexes dosed with the phenyl radiolabel and males dosed with the pyridinyl radiolabel, and renal fat and adrenal glands in females dosed with the pyridinyl label. Following repeated low dosing, maximum blood and plasma concentrations were noted at 2 hours post-dosing; the highest mean tissue concentration of radioactivity was observed 24 hours after the final (14^{th}) dose, with the highest concentrations observed in the liver, thyroid, and kidneys.

The major route of excretion at 168 hours post-dosing in rats, regardless of dose or radiolabel, was the feces via biliary elimination (67–92% of AD), with a lesser amount (6.5–23% of AD) eliminated via the urine. Excretion was rapid, with the majority of the AD eliminated within 48-72 hours after administration of the radiolabeled dose. Excretion was essentially complete by 168 hours post-dose.

Cyclobutrifluram was readily metabolized in rats, regardless of dose, sex or radiolabel position. Cyclobutrifluram was metabolised by hydroxylation, glucuronide, sulphate or S-cysteine conjugation of hydroxylated metabolites. The molecule was cleaved at the amide bond in addition to oxidative cleavage of the cyclobutane moiety. In excreta, nine metabolites accounting for >5% of the AD were identified for both radiolabels. Two of these metabolites were identified as SYN510275 (a cleaved metabolite) and SYN549104 (a hydroxylated metabolite of SYN549522). The remaining metabolites accounting for >5% of the AD were identified as di-hydroxy SYN549522 (Metabolite A), phenyl specific cleaved metabolite (Metabolite E), SYN549522 sulphate (Metabolite C) and three SYN547552 hydroxy glucuronide metabolites (Metabolites B, D and H). In addition, three minor metabolites (<5% of the AD) were identified as a SYN547552 hydroxy glucuronide isomer (Metabolite G) and S-cysteine conjugates of hydroxy SYN549522 isomers (Metabolites L and M). At least 42 other radiolabelled components were detected in excreta following administration of the phenyl radiolabel, and 26 components following administration of the pyridinyl radiolabel. These radiolabelled components were not identified, but no single component accounted for >3.5% of the AD.

Following dosing with the phenyl radiolabel, the major metabolite in the urine of intact rats was metabolite E, regardless of sex and dose. After dosing of the pyridinyl label, the most abundant component in urine was SYN510275. Other identified components detected following administration of either radiolabel were SYN549104 and Metabolite C with no single component accounting for >2.0% of the AD. In bile duct-cannulated rats, the main component in the urine of females, but not males, was metabolite B.

Following dosing with the pyridinyl label, the main metabolite in the urine of bile duct-cannulated rats was SYN510275, with no qualitative difference noted between sexes or dose levels. Other identified components found in the urine of bile duct-cannulated rats following administration of either radiolabel were SYN549104 and Metabolite C.

SYN549104 was the major component in the feces of rats of both sexes following low dose administration of either radiolabel, with Metabolite A and Metabolite C also detected. Following administration of the high dose, Metabolite B was the major component in feces; unchanged cyclobutrifluram was also present in the feces of high-dose rats of both sexes and from both radiolabel groups.

In acute toxicity studies, the technical grade active ingredient cyclobutrifluram was of low toxicity via the oral, dermal, and inhalation routes of exposure in rats. It was not irritating to the eyes or skin of rabbits and was negative for skin sensitization when tested in mice using the local lymph node assay (LLNA).

The end-use product A22011 Crop, containing cyclobutrifluram, was of low acute toxicity in rats via the oral, dermal and inhalation routes of exposure. It was minimally irritating to the eyes, and non-irritating to the skin of rabbits, and was negative for skin sensitization when tested in mice using the LLNA.

The end-use product A23156 Crop, containing cyclobutrifluram, was of low acute toxicity in rats via the oral and inhalation routes of exposure and it was considered to be of low acute toxicity via the dermal route. It was moderately irritating to the eyes and slightly irritating to the skin of rabbits and was positive for skin sensitization when tested in mice using the LLNA.

The end-use products VICTRATO and VICTRATO 2, containing cyclobutrifluram, were of low acute toxicity in rats via the oral, dermal and inhalation routes of exposure. The products were minimally irritating to the eyes and mildly irritating to the skin of rabbits and were negative for skin sensitization when tested in mice using the LLNA.

Repeat-dose oral toxicity studies with cyclobutrifluram were available in mice and rats via the dietary route, and in dogs via capsule. Repeat-dose studies were also available in rats via the dermal and inhalation routes of exposure. Following repeated oral exposure with cyclobutrifluram, the liver (mice, rats and dogs) and thyroid (rats) were identified as the primary target organs of toxicity with effects on the adrenals (mice, rats and dogs) and spleen (mice and rats) also observed. Liver effects included increased weight, elevated liver enzymes, hepatocellular hypertrophy and vacuolation. Liver tumours were additionally observed in male mice following long-term oral dosing. Effects on the thyroid were observed in rats following oral dosing and included follicular cell hypertrophy as well as tumours following longer term administration. The observed liver and thyroid tumours are discussed further below. Effects on spleen weight and increased extramedullary hemopoiesis in the spleen were observed in mice, and increased adrenal weight was observed in mice, rats and dogs. There was some evidence of increased toxicity with increased duration of dosing with cyclobutrifluram in mice and rats, based on increased severity of liver effects in mice and thyroid effects in rats following chronic dosing when compared to shorter-term durations.

Following short-term repeated dermal exposure of rats to cyclobutrifluram for 28 days, increased liver weight, alterations in liver enzymes and liver necrosis were observed, as well as adrenal vacuolation.

Repeated nose-only inhalation exposure of rats to cyclobutrifluram for 28 days resulted in portal of entry effects consisting of aggregation of macrophages in the lungs, smooth muscle cell hypertrophy of the bronchioles and alveolar wall, alveolar wall thickening, and inflammatory cell infiltration.

Cyclobutrifluram was negative in a battery of in vitro and in vivo genotoxicity studies, which included bacterial reverse mutation assays, a forward gene mutation assay in mouse lymphoma cells, three in vitro micronucleus assays in human peripheral blood lymphocytes, and an in vivo micronucleus test in mice.

In an 18-month dietary oncogenicity study in mice, an increased incidence of hepatic hemangiomas combined with hepatocellular carcinomas was observed in males at the highest dose level tested. A MOA was proposed for the liver tumours which was based on the following key events: activation of the constitutive androstane receptor (CAR), altered gene expression with increased expression of cytochrome P450, increased hepatocellular proliferation associated with hepatocellular hypertrophy and increased liver weight, and increased clonal expansion leading to altered foci. Several mechanistic studies were provided by the applicant to support the proposed MOA. These studies included an in vitro study assessing the ability of cyclobutrifluram to directly activate CAR, and an in vivo study in which male mice were administered cyclobutrifluram via the diet for 2, 7 and 28 days and then the livers of the sacrificed animals underwent biochemical and histopathological examinations. Subsequent special mechanistic studies were conducted using liver and plasma samples from this same study in whole genome microarray analysis, as well as in a comprehensive hybrid polar and lipidomic metabolomics analysis to compare metabolomic profiles and differentially abundant metabolites in response to cyclobutrifluram, to those induced by phenobarbital, a positive control of CAR activation.

A review of the proposed MOA and supporting mechanistic studies identified certain limitations, namely that the concordance of the dose-response relationship for some of the key events was not well supported, and the key event related to clonal expansion leading to altered foci was not investigated. Despite these limitations, it was concluded that the proposed MOA for liver tumours in mice is plausible, and that the tumours are likely forming via a threshold mechanism, based on the partially supportive results from the mechanistic studies and the lack of genotoxic potential, as well as the fact that it is well known that these tumour types develop via a threshold mechanism in mice. As such, it was considered that a linear low dose extrapolation (q_1*) approach to the cancer risk assessment would be overly conservative. Therefore, a threshold approach for the liver tumours was taken for risk assessment purposes.

In a 2-year dietary toxicity study in rats, an increased incidence of thyroid tumours was observed at the highest dose tested, specifically increased incidences of follicular cell adenomas in females and follicular cell carcinomas in males. These tumours were considered to be treatment-related, but of low concern due to the following considerations: there was no observed increase in carcinomas in females (as only benign tumours were observed), there was no increase in combined adenomas and carcinomas in males, the incidences of the observed tumours were not

statistically significantly increased compared to concurrent controls using pair-wise tests, and the overall incidence at the highest dose tested was relatively low. As such, a q_1* approach to the cancer risk assessment was deemed overly conservative, and it was concluded that a threshold approach would be appropriate for the assessment of cancer risk related to the thyroid tumours.

There was no evidence of increased sensitivity of the young to the effects of cyclobutrifluram in oral gavage developmental toxicity studies in rats and rabbits. In rabbits, body weight loss and decreased body weight gain were observed in maternal animals over the first few days of treatment, with no treatment-related effects observed in the developing fetuses. In rats, there were no adverse effects in the maternal animals and no treatment-related effects in the developing fetuses up to the highest dose tested of 250 mg/kg bw/day. It was determined that higher dose levels could have been tolerated in rat dams, and thus the dose level selection was not considered adequate in the rat study. This limitation was taken into account in the selection of the points of departure (PODs) and uncertainty factors (UF) for use in the risk assessment, in order to ensure adequate protection for potential prenatal toxicity at higher dose levels.

No evidence of increased sensitivity of the young was noted in the 2-generation dietary reproductive toxicity study in rats. Effects in the parental animals were consistent with those observed in the other rat studies in the database, namely increased thyroid weight with correlating thyroid follicular cell hypertrophy, and increased liver weight. Treatment-related effects in the offspring occurred at the same dose level at which effects in the parental animals occurred and consisted of decreases in body weight and body weight gain and a delay in preputial separation in F1 males. Reduced fertility index in F1 males, a reproductive effect, was also observed at the highest dose level. Concern for the potential seriousness of this finding was low as there were no other concerns for effects on reproductive parameters, including sperm and ovarian follicle measurements, or endocrine tissues in the database, the decreased fertility index was within the historical control range, and there was no effect on fertility in the P generation.

The neurotoxic potential of cyclobutrifluram was investigated in rats following acute gavage dosing. Treatment-related effects consisted of increased activity count, decreased motor activity, decreased landing foot splay and decreased body temperature. However, there was a lack of consistency in terms of timing and direction of change for some of these effects and they were only observed at the limit dose of testing. Furthermore, there were no clinical signs of neurotoxicity observed in a single dose time-to-peak-effect study or in other toxicity studies across the cyclobutrifluram database. Based on the lack of overt neurotoxicity and the absence of any neurohistopathological findings in the database, coupled with the observed rapid excretion and low concentrations of cyclobutrifluram in the brain and fat in the toxicokinetics studies, the overall concern for the findings in the acute neurotoxicity study were low and the requirement for a subchronic neurotoxicity study in rats was waived.

Additional toxicity studies were conducted with a metabolite of cyclobutrifluram, 2-(trifluoromethyl)nicotinic acid (also referred to as SYN510260 (CA5542) and SYN510275). CA5542 was determined to be of low acute oral toxicity in rats. Results from in vitro studies indicated that CA5542 may be severely irritating to the eye but not an irritant to the skin and that it may be a potential skin sensitizer. CA5542 was negative when tested in a series of in vitro genotoxicity assays.

The identification of select metabolites is presented in Appendix I, Table 3. The toxicology reference values for use in the human health risk assessment are summarized in Appendix I, Table 4. Results of the toxicology studies conducted in laboratory animals with cyclobutrifluram and relevant metabolites and with its associated end-use products, are summarized in Appendix I, Tables 5 and 6.

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 full complement of required studies including oral gavage developmental toxicity studies in rats and rabbits and a dietary 2-generation reproductive toxicity study in rats. Oral developmental toxicity dose range-finding studies in the rat and rabbit were also available. As discussed above, although dose level selection in the rat developmental toxicity study may not have been adequate, this study limitation was taken into account during the selection of the PODs and UF for use in the risk assessment to ensure adequate protection for potential pre-natal toxicity had higher dose levels been tested.

With respect to potential prenatal and postnatal toxicity, there was no evidence of sensitivity of the young in either the rat or the rabbit developmental toxicity study. A delay in preputial separation was observed in F1 male offspring in the 2-generation reproductive toxicity study; however, this finding was observed in the presence of parental toxicity, namely pathology of the thyroid gland. There was also a low level of concern for the seriousness of the observed decrease in fertility index, for the reasons outlined in the toxicology summary Section above. Based on these considerations, the *Pest Control Products Act* factor (PCPA factor) was reduced to onefold.

3.2 Toxicology reference values

3.2.1 Route and duration of exposure

Potential exposure to cyclobutrifluram may occur via the diet (food and drinking water). Workers are also expected to be exposed via the dermal and inhalation routes over short- to intermediate-term exposure durations. Residential exposure to cyclobutrifluram is not expected.

Occupational exposure to A22011 Crop and A23156 Crop is characterized as short- to intermediate-term in duration. For mixers, loaders and applicators, the exposure is predominantly by the dermal and inhalation routes, and for postapplication workers, it is predominantly by the dermal route.

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

Occupational exposure to VICTRATO and VICTRATO 2 is characterized as short- to intermediate-term in duration and is predominantly by the dermal and inhalation routes.

3.2.2 Occupational toxicology reference values

Short- and intermediate-term dermal

For short- and intermediate-term occupational exposures via the dermal route, the offspring and reproductive NOAEL of 9.0 mg/kg bw/day from the 2-generation rat reproduction study was selected for risk assessment. At the LOAEL of 43/53 mg/kg bw/day in parental males/females, delayed preputial separation and decreased fertility index were observed in F1 males. The available 28-day dermal toxicity study did not assess the relevant endpoints of concern (that is, effects on reproduction and on offspring development following prenatal exposure), thus necessitating the use of an oral toxicity study for risk assessment purposes.

The target margin of exposure (MOE) for these scenarios is 100, which includes standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability. The selection of this study and target MOE is considered to be protective of all populations, including nursing infants and the unborn children of exposed female workers.

Short- and intermediate-term inhalation

For short- and intermediate-term occupational exposures via the inhalation route, the NOAEC of 40.2 mg/m^3 (equivalent to 8.6 mg/kg bw/day) from the 28-day inhalation toxicity study in rats was selected for risk assessment. At the LOAEC of 80.3 mg/m^3 (equivalent to 17/18 mg/kg bw/day in males/females), decreased body weight and body weight gain and respiratory tract lesions (alveolar macrophage aggregation, bronchiole/alveolar wall smooth muscle cell hypertrophy, alveolar/alveolar duct wall thickening, and inflammatory cell infiltration) were observed in both sexes. This study was conducted via the relevant route and was considered an appropriate duration of exposure. Based on the generally low severity of the respiratory tract lesions observed at the LOAEC in the 28-day inhalation toxicity study, an uncertainty factor to extrapolate from a short-term study to the intermediate-term exposure scenario was not required.

The target MOE for these scenarios is 100, which includes standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability. The selection of this study and target MOE is considered to be protective of all populations, including nursing infants and the unborn children of exposed female workers.

3.2.3 Acute reference dose (ARfD)

Females 13–49 years of age

To estimate acute dietary risk to females 13–49 years of age, the maternal NOAEL of 75 mg/kg bw/day from the oral developmental toxicity study in the rabbit was selected for risk assessment purposes. At the maternal LOAEL of 125 mg/kg bw/day, body weight loss was noted in the maternal animals during the first few days of dosing, which is therefore relevant to an acute exposure scenario. Standard uncertainty factors of 10-fold for interspecies extrapolation and

10-fold for intraspecies variability were applied. The PCPA factor was reduced to onefold, as discussed in the *Pest Control Products Act* hazard characterization Section. An additional threefold uncertainty factor for database deficiencies was applied in order to afford sufficient protection to potential serious developmental effects occurring in the absence of maternal toxicity if higher dose levels were tested in the rat developmental toxicity study. The composite assessment factor (CAF) is therefore 300.

The ARfD is calculated according to the following formula:

$$\text{ARfD (females 13–49 years)} = \frac{\text{NOAEL}}{\text{CAF}} = \frac{75 \text{ mg/kg bw/day}}{300} = 0.3 \text{ mg/kg bw cyclobutrifluram}$$

This ARfD provides a margin of >800 (1000 before rounding to one significant figure) to the highest dose tested of 250 mg/kg bw/day in the rat developmental toxicity study, at which no adverse effects on maternal or developmental endpoints were observed.

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

To estimate acute dietary risk for the general population, the maternal NOAEL of 75 mg/kg bw/day from the oral developmental toxicity study in the rabbit was selected for risk assessment purposes. At the maternal LOAEL of 125 mg/kg bw/day, body weight loss was noted in the maternal animals during the first few days of dosing, which is therefore relevant to an acute exposure scenario. 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 therefore 100.

The ARfD is calculated according to the following formula:

$$\text{ARfD} = \frac{\text{NOAEL}}{\text{CAF}} = \frac{75 \text{ mg/kg bw/day}}{100} = 0.8 \text{ mg/kg bw cyclobutrifluram}$$

3.2.4 Acceptable daily intake (ADI)

To estimate risk following repeated dietary exposure, the NOAEL of 6.8 mg/kg bw/day from the 2-year dietary chronic toxicity/oncogenicity study in the rat was selected. At the LOAEL of 26/33 mg/kg bw/day in males/females, decreased body weight and body weight gain in both sexes, increased thyroid gland follicular cell carcinomas in males, and increased thyroid gland follicular cell adenomas in females were observed. This study provides the lowest NOAEL in the database. 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 1-fold. The CAF is therefore 100.

The ADI is calculated according to the following formula:

$$\text{ADI} = \frac{\text{NOAEL}}{\text{CAF}} = \frac{6.8 \text{ mg/kg bw/day}}{100} = 0.07 \text{ mg/kg bw/day of cyclobutrifluram}$$

The ADI provides a margin of 200 to the point of departure for liver tumours in mice, a margin of 128 to the NOAEL for decreased fertility in male rats in the 2-generation rat reproduction study, and a margin of >3500 to the highest dose tested in the rat developmental toxicity study.

3.2.5 Cancer assessment

As noted above, an increased incidence of liver tumours was observed in male mice and an increased incidence of thyroid tumours was observed in rats following chronic exposure. A MOA for liver tumour induction was proposed by the applicant that was similar to that for phenobarbital. Despite some limitations, the MOA was deemed plausible and the overall weight of evidence was considered sufficient to conclude that a linear low-dose extrapolation (q_1*) approach to the cancer risk assessment is overly conservative. For these reasons, a threshold approach for liver tumours was taken for the cancer risk assessment. The increased incidence of thyroid tumours observed in rats was considered treatment-related but of low concern for the reasons previously noted. As such, a q_1* approach to the cancer risk assessment was deemed overly conservative, and it was concluded that a threshold approach be taken for the assessment of cancer risk related to the thyroid tumours. Overall, the toxicology reference values selected for the non-cancer risk assessment are protective of any residual concerns regarding the carcinogenic potential of cyclobutrifluram.

3.2.6 Aggregate toxicology reference values

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

3.3 Dermal absorption

For the soil-directed spray products A22011 Crop and A23156 Crop, two in vitro dermal absorption studies were conducted, one in humans and one in rats. These studies were conducted for only one of the two formulations, in other words, A22011B (the formulation of A22011 Crop). Nonetheless, as both formulations were considered sufficiently similar, results of the tested formulation were extrapolated to the untested formulation (in other words, that of A23156 Crop). The human and rat in vitro dermal absorption studies were both considered scientifically acceptable; however, the human in vitro study was considered to be sufficient to select dermal absorption values, so the rat in vitro study was considered as supplemental information.

For workers' exposure to the products A22011 Crop and A23156 Crop, two dermal absorption values were established. A dermal absorption value of 2% was selected for mixers and loaders based on formulation concentrate dose group of the A22011B study. In addition, a dermal absorption value of 6% was selected for all other scenarios based on the average of low dose group of the A22011B study, which had the highest dermal absorption among the dose levels tested in the study.

For the seed treatment products VICTRATO and VICTRATO 2, two in vitro dermal absorption studies were conducted with human skin, each using the formulation of one of the two products, in other words, A22417B (the formulation of VICTRATO 2) and A22417C (the formulation of VICTRATO).

For workers' exposure to the products VICTRATO and VICTRATO 2, two dermal absorption values were established. A dermal absorption value of 1% was selected for mixers and loaders based on the human in vitro high dose groups of the A22417B and A22417C studies. For all other exposure scenarios, a dermal absorption value of 6% was selected based on the human in vitro low dose group of the A22417B study, which had the highest dermal absorption among the dose levels tested in both studies conducted with the seed treatment products. The dermal absorption value of 6% for all exposure scenarios, other than mixers and loaders, is further supported by results from the A22011B study, in which the average dermal absorption from the low dose group is also 6%.

Results of the dermal absorption studies are summarized in Appendix I, Tables 7–9.

3.4 Occupational and residential exposure assessment

3.4.1 Acute hazards of end-use products and mitigation measures

3.4.1.1 A22011 Crop and A23156 Crop

The acute hazard assessment indicated that A22011 Crop was of low acute toxicity in rats via the oral, dermal and inhalation routes of exposure. It was minimally irritating to the eyes, and non-irritating to the skin of rabbits, and was negative for skin sensitization when tested in mice using the LLNA. Based on these acute hazards, a long-sleeved shirt, long pants, chemical-resistant gloves, socks and shoes are required for workers during mixing, loading, application, clean-up and repair.

The acute hazard assessment indicated that A23156 Crop was of low acute toxicity in rats via the oral and inhalation routes of exposure and it was considered to be of low acute toxicity via the dermal route. It was moderately irritating to the eyes and slightly irritating to the skin of rabbits and was positive for skin sensitization when tested in mice using the LLNA. Based on these acute hazards, a long-sleeved shirt, long pants, chemical-resistant gloves, socks and shoes are required for workers during mixing, loading, application, clean-up and repair. Additionally, protective eyewear (goggles or face shield) are required during mixing, loading, clean-up and repair.

3.4.1.2 VICTRATO and VICTRATO 2

The acute hazard assessment indicated that VICTRATO and VICTRATO 2 are of low acute toxicity in rats via the oral, dermal and inhalation routes of exposure. They were minimally irritating to the eyes and mildly irritating to the skin of rabbits. The products were not a skin sensitizer in mice based on the results of a local lymph node assay. These products contain preservatives, a petroleum distillate, the allergen sulfites and several impurities. All impurities are present at concentrations that are not of toxicological concern.

Based on these acute hazards, a long-sleeved shirt, long pants, chemical-resistant gloves, socks and shoes are required for workers during mixing, loading, treating, clean-up, repair, and handling and planting of treated seed. In addition, for both formulations, a NIOSH-approved N95 (minimum) filtering facepiece respirator (dust mask) that is properly fit tested is also required for workers when there is potential for the products to be inhaled as dusts due to impurities that may be present in the dust.

3.4.2 Occupational exposure and risk assessment

3.4.2.1 Mixer, loader and applicator exposure and risk assessment for A22011 Crop and A23156 Crop

Individuals have potential for exposure to cyclobutrifluram during mixing, loading, application, clean-up and repair. Dermal and inhalation exposure estimates were generated from the Agricultural Handlers Exposure Task Force (AHETF) database for mixers, loaders and applicators applying A22011 Crop and A23156 Crop to Romaine leaf lettuce using groundboom, soil drench (including transplant water), and irrigation equipment. The personal protective equipment (PPE) in the risk assessment is based on handlers wearing a long-sleeved shirt, long pants and chemical-resistant gloves during mixing, loading, open-cab application, clean-up and repair activities. Gloves are not required for application within a closed cab (Appendix I, Table 10).

Dermal exposure was estimated by coupling the unit exposure values with the amount of product handled per day and the dermal absorption value of 2% for mixers and loaders, and 6% for all other activities. Inhalation exposure was estimated by coupling the unit exposure values with the amount of product handled per day with 100% inhalation absorption. Exposure was normalized to mg/kg bw/day by using 80 kg adult body weight.

Daily exposure estimates were then compared to the toxicology reference values (in other words, the no observed adverse effects levels (NOAELs) of 9 mg/kg bw/day for dermal exposure and 8.6 mg/kg bw/day for inhalation exposure) to obtain the margins of exposure (MOEs). The target MOE is 100 for both dermal and inhalation exposures. The daily dermal and inhalation exposure values and calculated MOEs were not combined since the dermal and inhalation toxicology reference values were generated from different studies and the observed clinical effects are different. Calculated MOEs are greater than the target MOE of 100 for all chemical handler scenarios for agriculture crops and are therefore not of health concern (Appendix I, Table 11).

3.4.2.2 Postapplication exposure and risk assessment for A22011 Crop and A23156 Crop

There is potential for exposure to workers entering areas treated with A22011 Crop or A23156 Crop to complete tasks such as scouting, setting irrigation lines, transplanting and hand weeding. Given the nature of activities performed, exposure should be primarily via the dermal route based on dermal contact with treated surfaces. Inhalation exposure is not expected as cyclobutrifluram is considered non-volatile with a vapour pressure of $< 6.2 \times 10^{-12}$ kPa (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 (7.5×10^{-4} mm Hg) at 20-30°C]. As such, a quantitative inhalation risk assessment is not required. Inhalation risk is not of health concern for postapplication workers as cyclobutrifluram is considered to be non-volatile and the restricted-entry interval of 12 hours will allow residues to dry, suspended particles to settle and vapours to dissipate.

Dermal exposure to workers entering treated areas is estimated by coupling dislodgeable foliar residue (DFR) values with activity-specific transfer coefficients (TCs). Activity TCs are based on data from the Agricultural Re-entry Task Force (ARTF). As chemical-specific DFR data were not submitted, a standard DFR value of 25% of the application rate coupled with 10% daily dissipation of residues were used in the exposure assessment.

Exposure estimates were compared to the toxicology reference value to obtain the margin of exposure (MOE); the target MOE is 100. Only exposures and risks to the activities with the highest TCs are presented as MOEs for these activities exceed the target MOE of 100, and are thus, not of health concern (Appendix I, Table 12). An REI of 12 hours is adequate for all postapplication activities.

3.4.2.3 Occupational exposure and risk assessments for VICTRATO and VICTRATO 2

3.4.2.3.1 Seed treatment exposure and risk assessments for VICTRATO and VICTRATO 2

Soybean seed can be treated with VICTRATO and VICTRATO 2 in commercial seed treatment facilities, by commercial mobile treaters or on-farm. Individuals have the potential for exposure to cyclobutrifluram while treating soybean seed in commercial seed treatment facilities or by commercial mobile treaters using open or closed transfer equipment. Individuals also have potential for exposure while bagging, sewing and stacking bags of treated seed and during cleaning and repair of equipment. Occupational exposure to VICTRATO and VICTRATO 2 for seed treatment workers is characterized as short- to intermediate-term in duration and occurs predominantly by the dermal and inhalation routes.

3.4.2.3.2 Dust-off study

A dust-off study was conducted to compare the dust-off potential of soybean and other seeds untreated and treated with VICTRATO 2 as the formulations of VICTRATO and VICTRATO 2 are similar, and with several known surrogate seed treatment formulations. The various seeds were treated with a slurry of each seed treatment formulation, and dust-off levels from untreated and treated seed samples were measured using a Heubach dust measurement apparatus.

The average dust-off levels of soybean seed treated with VICTRATO 2 were lower than the dust levels measured in untreated soybean seed. In addition, the average dust-off levels in soybean seed treated with VICTRATO 2 were compared with the dust-off levels measured previously in other seed types and various formulations used in surrogate exposure studies for risk assessment of cyclobutrifluram. These data show that the previously measured dust-off levels in canola, soybean, corn, and wheat untreated or treated with various other formulations were substantially higher than the dust-off levels measured in soybean treated with VICTRATO 2 in the current study.

Therefore, based on the dust-off data, the selected surrogate passive dosimetry exposure studies are not expected to underestimate the soybean seed treatment workers and planters exposures to VICTRATO and VICTRATO 2.

3.4.2.3.3 Commercial seed treatment (Facilities including mobile treaters) exposure and risk assessment for VICTRATO and VICTRATO 2

VICTRATO and VICTRATO 2 can be used for the commercial treatment of soybean seed, including treatment by mobile treaters.

As chemical-specific unit exposure data were not submitted for VICTRATO and VICTRATO 2, surrogate passive dosimetry exposure studies owned by the Agricultural Handlers Exposure Task Force (AHETF), of which the applicant is a member and has full access to the data, were used to estimate the worker exposure.

The choice of the surrogate exposure study was based on results of the dust-off study, and also on various key factors influencing the exposure scenario, such as the formulation type, the seed type, the facility, the mixing/loading and treating equipment, the workers' tasks, the exposure duration, the PPE and engineering controls, as well as the quality of the data, such as the number of replicates, the validation recoveries and the unit exposure results.

To assess the exposure from treating soybean seed, the AH803 study and the AH806 study were selected. The AH803 study monitored workers commercially treating wheat seed using open transfer systems. The 90th percentile unit exposure values from the AH803 study were selected due to the limited number of replicates that were monitored performing the open mixing/loading task. The AH806 study monitored workers involved with commercial seed treatment of corn and canola (monitored separately) during closed transfer systems. Only the monitoring from the corn seed treatment was used for this current risk assessment based the proposed PPE and use pattern.

From these studies, dermal and inhalation exposure estimates were derived for workers commercially treating soybean seed using closed or open transfer commercial treating equipment, as well as workers bagging treated seed, sewing, stacking bags or any other activity involving handling treated seed. The estimates are based on workers wearing a long-sleeved shirt, long pants and chemical-resistant gloves.

Based on the dust-off study data discussed above, the dust-off levels in untreated corn and wheat seeds were higher than the levels in the untreated and VICTRATO 2 treated soybean seed. As such, to estimate occupational exposure and health risks of soybean seed treated with

VICTRATO and VICTRATO 2, unit exposures from the surrogate commercial seed treatment passive dosimetry exposure studies conducted on corn (closed transfer) or wheat (open transfer) were acceptable after comparing the parameters of these surrogate studies with the proposed use of VICTRATO and VICTRATO 2.

For treaters, baggers, sewers and stackers, dermal exposure was estimated by coupling the unit exposure values with the amount of product handled per day obtained from the active ingredient application rate and the amount of seeds treated in a day (in other words, commercial throughput). For cleaners, the exposure estimates were calculated by coupling the dermal or inhalation unit exposure estimates with the active ingredient application rate. The dermal absorption values of 1% for treaters and 6% for all other workers were used for the dermal exposure assessment. For the inhalation exposure, 100% inhalation absorption was assumed. Exposure was normalized to mg/kg bw/day by using 80 kg adult body weight. Dermal and inhalation exposures cannot be combined as there are different toxicological effects from both exposure routes. Exposure estimates were compared to the selected toxicology reference values to obtain the margin of exposures (MOEs); the target MOE is 100 for dermal or inhalation exposure. The dermal and inhalation exposure and health risk estimates are presented in Appendix I, Table 13. As calculated MOEs are greater than the target MOE of 100 for all scenarios for dermal or inhalation, no health risks of concern are expected for workers treating soybean seed with VICTRATO and VICTRATO 2 or conducting any other activity involved in commercial seed treatment provided workers wear a long-sleeved shirt, long pants and chemical-resistant gloves as specified on the labels.

3.4.2.3.4 On-farm seed treatment exposure and risk assessment for VICTRATO and VICTRATO 2

Soybean seed can be treated on-farm with VICTRATO and VICTRATO 2.

As chemical-specific unit exposure data were not submitted, unit exposure estimates from the AH610 surrogate passive dosimetry exposure study, owned by the AHETF, were used to estimate the exposure of on-farm workers. This is a well conducted study for the on-farm treatment and planting of wheat seeds.

The submitted dust-off data showed that the dust-off levels were highest in wheat seed (untreated or treated with surrogate formulation) compared to other seed types including soybean seed treated with the proposed formulations. Therefore, to estimate exposure and health risks for workers conducting on-farm soybean seed treatment and planting, unit exposures from the previously conducted surrogate passive dosimetry exposure study on wheat were acceptable.

Daily dermal or inhalation exposure was estimated by coupling the dermal or inhalation unit exposure values from the AH610 surrogate exposure study with the amount of active ingredient handled per day obtained from the active ingredient application rate and the amount of seeds treated and planted in a day on-farm. The dermal absorption values of 1% for treaters and 6% for all other workers were used for the dermal exposure assessment. For the inhalation exposure, 100% inhalation absorption was assumed.

The daily dermal and inhalation exposures were normalized to mg/kg bw/day by using 80 kg adult body weight. Dermal and inhalation exposures were not combined since the toxicology reference values are based on different toxicology effects. Exposure estimates were compared to the selected toxicology reference values to obtain the MOEs; the target MOE is 100 for dermal or inhalation exposure.

The exposure and risk estimates for on-farm workers are presented in Appendix I, Table 14. As the calculated MOEs are greater than the target MOE of 100 for dermal or inhalation, no health risks of concern are expected for on-farm workers mixing, loading, treating and cleaning-up or maintaining and repairing seed treatment equipment, and planting treated seed provided workers wear a long-sleeved shirt, long pants and chemical-resistant gloves, and use a closed-cab tractor for planting.

3.4.2.3.5 Planting of VICTRATO and VICTRATO 2 treated seed

Commercially treated seed are either bagged or stored in bulk. During planting, workers load the treated seed into a planter from bags or from bulk containers using an auger. Workers have the potential for exposure to VICTRATO and VICTRATO 2 while loading and planting treated seed. Surrogate planting exposure data were used to estimate risk to workers planting treated seed.

To assess the exposure scenarios of planting treated soybean seeds, the AH825 surrogate exposure study was selected, which is owned by the AHETF. This is a well conducted study with no major limitations. It monitored workers opening paper bags of treated corn seeds; manually loading them in the planter; unloading the remaining seeds; planting using a closed-cab tractor and performing small repairs. The use of unit exposure values from this study is not expected to underestimate exposure to workers loading seeds from bulk containers since the exposure from this scenario is lower than the exposure from loading seeds from bags.

The dust-off level study data showed that the dust-off levels in untreated or treated corn with the product used in the selected surrogate exposure study for planting were higher than the levels in soybean treated with VICTRATO 2. Therefore, unit exposures from the selected surrogate planting exposure study conducted on corn were considered appropriate for the occupational exposure and risk assessment for planting of VICTRATO and VICTRATO 2 treated soybean seed.

Dermal and inhalation exposure and health risk estimates were derived for workers planting VICTRATO and VICTRATO 2 treated soybean seed using closed-cab tractors. The exposure duration for planters was considered short-term. The exposure estimates were based on planters wearing a long-sleeved shirt, long pants, chemical-resistant gloves, shoes and socks.

Dermal exposure was estimated by coupling the unit exposure values with the amount of active ingredient handled per day obtained from the active ingredient application rate and the amount of treated seed planted per day. The dermal absorption value of 6% was used for the planter's exposure assessment. Inhalation exposure was estimated by coupling the unit exposure values with the amount of treated seed planted per day and assuming 100% inhalation absorption. Exposure was normalized to mg/kg bw/day by using 80 kg adult body weight. The dermal and

inhalation exposure estimates were compared to the selected toxicology reference value to obtain the MOE. The exposure and risk estimates for workers planting soybean seed treated with VICTRATO and VICTRATO 2 are presented in Appendix I, Table 15. As the calculated MOEs are greater than the target MOE of 100 for dermal or inhalation, no health risks of concern are expected for planters provided they wear a long-sleeved shirt, long pants and chemical-resistant gloves and use a closed-cab tractor for planting.

3.4.3 Residential exposure and risk assessment

3.4.3.1 Handler exposure and risk assessment

A22011 Crop, A23156 Crop, VICTRATO and VICTRATO 2 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

A22011 Crop, A23156 Crop, VICTRATO and VICTRATO 2 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 enforcement in plants is cyclobutrifluram. The residue definition for risk assessment in primary crops is cyclobutrifluram and metabolites SYN510275, SYN510260 and SYN549104, and in rotational crops is cyclobutrifluram and metabolites SYN510275, SYN510260, SYN549104 and trifluoroacetic acid (TFA). The residue definition for enforcement and risk assessment in edible animal commodities is cyclobutrifluram and the metabolite SYN510275. All residue definitions are expressed in parent equivalents.

The data gathering and enforcement analytical methods are valid for the quantitation of residues of cyclobutrifluram and the metabolites SYN510275, SYN510260, SYN549104 in crops, and cyclobutrifluram and the metabolite SYN510275 in livestock matrices. The residues of cyclobutrifluram and metabolites SYN510275, SYN510260 and SYN549104 are stable in wheat grain, cucumber, dry bean seed and soybean seed for up to 11 months when stored in a freezer at -20°C. Quantifiable residues are not expected to occur in livestock commodities with the current use pattern. Crop field trials conducted throughout the United States in or on Romaine lettuce,

and throughout the United States and major production regions of Brazil in or on soybean seeds, using end-use products containing cyclobutrifluram at exaggerated rates, are sufficient to support the proposed maximum residue limits. Field rotational crop studies were conducted in/on wheat, radish and spinach/lettuce. The data are adequate to demonstrate that labelled crops can be replanted immediately, and that 120-day and 365-day plantback intervals are appropriate for cereals and all other non-labelled crops, respectively.

3.5.2 Exposure from residues in drinking water

3.5.2.1 Concentrations in drinking water

A Level 1 drinking water assessment was conducted using conservative assumptions with respect to environmental fate, application rate and timing, and geographic scenario. Level 1 estimated environmental concentrations (EECs) are conservative values intended to screen out pesticides that are not expected to pose any concern related to drinking water sources (groundwater and surface water). EECs for cyclobutrifluram in drinking water sources were calculated using the Pesticide in Water Calculator (PWC) version 2.001.

For surface water, PWC calculates the amount of pesticide entering a water body by runoff and spray drift, and the subsequent degradation of the pesticide in the water system. Groundwater EECs are calculated by simulating leaching through a layered soil profile and reporting the average concentration in the top 1-metre of a water table for several scenarios representing different regions of Canada. Only the highest EECs from across the groundwater scenarios are reported. All scenarios were modelled for a 50-year period.

A conservative use pattern was selected for the Level 1 drinking water modelling to represent all proposed uses: one single application of 100 g a.i./ha by ground application equipment or as a seed treatment. Cyclobutrifluram was modelled as a combined residue with the transformation products SYN510275, CGA177291, SYN549104, and trifluoroacetic acid (TFA). The combined residue was determined based on potential for human exposure and toxicity. Although TFA may enter the environment from numerous natural and anthropogenic sources, it was included in the combined residue in order to estimate its presence in drinking water due to the application and subsequent transformation of cyclobutrifluram. The major fate inputs for drinking water modelling and the drinking water EECs are presented in Tables 3.5.2.1.1, 3.5.2.1.2 and 3.5.2.1.3, respectively.

Details of water modelling inputs and calculations are available upon request.

Table 3.5.2.1.1 Major fate inputs for the modelling

Fate parameter	Excluding TFA	Including TFA	Drinking water
K_{oc} (L/kg)	3.6	3.6	20th percentile of 5 values for SYN510275 from a single study
Water half-life[(1)]	Stable	Stable	Quantifiable degradation was not observed during the study

Fate parameter	Excluding TFA	Including TFA	Drinking water
Sediment half-life(2)	Stable	Stable	Quantifiable degradation was not observed during the study
Photolysis half-life (d)	Stable	Stable	Single study
Hydrolysis	Stable	Stable	Single study
Soil half-life (d)	931	1410	90% confidence bound on the mean of 5 soils from a single study

(1) Aquatic whole system (aerobic)
(2) Anaerobic aquatic whole system

Table 3.5.2.1.2 Level 1 Estimated Environmental Concentrations of the combined residue of cyclobutrifluram, SYN510275, CGA177291, and SYN549104 in potential sources of drinking water as the parent equivalent

Use pattern	Groundwater (µg a.i./L)		Surface water (µg a.i./L)		
	Peak[1]	Average[2]	Daily[3]	Yearly[4]	Overall[5]
100 g a.i./ha/year	140	120	8.1	1.3	0.52

[1] peak concentration
[2] post-breakthrough average concentrations
[3] 90th percentile of the highest 1-day average concentration from each year
[4] 90th percentile of yearly (365-day) average concentrations
[5] Average of all yearly (365-day) average concentrations

Table 3.5.2.1.3 Level 1 Estimated Environmental Concentrations of the combined residue of cyclobutrifluram, SYN510275, CGA177291, SYN549104, and trifluoroacetic acid in potential sources of drinking water as the parent equivalent

Use pattern	Groundwater (µg a.i./L)		Surface water (µg a.i./L)		
	Peak[1]	Average[2]	Daily[3]	Yearly[4]	Overall[5]
100 g a.i./ha/year	140	130	8.1	1.3	0.53

[1] peak concentration
[2] post-breakthrough average concentrations
[3] 90th percentile of the highest 1-day average concentration from each year
[4] 90th percentile of yearly (365-day) average concentrations
[5] Average of all yearly (365-day) 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 cyclobutrifluram: proposed MRLs, recommended U.S. tolerances when higher than the corresponding proposed Canadian MRLs and for imported commodities, 100% crop treated, default processing factors (where applicable), and inclusion of the common metabolite trifluoroacetic acid (TFA) for rotational crops and drinking water.

The basic acute dietary exposure (food alone; 95th percentile deterministic) from all supported cyclobutrifluram food commodities and imported commodities is estimated to be less than 1% of the ARfD for females 13–49 years old (0.000306 mg/kg bw/day) and the general population (0.000612 mg/kg bw/day), which is not of health concern. When TFA in rotational crops is added, the exposure estimate is less than 2% of the ARfD for females 13–49 years old (0.000186 mg/kg bw/day) and the general population (0.000269 mg/kg bw/day), which is not of health concern. Aggregate exposure from food and drinking water is considered acceptable at less than 4% of the ARfD for all population subgroups, less than 3% (0.007511 mg/kg bw/day) of the ARfD for females 13–49 years old and less than 1% (0.0007710 mg/kg bw/day) of the ARfD for the general population. When TFA in rotational crops and drinking water is added, aggregate exposure is also not of health concern at less than 4% of the ARfD for all population subgroups, including females 13–49 years of age. The highest exposed population subgroup was infants.

3.5.3.2 Chronic dietary exposure results and characterization

The following criteria were applied to the basic chronic analysis for cyclobutrifluram: proposed MRLs, recommended U.S. tolerances when higher than the corresponding proposed Canadian MRLs and for imported commodities, 100% crop treated, default processing factors (where applicable), and inclusion of the common metabolite TFA for rotational crops and drinking water.

The basic chronic (non-cancer and cancer) dietary exposure (food alone) from all supported cyclobutrifluram food commodities and imported commodities for all representative population subgroups, including infants and children, is less than 2% (0.001012 mg/kg bw/day) of the acceptable daily intake (ADI). When TFA in rotational crops is added, the exposure estimate is less than 2% (0.001248 mg/kg bw/day) of the ADI for the total population and all representative population subgroups, which is not of health concern. Aggregate exposure from food and drinking water is considered acceptable. The PMRA estimates that chronic dietary exposure to cyclobutrifluram from food and drinking water is 4.0% (0.002817 mg/kg bw/day) of the ADI for the total population. The highest exposure and risk estimate is for infants (less than 1 year old) at less than 15% (0.010099 mg/kg bw/day) of the ADI.

When TFA in rotational crops and drinking water is added, the exposure estimate is 4.1% (0.002896 mg/kg bw/day) of the ADI for the total population. The highest exposure and risk estimate is less than 15% (0.010257 mg/kg bw/day) of the ADI for infants (<1 year).

3.6 Aggregate exposure and risk assessment

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

3.7 Cumulative assessment

The *Pest Control Products Act* requires the Agency to consider the cumulative health effects of pest control products that have a common mechanism of toxicity. Accordingly, an assessment of a potential common mechanism of toxicity with other pesticides was undertaken for the active ingredient cyclobutrifluram.

3.7.1 Succinate dehydrogenase inhibitors (SDHI)

Cyclobutrifluram belongs to a class of fungicides known as the succinate dehydrogenase inhibitors (SDHI). Other SDHI fungicides registered in Canada and have MRLs for imported commodities include benzovindiflupyr, bixafen, boscalid, carbathiin, fluopyram, flutolanil, fluxapyroxad, inpyrfluxam, isofetamid, isopyrazam, penflufen, penthiopyrad, pydiflumetofen, pyraziflumid, and sedaxane. Liver and thyroid toxicity linked to hepatic enzyme induction appears to be a common mechanism of action for several SDHI fungicides.

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

3.7.1.1 Exposure pathways and co-occurrence of exposure

There are currently 13 registered SDHI fungicides in Canada (benzovindiflupyr, bixafen, boscalid, carbathiin, fluopyram, fluxapyroxad, inpyrfluxam, isofetamid, penflufen, penthiopyrad, pydiflumetofen, pyraziflumid, and sedaxane) for a foliar and/or seed treatment and/or soil directed application in a number of commodities. In addition, MRLs are established for two additional SDHI fungicides on imported commodities, namely flutolanil and isopyrazam. Oxycarboxin was previously registered, but has since been discontinued. There is a potential for co-occurrence of exposure for registered end-use products in the SDHI class and for the SDHI fungicides with established Canadian MRLs on imported commodities.

3.7.1.2 Non-dietary exposure

Cyclobutrifluram is for use only on soybeans and romaine lettuce in Canada. As no residential uses are proposed for cyclobutrifluram, no residential (non-dietary) exposure is anticipated. Accordingly, the potential contribution of cyclobutrifluram to the cumulative exposure of SDHI fungicides is through dietary exposure alone.

Penthiopyrad is registered in Canada on residential turf. In addition, seven SDHI active ingredients (benzovindiflupyr, boscalid, fluopyram, fluxapyroxad, isofetamid, penthiopyrad and pydiflumetofen) are registered in Canada for use on golf course turf.

Based on the registered use patterns of the SDHI fungicide on turf and their existing risk assessments, the exposure scenarios that result in the highest potential residential exposure and risk are from penthiopyrad on residential turf for toddlers and from boscalid on golf courses for adults, youth and children (less than 5.1% of the risk threshold). It is noted that the risk estimates were calculated using the most conservative points of departure for penthiopyrad and boscalid, which are not based on common effects of liver and thyroid toxicity for the duration and routes relevant for these exposure scenarios.

3.7.1.3 Dietary exposure

3.7.1.3.1 Exposure from food

Several of the SDHI fungicides are registered as seed treatments only (carbathiin and sedaxane) or as a combination of seed and foliar or in-furrow treatments (boscalid, cyclobutrifluram, flutolanil, inpyrfluxam, penflufen, pydiflumetofen, penthiopyrad, fluxapyroxad, and fluopyram).

Food monitoring data are available for most of the SDHI fungicides. Of the fifteen SDHIs considered, there are no CFIA monitoring data for nine active ingredients, partly because of their recent registrations: bixafen (registered in September 2019), inpyrfluxam (registered in August 2020), pydiflumetofen (May 2018), and pyraziflumid (March 2023). PDP monitoring data are available for all SDHI fungicides except for pyraziflumid (registered in 2023). The U.S. dataset (PDP) covers a wider use pattern than the Canadian dataset (CFIA), and as such is much larger. Specifically, there were nearly three times as many samples taken and analyzed for the SDHIs in the U.S. compared with Canadian datasets.

Where available, a decade worth of monitoring data (~680,000 measurements combined from CFIA and PDP databases) for the currently registered SDHI fungicides and the two SDHI fungicides with Canadian MRLs on imported commodities were analyzed (Table 3.7.1.3.1.1). For the vast majority of measurements, no detectable residues were observed. Only ~3.3% of samples had residues greater than or equal to the limit of detection, and all of these residues were well below the established MRLs.

Table 3.7.1.3.1.1 Summary of residue monitoring data by the Canadian Food Inspection Agency (CFIA, 2012–2021) and the USEPA Pesticide Data Program (PDP, 2014–2023) for SDHI fungicides for various food commodities

Pest control product	Data source	# Samples tested (years of monitoring data)	# Sample(s) with residues greater than the LOD	% Positive	Residue range (ppm) in positive samples (greater than or equal to LOD)
Benzovindiflupyr	CFIA	No data			
	PDP	19,729 (6 years; 2018–2023)	56	0.28%	0.001–0.035
2. Bixafen	CFIA	No data			
	PDP	3653 (2 years; 2022–2023)	0	0	-
3. Boscalid	CFIA	39,604 (10 years; 2012–2021)	3730	9.4%	0.0004–9.10 [Maximum residue of 9.10 ppm was observed in leaf lettuce; MRL of 35 ppm]
	PDP	101,007 (10 years; 2014–2023)	9335	9.2%	0.002–15.7 [Maximum residues of 15.7 ppm were observed in kale greens; MRL of 50 ppm]
4. Carbathiin/ carboxin	CFIA	52,547 (10 years; 2012–2021)	2	0.004%	0.0002–0.2
	PDP	42,557 10 years; 2014–2023)	0	-	-
5. Fluopyram	CFIA	1490 (5 years; 2017–2021)	355	23.8	0.0001–0.67

Pest control product	Data source	# Samples tested (years of monitoring data)	# Sample(s) with residues greater than the LOD	% Positive	Residue range (ppm) in positive samples (greater than or equal to LOD)
	PDP	80,414 (10 years; 2014–2023)	4815	6.0%	0.001–2.94 [Maximum residues of 2.94 ppm were observed in kale greens; MRL of 50 ppm]
6. Flutolanil [No Canadian registration]	CFIA	39,524 (10 years; 2012–2021)	54	0.14%	0.0004–0.098
	PDP	39,387 (2014–2023)	31	0.1%	0.005-0.022
7. Fluxapyroxad	CFIA	129 (7 years; 2015–2021)	0	-	-
	PDP	67,600 (10 years; 2014–2023)	1852	2.7%	0.001–2.0 [Maximum residues of 2.0 ppm were observed in spinach; MRL of 30 ppm]
8. Inpyrfluxam	CFIA	No data			
	PDP	2023 data (n = 262); no detects			
9. Isofetamid	CFIA	No data			
	PDP	17,762 (8 years; 2016–2023)	91	0.5%	0.001–0.53
10. Isopyrazam [No Canadian registration]	CFIA	No data			
	PDP	16,905 (6 years; 2018–2023)	1	0.006%	0.006
11. Penflufen	CFIA	No data			
	PDP	31,561	0	0%	NA

Pest control product	Data source	# Samples tested (years of monitoring data)	# Sample(s) with residues greater than the LOD	% Positive	Residue range (ppm) in positive samples (greater than or equal to LOD)
		(10 years; 2014–2023)			
12. Penthiopyrad	CFIA	No data			
	PDP	75,599 (10 years, 2014–2023)	1957	2.6%	0.001–14.7 [Maximum residues of 14.7 ppm were observed in kale; MRL of 50 ppm]
13. Pydiflumetofen	CFIA	No data			
	PDP	25,633 (5 years; 2019–2023)	390	1.5%	0.001–0.23
14. Pyraziflumid	CFIA	No data			
	PDP				
15. Sedaxane	CFIA	No data			
	PDP	24,093 (10 years; 2014–2023)	0	0%	NA
Overall	**Canada (CFIA)**	**133,294**	**4141**	**3.1%**	**NA**
	USA (PDP)	**546,162**	**18,528**	**3.4%**	**NA**
	Overall	**679,456**	**22,669**	**3.3%**	**NA**

LOD = limit of detection; NA = not applicable

Food residue monitoring data were analyzed for potential co-occurrence of SDHI residues. For the U.S. dataset, the most frequent pesticides detected in samples where there were co-occurrences were boscalid, fluopyram, penthiopyrad, fluxapyroxad, and pydiflumetofen. Of the 24,324 samples analyzed with co-occurrences, only 3.9% had co-occurrences for at least two of these SDHIs, and none of the samples analyzed had co-occurrences for all five.

For the Canadian dataset, only four of the fifteen SDHIs considered in the assessment were included in the co-occurrence analysis (boscalid, carboxin, fluopyram and flutolanil). For the remaining eleven, the data were either limited or unavailable. Only 273 samples had co-occurrences, and most of these (270) were for boscalid and fluopyram only.

The SDHIs included in this analysis have different toxicology reference values. As such, in order to assess the cumulative risk of the co-occurring SDHIs, 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. Fluopyram met these criteria and was selected as the index chemical for this cumulative risk assessment, as it has one of the lowest ADIs and is the most frequently detected SDHI in food monitoring. In addition, fluopyram is registered on most of the food crops and its use pattern encompasses those of other registered SDHIs.

An analysis was conducted using the previously-conducted refined (intermediate level) chronic dietary exposure assessment (DEA) of fluopyram and all the food monitoring samples in which co-occurrence of SDHIs were detected (in other words, with co-occurrences of ≥2 SDHI residues), which will be referred to as “SDHI co-occurrence samples” herein. For each SDHI co-occurrence sample, using fluopyram as the index chemical, residues of each SDHI were adjusted for relative potency and molecular weight equivalency and summed to calculate the total SDHI residue level. From these residue levels of the SDHI co-occurrence samples (expressed as fluopyram equivalents and summed), the mean residue level was calculated for each food commodity for which SDHI co-occurrence was detected. The mean total SDHI residue levels for each food commodity in the co-occurrence samples were found to be lower compared to the residue input used in the previously-conducted fluopyram DEA.

Additionally, to determine how co-occurrences of SDHI residues in different food commodities impact the risk assessment, the dietary risk assessment input for fluopyram for these food commodities were replaced by the mean total SDHI residue levels (for co-occurrence samples) in DEEM-FCID™, Version 4.02, 05-10-c. For commodities where no co-occurrences were detected, residue input in the existing DEA (in other words, from field trial data with refinement for processing factor and percent crop treated) was used. This assessment indicated that the food only exposure in the highest exposed sub-population is 71.0% of the ADI; which is lower than the food only exposure of 80.7% of the ADI in the existing fluopyram dietary risk assessment. Based on this semi-quantitative assessment, it is concluded that the cumulative dietary risk from food based on residue monitoring data for all SDHIs would be lower than that for the existing risk assessment for the index chemical, and hence is not of health concern. It is noted that replacing all residue input in the DEA by the monitoring data would have substantially reduced the exposure assessment but was not pursued further. This is because even using the most conservative values from the monitoring data (for example, residues in samples with co-

occurrences of multiple actives) in crops where co-occurrences were detected was lower than the existing risk assessment for fluopyram on file. It is acknowledged that while monitoring data for pyraziflumid and cyclobutrifluram are not available, given the low level of food residues detected for all SDHIs monitored, it is not expected to change the risk assessment. Therefore, the cumulative risk from exposure to food residues of all SDHI fungicides within the current use conditions is not expected to pose unacceptable health risks to consumers.

3.7.1.3.2 Exposure from drinking water

Water monitoring data are also available for most of the SDHI fungicides registered in Canada, except for pyraziflumid, through the Canadian Water Monitoring Program for Pesticides (CWMPP) for the years 2022–2024 inclusive (https://health-infobase.canada.ca/pesticides/water-monitoring/). In the CWMPP data, of the 6958 unique water samples tested (total 77 000 measurements for SDHIs), 15% had quantifiable residues. The SDHI most frequently detected was fluopyram at 70%. A total of 3222 samples (46%) had co-occurrence of SDHIs, with a maximum of seven SDHIs co-occurring in a sample.

The CWMPP data were the most robust in terms of the number of SDHI fungicides analyzed and the sampling frequency. Among all datasets considered, including provincial datasets, the highest concentration of each of the SDHI fungicides was reported in the CWMPP data. As such, only the CWMPP data set was used for the cumulative health risk assessment.

Using fluopyram as the index chemical, the maximum concentrations detected for each SDHI were adjusted for relative potency and molecular weight equivalency, and then summed to determine the total concentration of fluopyram-equivalent SDHI residues from water. The highest value from these adjusted concentrations was 10.6 µg/L. This concentration was then compared to the human health reference value (HHRV) of fluopyram (77 µg/L). This sample came from a site that is considered relevant for estimating drinking water concentrations, coming from a river in Saskatchewan in a densely agricultural area, with a golf course upstream. Based on this analysis, the maximum contribution of cumulative exposure of SDHIs from drinking water would be 13.8% of the ADI. This estimate is less than the risk estimated from drinking water in the existing chronic risk analysis of the fluopyram DEA (16.6%) using a modelled EEC.

3.7.1.4 Conservatism in the semi-quantitative risk assessment of SDHI fungicides

Dietary (food and drinking water) and residential routes of exposure contribute to the cumulative health risk of SDHI fungicides. The following summarizes the results and conservatisms of the semi-quantitative risk assessment of this common mechanism group.

The risk assessment approach described above, using food and water monitoring data, demonstrated that cumulative dietary exposure (food plus water) to registered SDHI pesticides, is unlikely to pose health risks of concern. The approach taken has several conservatisms:

- It only considered samples with detection and co-occurrence.
- Maximum concentrations were used for the risk analysis from drinking water, which is a conservative assumption for a chronic dietary exposure assessment.

- The relative potency factors used for the risk assessment for each SDHI were calculated using the most conservative points of departure, that are not necessarily based on common effects of liver and thyroid toxicity (which are likely to be higher).

In addition, residential exposure contributes to no more than 5.1% of the risk cup. This risk estimate was calculated using the most conservative point of departure, which is not based on common effect of liver and thyroid toxicity for the exposure duration and routes relevant for the residential exposure scenarios of SDHIs.

As such, based on this semi-quantitative assessment, the cumulative risks from potential co-exposure to SDHIs through food, drinking water and residential exposure, where relevant, are acceptable.

3.7.2 Trifluoroacetic acid (TFA)

Trifluoroacetic acid (TFA), a metabolite of cyclobutrifluram, is also 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 cyflumetofen, fluazinam, fomesafen, saflufenacil, tiafenacil, trifloxystrobin, and trifluralin.

Although a comprehensive quantitative cumulative exposure assessment of TFA for the present registration for cyclobutrifluram was not conducted, it can be concluded that the individual contribution to TFA levels in the environment from cyclobutrifluram is low in the context of the multiple sources of TFA in the environment for the reasons described below.

As described in Section 3.5.3, the main source of TFA from the proposed use of cyclobutrifluram is from rotational crops. Specifically, TFA from rotational crops contributed to <0.3% of the ADI and <0.04% of the ARfD of cyclobutrifluram. The addition of TFA to the drinking water modelling exercise had little impact on the EEC value, and contributed to <1% of the ADI for chronic exposure, and had no impact on acute exposure.

In the assessment of TFA from the contribution from cyclobutrifluram, the use of the confined accumulation studies to estimate TFA in rotational crops is highly conservative since such studies are conducted as closed systems where dissipation from leaching, runoff, and other mechanisms is minimal. As such, confined crop rotation studies typically overestimate residues as compared to field accumulation studies which are conducted under actual field conditions.

The TFA assessment from the contribution from cyclobutrifluram also used the European Union (EU) Market Basket Survey (MBS) for TFA (2017). In the EU MBS, samples of various food commodities (conventional and organic) were taken from local markets in Germany and were analyzed for TFA residues. Comparing the frequency of TFA-findings at or above the reporting limit in most conventional and organic products, a strong relationship between TFA residues and conventional farming was evident. However, although the frequency of high level findings in organic products is much lower than in conventional products of the same type, it still cannot be assumed that the residues result from pesticide applications alone, since a very large percentage of the tested organic products was found to contain TFA at lower levels. Out of various food

commodity types, the conventional dry pulse products had the highest TFA residue levels. As such, in the TFA assessment from the contribution from cyclobutrifluram, the ratio of TFA (maximum residues) seen in the MBS between pulses and crops in the confined crop rotational study (cereals, leafy vegetables, root vegetables) was used to calculate the residues of all potential rotational crops that were not represented in the confined accumulation studies. As indicated in the EU MBS, the TFA residue levels in the survey include TFA from all sources including pesticidal and non-pesticidal sources. Therefore, the use of MBS results to calculate TFA residues in rotational crops, assuming the residues originate exclusively from cyclobutrifluram, is a highly conservative assumption.

As described in the TFA assessment in RD2022-09 for tiafenacil, it was noted that levels of TFA released into the environment from current agricultural uses in Canada are generally minor compared to other sources.

EFSA (2014) performed a comprehensive dietary consumer exposure assessment from all sources of TFA when assessing the pesticide saflufenacil. As such, the sources of exposure taken into consideration in this assessment were TFA residues from primary and rotational crops using saflufenacil, TFA residues on those same crops from other pesticides that are metabolised to TFA, and other TFA residues in food resulting from environmental contaminants. In this assessment, no risks of concern were identified.

For the USEPA and JMPR assessments of cyclobutrifluram, TFA was not included in the residue definition. The rationale for this stance from the USEPA was based on consideration of its physical/chemical properties as well as its comparative toxicity to cyclobutrifluram. The USEPA also cited the 2014 EFSA assessment, where it was concluded that TFA is not likely to pose a concern for human health. In the case of the JMPR assessment, TFA was excluded from the residue definitions for enforcement since it is ubiquitous in the environment and for risk assessment since it is ubiquitous and has a different toxicity profile compared to cyclobutrifluram. On this basis, JMPR concluded that TFA should be assessed separately.

Based on qualitative assessment as discussed above, exposure to TFA from pesticidal sources is not considered to be a health risk of concern; however, the PMRA plans to include TFA in the cumulative risk assessment strategic plan, prioritize the work in consideration with the resources available and leverage the assessment completed by EFSA in 2014.

3.8 Maximum residue limits

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

Table 3.8.1 Recommended maximum residue limits

MRL (ppm)	Food commodity
0.03	Leaf lettuce
0.02	Eggs, meat, meat byproducts and fat of cattle, goats hogs, horses, poultry and sheep milk
0.01	Dry soybeans

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 2, 16 and 17.

3.9 Health incident reports

Cyclobutrifluram is a new active ingredient pending registration for use in Canada, and as of 7 March 2025, no human or domestic animal incidents involving cyclobutrifluram were submitted to the PMRA.

4.0 Impact on the environment

4.1 Fate and behaviour in the environment

Cyclobutrifluram transforms into six major transformation products (SYN510275, CGA177291, EXC8199, SYN551241, SYN551231, and trifluoroacetic acid (TFA)) in the environment and one minor transformation product (SYN549104) (Appendix I, Table 18). Environmental fate parameters for cyclobutrifluram, SYN510275, and SYN549104 are provided in Appendix I, Table 19.

Hydrolysis is not a major route of transformation for cyclobutrifluram. At environmentally relevant pH and temperatures, cyclobutrifluram is expected to be hydrolytically stable.

Cyclobutrifluram is persistent in most soils, where it is broken down to a limited extent by microorganisms. The major transformation product trifluoroacetic acid (TFA) can form in soil under aerobic conditions. No major transformation products were detected in anaerobic soils. The minor transformation product SYN549104 was measured in field studies and is expected to form in the terrestrial environment. During separate transformation product aerobic biotransformation studies, SYN510275 was found to be moderately persistent to persistent, and SYN549104 was found to be slightly to moderately persistent. Cyclobutrifluram is broken down by chemical reactions in soil in the presence of light. Three major transformation products were identified in the soil phototransformation studies (SYN510275, CGA177291, and EXC8199).

Terrestrial field dissipation studies were conducted at bare soil sites in Washington State (USA) and Ontario (Canada); a site cropped with potato was also used in Washington State. In both studies, the half-life (DT_{50}) values were less than 40 days. The amount of cyclobutrifluram remaining in the soil was less than 10% after 120 days and less than 5% on study completion (after 545 days) at both Washington sites. In the Ontario study, less than 25% of cyclobutrifluram remained in the soil after 486 days. Cyclobutrifluram and its transformation products have the potential to leach through the soil, with cyclobutrifluram being detected in soil layers as deep as 70 to 100 cm. As such, carryover to the next growing season is not expected to be a concern.

The weight-of-evidence (in other words, field study data, mobility information, leaching criteria of Cohen et al., (1984), groundwater ubiquity scores (GUS), and groundwater modelling) indicates that cyclobutrifluram and its transformation products may leach to groundwater (Appendix I, Table 20). A best management practice label statement is required to inform users that use of products containing cyclobutrifluram in areas where soils are permeable, particularly where the water table is shallow, may result in groundwater contamination.

Cyclobutrifluram can enter the aquatic environment through spray drift and run-off from the application site. Cyclobutrifluram is soluble in water and hydrolysis is not an important route of transformation. Cyclobutrifluram is persistent in both aerobic and anaerobic aquatic systems, with half-lives greater than 670 days in the total systems (water + sediment). No major transformation products were formed in either aerobic or anaerobic water/sediment system. However, in the presence of light, cyclobutrifluram is broken down in water via aqueous phototransformation, with three major transformation products produced (SYN510275, SYN551231, and SYN551241).

Although the log K_{ow} value of 3.2 suggests cyclobutrifluram has the potential to bioaccumulate, a bioconcentration study indicates that cyclobutrifluram is not expected to bioaccumulate in fish (BCF <45) and is rapidly eliminated from the fish (up to 97% of residues) after depuration for 14 days. Predicted log K_{ow} values for the transformation products suggest they are not expected to bioaccumulate.

Cyclobutrifluram has a low vapour pressure and is not expected to volatilize from moist soil or water surfaces (Henry's law constant = 7.3×10^{-5} $Pa.m^3/mole$). The low vapour pressure and the persistence of cyclobutrifluram in soil and aquatic matrices suggest a low potential for cyclobutrifluram to dissipate into air.

4.2 Environmental risk characterisation

An environmental risk assessment was conducted as described in the guidance document, Health Canada's Approach to Environmental Risk Assessment for Pest Control Products, to estimate the potential for adverse effects on non-target species. Environmental exposure and ecotoxicology information were integrated by comparing estimated environmental concentrations (EECs) to effects-based values used to assess risk (effects metrics). EECs were estimated using standard models that consider application rate(s) and chemical and environmental fate properties, including pesticide dissipation between applications. The EECs used in this risk assessment are presented in Appendix I, Table 21.

Acute and chronic ecotoxicological data for non-target terrestrial, freshwater and marine organisms are summarized in Appendix I, Table 22. 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 23 to 28.

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 availability of treated seed and the habits of mammals. 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, bees and other beneficial arthropods, birds, wild mammals and terrestrial vascular plants may be exposed to cyclobutrifluram through direct contact with spray, contact with sprayed surfaces, contact with soil containing treated seeds, or from ingestion of treated seeds or food containing residues of cyclobutrifluram. A risk assessment for cyclobutrifluram and the end-use products A22011 Crop, A23156 Crop, VICTRATO, and VICTRATO 2 was undertaken based on available toxicity data.

The screening level risk assessment for terrestrial organisms is presented in Appendix I, Tables 23 to 26. At the screening level, the on-field EECs for the soil-applied end-use products (A22011 Crop and A23156 Crop) were calculated for soil and plant surfaces based on a direct overspray, considering a single maximum application rate of 100 g a.i./ha per year (Appendix I, Table 21). Soil EECs were converted from g a.i./ha to mg a.i./kg dw soil using the assumption that cyclobutrifluram is homogeneously mixed in the top 15 cm soil layer with a soil bulk density of 1.5 g/cm^3. The on-field EEC for the major transformation product, SYN510275, in water was calculated based on the single maximum application rate of 100 g a.i./ha per year, with the conservative assumption of 100% conversion of the parent compound on a molar basis. The off-field EECs and estimated dailydietary exposures (EDEs) were not calculated unless a refined risk assessment was required to further characterise the risk of cyclobutrifluram and its major transformation products.

At the screening level risk assessment for bees, the on-field EDEs associated with the use of seed treatment end-use products (VICTRATO and VICTRATO 2) were calculated based on a default residue level of 1 µg a.i./g seed (Appendix I, Table 21).

At the screening level risk assessment for birds and mammals, the on-field EECs associated with the use of seed treatment end-use products (VICTRATO and VICTRATO 2) were calculated based on a converted rate of 63 g a.i./ha per year, which was derived from the maximum application seeding rate 50 g a.i./100 kg seed (Appendix I, Table 25).

Non-target terrestrial organisms might also be exposed to cyclobutrifluram via spray drift from the use of soil-applied end-use products (A22011 Crop and A23156 Crop). The off-field exposure for non-target terrestrial organisms was not further characterised for cyclobutrifluram and its major transformation products during screening level risk assessment, unless a refined risk assessment was required.

Earthworms and bees

Earthworms could be exposed to cyclobutrifluram when it is applied to soil or used to treat seeds. Foraging bees may be exposed to cyclobutrifluram spray droplets during application (contact exposure) or through the ingestion of pollen and nectar containing residues of cyclobutrifluram (oral exposure). Additionally, bee brood may be exposed to cyclobutrifluram if foraging bees bring contaminated pollen and nectar back to the hive. The screening level risk quotients (RQs) for these organisms were below the LOC (Appendix I, Table 23 and 24). As such, the risks to earthworms and bees are acceptable.

Beneficial arthropods

Beneficial arthropods could be exposed to cyclobutrifluram spray droplets, by contact with sprayed surfaces during soil application, or when it is used for seed treatment which results in soil exposure. Toxicity tests for beneficial arthropods were conducted with two end-use products containing cyclobutrifluram, A22011B (450 g a.i./L, soil-applied) and A22417C (500 g a.i./L, seed treatment). No acute or chronic effects were observed for beneficial arthropods at the highest concentration tested.

The screening level risk assessment for beneficial arthropods, using effects metrics from toxicity tests where the test organisms were exposed to dried residues of A22011B and A22417C, is presented in Appendix I, Table 23. The screening level risk assessment only evaluated on-field exposure to foliar-dwelling (in other words, predatory mite, *Typhlodromus pyri*, and parasitic arthropod, *Aphidius rhopalosiphi*) and soil-dwelling (in other words, *Hypoaspis aculeifer*) arthropods. The screening level risk assessment used a LOC of 2 for spray applications on glass plates, given that significant ecological effects for these species at the population level are not expected below this value. The screening level RQs were below the LOC and therefore risks to beneficial arthropods are acceptable.

Terrestrial vertebrates—birds and wild mammals

Birds and wild mammals may be exposed to cyclobutrifluram through contact with sprayed surfaces, ingestion of treated seeds and/or food items containing residues of cyclobutrifluram as a result of soil application.

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

For the seed treatment end-use products, a screening level risk assessment was conducted to evaluate the acute and reproductive risks to birds and mammals based on the estimated concentration of cyclobutrifluram treated seeds in the diet. The exposure of birds and mammals to a pesticide through consumption of treated seed is a function of the amount of pesticide on the seed, the body weight and food ingestion rate of the animal, and the number of seeds available for consumption. The EDE is determined for a range of size classes of birds (20, 100, 1000 g) and mammals (15, 35, 1000 g). For each body weight, the food ingestion rate is based on equations from Nagy (1987). For each size of organism, the EDE is calculated using the following equation:

EDE = FIR × number of seeds/g

- The EDE is expressed as the number of seeds consumed per day; and
- FIR: Food ingestion rate, in g dry weight per day

The screening level risk assessment for the soil-applied and seed treatment end-use products considered a conservative exposure scenario based on:

- The maximum cyclobutrifluram residue concentrations in contaminated food items or on treated seeds;
- A diet that is composed entirely (100%) of a particular dietary item or treated seeds;
- The feeding guild assumed to have the highest exposure for each animal weight category; and
- All of the treated seed that is planted is available for consumption ad libitum, over an extended period of time.

Feeding preference, availability of treated seeds, or potential avoidance behaviour toward treated seed are not considered at the screening level. If a concern was identified at the screening level (in other words, RQ > LOC), the risk was then further characterised.

Based on the screening level risk assessment for the soil-applied end-use products, the on-field acute and reproductive risks to birds and small wild mammals from the use of cyclobutrifluram were below the LOC (Appendix I, Table 25).

Based on the screening level risk assessment for the seed treatment end-use products, the on-field acute and reproductive risks to birds from the use of cyclobutrifluram were below the LOC (Appendix I, Table 26). The acute risk to small mammals (15 g), medium mammals (35 g), and the acute and reproductive risks to large mammals (1000 g) from the use of cyclobutrifluram

were also below the LOC (Appendix I, Table 26); however, the RQs for reproductive risk for small and medium sized mammals both marginally (RQ < 2) exceeded the LOC of 1 (Appendix I, Table 26). As such, the on-field risks to these groups were further characterized by expanding the assessment to include the availability of treated seed and the habits of mammals. The RQs for refined reproductive risks to small and medium sized mammals both marginally (RQ < 2) exceeded the LOC (Appendix I, Table 27). Both the screening and refined values assume that the mammals are foraging exclusively on the treated areas for ~100 days, and the diet of these mammals would be composed 100% of treated seeds with the maximum concentration of cyclobutrifluram over this period of time. After planting of treated seeds, it is unlikely that a mammal will be eating a diet consisting only of cyclobutrifluram treated food for 100 days under natural conditions. In addition, the treated seeds will only be available for a short period of time before either the seed germinates or degrades under exposure to moisture. According to the label directions for the seed treatment end-use products, all spilled or exposed seeds must be incorporated into the soil or otherwise cleaned up from the soil surface. Therefore, risk of reproductive effects in small wild mammals from exposure to cyclobutrifluram is considered unlikely when label directions are followed. Therefore, risks to birds and mammals are acceptable. A standard best management practice statement related to spilled and exposed seed is required on product labels.

Terrestrial vascular plants

The screening level risk assessment for non-target terrestrial plants considered a direct overspray of cyclobutrifluram. The screening level RQs were below the LOC (Appendix I, Table 23) and therefore the risks for non-target terrestrial plants are acceptable.

4.2.2 Risks to aquatic organisms

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

The EEC for cyclobutrifluram in surface water was calculated based on a direct overspray to a one-hectare wetland at the single application rate of 100 g a.i./ha. The EEC for the major transformation product, SYN510275 was calculated considering 100% transformation of cyclobutrifluram on a molar basis.

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.

Cyclobutrifluram is classified as practically non-toxic to moderately toxic to all freshwater and marine aquatic organisms, with the exception of marine aquatic invertebrates, to which cyclobutrifluram is highly toxic (Appendix I, Table 22). Based on the available data, the major transformation product of cyclobutrifluram, SYN510275, is less toxic than cyclobutrifluram to aquatic organisms (practically non-toxic to freshwater fish, invertebrates, and algae; Appendix I, Table 22). The other transformation products are not expected to have greater toxicity in the environment than cyclobutrifluram based on the similarities of their chemical structures to either cyclobutrifluram or SYN510275.

The screening-level aquatic risk quotients for cyclobutrifluram and its major transformation product SYN510275 were less than the LOC (Appendix I, Table 28). Therefore, risks to aquatic organisms are acceptable. Precautionary statements are required on labels to inform users of the toxicity of cyclobutrifluram to aquatic organisms. Standard best management practice statements related to reducing runoff are required on product labels.

4.2.3 Environmental incident reports

Cyclobutrifluram is a new active ingredient pending registration for use in Canada. As of 29 March 2025, no environmental incident reports have been submitted to the PMRA.

5.0 Value

Cyclobutrifluram is a new conventional active ingredient for nematode and disease management in Canada. Currently, there is no alternative product available to control the nematodes on romaine lettuce indicated on the A22011 Crop and A23156 Crop labels except for chemical fumigation prior to planting, which is not economically viable. For the uses on the VICTRATO and VICTRATO 2 labels, several nematicide or fungicide seed treatments are registered for suppression of soybean cyst nematode or control of *Fusarium virguliforme* causing sudden death syndrome on soybeans. These products will provide Canadian growers with a new mode of action for nematode management on romaine lettuce and soybean, and an additional active ingredient within FRAC Group 7 for use against sudden death syndrome on soybeans.

Scientific rationales and efficacy results from field trials on different varieties of romaine lettuce in the USA and Canada demonstrated that A22011 Crop or A23156 Crop were effective against root knot nematode on lettuce when applied by soil banded or soil drenched applications at planting. Both A22011 Crop and A23156 Crop have demonstrated an acceptable level of nematode suppression as compared to the non-treated control in field trials.

Scientific rationales and efficacy results from field and greenhouse trials on soybean in Brazil, the USA and Canada demonstrated that VICTRATO or VICTRATO 2 were effective against soybean cyst nematode or early season infection by *F. virguliforme* on soybean when applied as seed treatments. Data confirmed that VICTRATO or VICTRATO 2 suppressed soybean cyst nematode at the labelled low rate but controlled soybean cyst nematode at the high rate. Data also confirmed that both products control the early season infection by *F. virguliforme.* The use of rhizobia inoculant and tank mixing uses of VICTRATO or VICTRATO 2 with listed fungicides or insecticides can be accepted from a value perspective.

No phytotoxicity or injury to the crops was observed in the trial studies. When used according to label directions, application of these products is not expected to result in any non-safety adverse effects to the labelled crops.

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 product.

During the review process, cyclobutrifluram and its transformation products were assessed in accordance with the PMRA Regulatory Directive DIR99-03[6] and evaluated against the Track 1 criteria. The PMRA has reached the conclusion that cyclobutrifluram and its transformation products do not meet all of the TSMP Track 1 criteria.

Please refer to Appendix I, Table 29 for further information on the TSMP assessment.

6.2 Formulants and contaminants of health or environmental concern

During the review process, contaminants in the active ingredient as well as formulants and contaminants in the end-use products are compared against Parts 1 and 3 of the *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern*.[7] The list is used as described in the PMRA Science Policy Note SPN2020-01[8] and is based on existing policies and regulations, including the Toxic Substance Management Policy and *Formulants Policy*,[9] and taking into consideration the *Ozone-depleting Substances and Halocarbon Alternatives Regulations* under the *Canadian Environmental Protection Act (*substances designated under the *Montreal Protocol).*

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

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

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

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

The PMRA has reached the conclusion that cyclobutrifluram and its end-use products A22011 Crop, A23156 Crop, VICTRATO, and VICTRATO 2 do not contain any formulants or contaminants identified in the *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern*.

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

7.0 Proposed regulatory decision

Health Canada's PMRA, pursuant to subsection 28(1) of the *Pest Control Products Act*, is proposing registration for the sale and use of Cyclobutrifluram Technical, A22011 Crop, A23156 Crop, VICTRATO and VICTRATO 2, containing the technical grade active ingredient cyclobutrifluram, a nematicide and fungicide for use on romaine lettuce and as a soybean seed treatment.

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.

Additional information being requested

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

List of abbreviations

↑	increased
↓	decreased
>	greater than
<	lesser than
≥	greater than, or equal to
♂	male
♀	female
µg	microgram(s)
λ	wavelength
°C	degrees centigrade
°N	degree North
^{14}C	carbon-14
A/G	albumin/globulin ratio
a.i.	active ingredient
abs	absolute
AD	administered dose
ADI	acceptable daily intake
AHETF	Agricultural Handlers Exposure Task Force
AHR	aryl hydrocarbon receptor
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AOPWIN	Atmospheric Oxidation Estimation Program for Windows
AR	applied radioactivity
ARfD	acute reference dose
ARTF	Agricultural Reentry Task Force
AST	aspartate aminotransferase
atm	atmosphere
ATP	adenosine triphosphate
ATPD	area treated per day
AUC	area under the curve
BAF	Bioaccumulation Factor
BBCH	Biologishe Bundesanstalt, Bundessortenamt and Chemical industry
BCF	Bioconcentration Factor
BCF_{KLG}	growth and lipid corrected bioconcentration factor
BROD	7-benzyloxyresorufin-O-debenzylase
bw	body weight
bwg	body weight gain
C_{max}	maximum concentration
CAF	composite assessment factor
CAR	constitutive androstane receptor
CAS	Chemical Abstracts Service
CEPA	*Canadian Environmental Protection Act*
CFIA	Canadian Food Inspection Agency (CFIA)
CHO	Chinese hamster ovary
cm	centimetre
cm^3	cubic centimetre

CR	chemical-resistant
CRA	cumulative risk assessment
CWMPP	Canadian Water Monitoring Program for Pesticides
CYP	cytochrome P
d	day
DAM	differentially abundant metabolites
DB-ALM	Database on Alternative Methods
DEA	dietary exposure assessment
DEEM	Dietary Exposure Evaluation Model
DFOP	double first-order in parallel
DFR	dislodgeable foliar residue
DIR	directive
DMSO	dimethyl sulfoxide
DPRA	direct peptide reactivity assay
DT_{50}	dissipation time 50% (the dose required to observe a 50% decline in concentration)
dw	dry weight
EC_{50}	effective concentration on 50% of the population
EDE	estimated daily dietary exposure
EEC	estimated environmental concentration
EFSA	European Food Safety Authority
EROD	Ethoxyresorufin-O-deethylase
ER_{25}	effective rate for 25% of the population
ER_{50}	effective rate on 50% of the population
EU MBS	European Union Market Basket Survey
F1	first filial generation
fc	food consumption
fe	food efficiency
FIR	food ingestion rate
FOB	functional observational battery
FRAC	Fungicide Resistance Action Committee
g	gram(s)
GD	gestation day
GGT	gamma-glutamyl transpeptidase
GIT	gastrointestinal tract
GUS	groundwater ubiquity score
H	Henry's law constant
h	hour
ha	hectare(s)
HAFT	highest average field trial
HDPE	high-density polyethylene
HHRV	human health reference value
Hb	hemoglobin
HCT	hematocrit
HDT	highest dose tested
HGPRT	hypoxanthine-guanine phosphoribosyltransferase
HPLC	high performance liquid chromatography
HPLC-MS/MS	high performance liquid chromatography with tandem mass spectrometry

hr(s)	hour(s)
ILV	independent laboratory validation
IORE	indeterminate order rate equation
IPA	ingenuity pathway analysis
IRAC	Insecticide Resistance Action Committee
IUPAC	International Union of Pure and Applied Chemistry
i.v.	intravenous
IVIS	in vitro irritation score
JMPR	FAO/WHO Joint Meeting on Pesticide Residues
kg	kilogram(s)
K_d	soil-water partition coefficient
K_{oc}	organic-carbon partition coefficient
K_{ow}	*n*–octanol-water partition coefficient
kPa	kilopascal
L	litre
LAFT	lowest average field trial
LC_{50}	lethal concentration 50%
LD_{50}	lethal dose 50%
LDH	lactate dehydrogenase
LLNA	local lymph node assay
LOAEC	lowest observed adverse effect concentration
LOAEL	lowest observed adverse effect level
LOC	level of concern
LOD	level of detection
LOQ	limit of quantitation
LR_{50}	lethal rate 50%
m	metre
m^2	metres squared
MAS	maximum average score
MBq	millibecquerel
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MIS	maximum irritation score
mg	milligram
mL	millilitre
M/L/A	mixer/loader/applicator
mm	millimetre
MOA	mode of action
MOE	margin of exposure
mol	mole
MRL	maximum residue limit
MS	mass spectrometry
N/A	not applicable
NAFTA	North American Free Trade Agreement
NHANES/WWEIA	National Health and Nutrition Examination Survey/What We Eat in America
NIOSH	National Institute for Occupational Safety and Health
ng	nanogram

nm	nanometres
NOAEC	no observed adverse effect concentration
NOAEL	no observed adverse effect level
NOEC	no observed effect concentration
NOED	no-observed effect dose
NOEDD	no-observed effect dietary dose
NOER	no-observed effect rate
NR	not reported
NZW	New Zealand white
OC	organic carbon content
OD490	optical density at 490 nanometers
OECD	Organisation for Economic Cooperation and Development
OH	hydroxyl radical
P	parental generation
Pa	Pascal
PAI	pure active ingredient
PB	phenobarbital
PBI	plantback interval
PCPA	Pest Control Products Act
PDP	Pesticide Data Program
PHI	preharvest interval
pK_a	dissociation constant
PMRA	Pest Management Regulatory Agency
PND	postnatal day
POD	point of departure
PPAR	αperoxisome proliferator-activated receptor alpha
PPE	personal protective equipment
ppm	parts per million
PROD	pentoxyresorufin o-dealkylase
PWC	Pesticide in Water Calculator
PXR	pregnane X receptor
q_1*	cancer potency factor
QSAR	quantitative structure-activity relationship
RBC	red blood cells
RD	residue definition
REI	restricted-entry interval
rel	relative
RQ	risk quotient
RXR	retinoid X receptor
SC	soluble concentrate
SDEV	standard deviation
SDH	succinate dehydrogenase
SDHI	succinate dehydrogenase inhibitors
SFO	Single first order
SI	stimulation index
SPCC	synthetic peptide containing cysteine
SPCL	synthetic peptide containing cysteine and lysine
SPN	Science Policy Note

STMdR	supervised trial median residue
STMR	supervised trial mean residue
T4	thyroxine
TC	transfer coefficient
TEER	transepithelial electrical resistance
TFA	trifluoroacetic acid metabolite
TFD	terrestrial field dissipation
TOC	total organic carbon
t_R	representative half-life
TRR	total radioactive residue
TSCF	transpiration stream concentration factor
TSMP	Toxic Substances Management Policy
UDP-GT	uridine diphosphate glucuronyltransferase
UF	uncertainty factor
U.S.	United States
USDA	United States Department of Agriculture
USEPA	United States Environmental Protection Agency
UV	ultraviolet
v/v	volume per volume dilution
WBC	white blood cells
wk	week(s)
wt	weight

Appendix I Tables and figures

Table 1 Residue analysis in environmental media

Matrix	Method ID	Analyte	Method type	LOQ	Reference
Soil and thatch sod	GRM076.01A	Cyclobutrifluram SYN549104 SYN510275 CGA177291 EXC8199	HPLC-MS/MS	1 µg/kg	PMRA# 3273115, 3273116, 3273117
Sediment	ECO_084_02A	Cyclobutrifluram	HPLC-MS/MS	0.05 mg/kg	PMRA# 3273124
Surface and ground water	GRM076.04A	Cyclobutrifluram	HPLC-MS/MS	0.025 µg/L	PMRA# 3273118, 3273119, 3273120

Table 2 Residue analysis in plant and animal commodities

Analytical methods	Matrix	Analytes[1]	Method ID/type	LOQ	Reference
Livestock commodities					
Enforcement Method Data-Gathering Method	Bovine liver, kidney, fat, muscle and whole milk; Whole egg	Cyclobutrifluram and metabolite SYN510275	GRM076.10A (QuEChERS)/ HPLC-MS/MS	0.01 ppm for each analyte in all matrices	PMRA# 3273112
ILV of Enforcement Method	Bovine liver, kidney, fat, muscle and whole milk; Whole egg	Cyclobutrifluram and metabolite SYN510275	GRM076.10A (QuEChERS)/ HPLC-MS/MS	0.01 ppm for each analyte in all matrices	PMRA# 3334686
Radiovalidation	Hen liver, muscle, fat, egg white and yolk	[Phenyl-U-^{14}C] and [Pyridinyl-2-^{14}C] Cyclobutrifluram	N/A	N/A	pp. 251-252 of : PMRA# 3273208,

Analytical methods	Matrix	Analytes[1]	Method ID/type	LOQ	Reference
Plant Commodities					
Enforcement Method	Head lettuce, soybean seed, dry bean, wheat grain, orange fruit, and wheat straw	Cyclobutrifluram and metabolites SYN510260 and SYN510275	QuEChERS method EN 15662:2018/ HPLC-MS/MS	0.01 ppm for each analyte in all matrices	PMRA# 3273111
Data-Gathering Method	Soybean forage, lettuce, wheat hay, corn forage, sugar beets, grapes, oil, grass clippings	Cyclobutrifluram	GRM076.02A (QuEChERS)/ HPLC-MS/MS	0.01 ppm in all matrices	PMRA# 3273105
	Cucumber, wheat grain, coffee bean, soybean seed, sugarcane	Cyclobutrifluram and metabolites SYN510260 and SYN510275	GRM076.07A (revision of GRM076.02A)/ HPLC-MS/MS	0.01 ppm for each analyte in all matrices	PMRA# 3273108
	Cucumber, wheat grain, coffee bean, soybean seed and sugarcane	Metabolite SYN549104 (detected as the epimer form SYN552202)	GRM076.11A/ HPLC-MS/MS	0.01 ppm in all matrices	PMRA# 3273109
ILV of Enforcement Method	Head lettuce, soybean seed, dry bean, wheat grain, orange fruit, and wheat straw	Cyclobutrifluram and metabolites SYN510260 and SYN510275	QuEChERS method EN 15662:2018/ HPLC-MS/MS	0.01 ppm for each analyte in all matrices	PMRA# 3273111

Analytical methods	Matrix	Analytes[1]	Method ID/type	LOQ	Reference
Radiovalidation	Wheat straw and grain	[Phenyl-U-^{14}C] and [Pyridinyl-2-^{14}C] Cyclobutrifluram	N/A	N/A	p. 184 of: PMRA# 3273202
	Potato mature tubers and mature foliage	[Pyridinyl-2-^{14}C] Cyclobutrifluram	N/A	N/A	p. 177 of: PMRA# 3273205
	Soybean grain	[Pyridinyl-2-^{14}C] Cyclobutrifluram	N/A	N/A	p. 144 of: PMRA# 3273206

[1] In each method, the analysis and quantitation are for individual compounds. Residues of metabolites are not converted to cyclobutrifluram equivalents.

Table 3 Identification of select metabolites of Cyclobutrifluram

Code	Chemical name	Source
SYN510260 (CA5542),	2-(trifluoromethyl)pyridine-3-carboxylic acid	Wheat grain
SYN510275	2-(trifluoromethyl)pyridine-3-carboxylic acid	Rat, hen, goat, wheat straw, potatoes, soybean forage, hay, straw and grain
SYN549104	hydroxylated metabolite of SYN549522 (*N*-[(1*S*,2*R*)-2-(2,4-dichlorophenyl)-2-hydroxy-cyclobutyl]-2-(trifluoromethyl)pyridine-3-carboxamide	Rat, hen, goat, wheat straw, potatoes, soybean grain
Metabolite A	di-hydroxy SYN549522	Rat excreta
Metabolite B (SYN547522)	SYN547552 hydroxy glucuronide metabolite	Rat excreta
Metabolite C	SYN549522 sulphate	Rat excreta
Metabolite D	SYN547552 hydroxy glucuronide metabolite	Rat excreta
Metabolite E	phenyl specific cleaved metabolite	Rat excreta
Metabolite G	SYN547552 hydroxy glucuronide isomer	Rat excreta
Metabolite H	SYN547552 hydroxy glucuronide metabolite	Rat excreta
Metabolite L	SYN547552 hydroxy glucuronide isomer	Rat excreta
Metabolite M	SYN547552 hydroxy glucuronide isomer	Rat excreta

Table 4 Toxicology reference values for use in health risk assessment for Cyclobutrifluram

Exposure scenario	Study	Point of departure and endpoint	CAF[1] or target MOE
Acute dietary general population	Oral developmental toxicity study in rabbits	NOAEL = 75 mg/kg bw/day Body weight loss in maternal animals early in dosing period.	100
ARfD (general population) = 0.8 mg/kg bw			
Acute dietary females 13–49 years old	Oral developmental toxicity study in rabbits	NOAEL = 75 mg/kg bw/day[3] Body weight loss in maternal animals early in dosing period.	300
ARfD (females 13–49 years old) = 0.3 mg/kg bw			
Repeated (chronic) dietary	2-year dietary chronic toxicity/carcinogenicity study in rats	NOAEL = 6.8 mg/kg bw/day Decreased body weight and body weight gain, thyroid gland follicular cell adenomas (♀) and carcinomas (♂)	100
ADI = 0.07 mg/kg bw/day			
Short- to intermediate-term dermal[2]	2-generation dietary reproductive toxicity study in rats	NOAEL = 9.0 mg/kg bw/day Delayed preputial separation and decreased fertility index in F1 males.	100
Short- to intermediate-term inhalation	28-day inhalation toxicity study in rats	NOAEL = 8.6 mg/kg bw/day Decreased body weight and body weight gain and respiratory tract lesions (alveolar macrophage aggregation, bronchiole/alveolar wall smooth muscle cell hypertrophy, alveolar/alveolar duct wall thickening, inflammatory cell infiltration) in both sexes.	100
Cancer	A threshold approach was taken for the assessment of cancer risk related to liver tumours in mice and thyroid tumours in rats.		

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 was used in a route-to-route extrapolation.

3 Although not specifically related to in utero exposure, this endpoint, in combination with an uncertainty factor of threefold for database deficiencies, was considered appropriate in order to afford sufficient protection to potential serious developmental effects occurring in the absence of maternal toxicity if higher dose levels were tested in the rat developmental toxicity study.

Table 5 Toxicity profile of technical Cyclobutrifluram

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 #	Study results
Toxicokinetic Studies	
Absorption, biliary elimination, excretion, distribution (oral gavage, intravenous) Wistar rats PMRA# 3273127	Cyclobutrifluram radiolabeled at either the [Phenyl-U-^{14}C] or [Pyridinyl-2-^{14}C] position was administered as a single dose of 5 or 500 mg/kg bw (gavage) or 1 mg/kg bw (i.v) **Absorption:** For both radiolabels, total absorption from the GIT was 97–99% of the administered dose (AD) at the low-dose level, and 52–75% of the AD at the high-dose level, based on the radioactivity measured in bile, urine, cage wash, plasma, RBC and carcass. **Excretion:** Regardless of dose level, the major route of excretion of the radiolabel following oral dosing was in feces via biliary elimination (67–92% of AD) followed by urinary excretion (6.5–23% of AD) at 168 hrs post-dosing. At 72 hrs after oral administration of a single low or high dose, ~90% and 59–73% of the AD, respectively, was eliminated via the bile. Following a single i.v. dose the major route of elimination was via the feces. Excretion was rapid, with the majority of the AD eliminated within 48–72 hrs after oral or i.v. administration of the radiolabeled dose. Excretion was complete by 168 hrs post-dose with <1.6% of the AD remaining in excreta samples. Excretion was comparable between the high- and low-dose levels and between the [Phenyl-U-^{14}C] and [Pyridinyl-2-^{14}C] radiolabels. **Distribution:** Regardless of radiolabel, dose level, or sex, the concentration of radioactivity 168 hrs post dosing was highest in the liver. Radiolabel concentration in ♀ was half that of ♂. Other tissues with relatively high levels of radioactivity included the thyroid, whole blood, and kidneys.
Tissue depletion and elimination (oral gavage) Wistar rats PMRA# 3273130	Cyclobutrifluram radiolabeled at either the [Phenyl-U-^{14}C] or [Pyridinyl-2-^{14}C] position was administered as a single dose of 5 or 500 mg/kg bw (both sexes) or as a daily dose of 5 mg/kg bw/day for 14 consecutive days (♂ only). **Distribution:** Extensive distribution throughout tissues was observed, regardless of dosing, radiolabel or sex. In single low dose animals, maximum blood and plasma concentration of radioactivity were noted at 0.5 hr [Phenyl-U-^{14}C] or at 2 hrs [Pyridinyl-2-^{14}C] post-dosing. At this time, the majority of the AD was present in the tissues GIT and carcass (86% and 93% of the AD for [Phenyl-U-^{14}C] and [Pyridinyl-2-^{14}C],

Study type/ Animal/ PMRA #	Study results
	respectively). For both radiolabels, at the first measured time point, the liver had the highest concentration of radioactivity followed by the adrenal glands. Most tissues contained higher levels of radioactivity than that in circulation at 0.5 hr and 2 hrs for the phenyl and pyridinyl radiolabels, respectively. By 96 hrs, the concentration of radioactivity in tissues was below that in circulation and accounted for 3% (tissue/GIT/carcass) in [Phenyl-U-^{14}C] dosed animals and 5.5% (tissue/GIT/carcass) in [Pyridinyl-2-^{14}C] dosed animals. In single high dose animals, the tissues with the highest concentration at the first sampling time point (2 hrs) were the liver and the adrenal glands in both sexes dosed with [Phenyl-U-^{14}C] and ♂ dosed with [Pyridinyl-2-^{14}C], and were renal fat and adrenal glands in ♀ dosed with [Pyridinyl-2-^{14}C]. Regardless of radiolabel, concentration plateau was observed at 24 hrs. At 24 hrs, tissue, GIT, and carcass accounted for 44% ([Phenyl-U-^{14}C]) or 31% [Pyridinyl-2-^{14}C]. By 96 hrs, the concentration of radioactivity in tissues was below that in circulation and accounted for 1.5-1.6% (tissue/GIT/carcass). Following repeated dosing, radioactivity was widely distributed to the tissues, with the highest mean tissue concentration observed 24 hrs after the final (14th) dose. Maximum blood and plasma concentrations were noted at 2 hrs post-dosing. Tissues with the highest concentrations were the liver, thyroid, and kidneys. Following a decline in radioactivity for 168 hrs, the highest concentrations of radioactivity were observed in the liver and spleen. The major route of elimination was via the feces. Half-life in plasma ($t_{½}$) = 22-35 hrs following low and high doses.
Biotransformation (oral gavage) Wistar rats PMRA# 3273128	Cyclobutrifluram radiolabeled at either the [Phenyl-U-^{14}C] or [Pyridinyl-2-^{14}C] position was administered as a single dose of 5 or 500 mg/kg bw. Radiolabel components were quantified from samples of urine, feces, bile, plasma. Cyclobutrifluram was readily metabolized regardless of dose, sex, or radiolabel. **Urine:** No unchanged cyclobutrifluram was detected in urine following administration of either radiolabel. The major components in urine were Metabolite E (1.1% to 8.7% of the AD) and SYN510275 (5.3% to 12.5% of the AD) for phenyl- and pyridinyl-labelled compound, respectively. Other metabolites included SYN549104, and Metabolites B, C. There was little

Study type/ Animal/ PMRA #	Study results
	difference between urinary metabolites between sexes, dose levels, or radiolabel positions. The metabolic steps prior to elimination in urine involved hydroxylation, glucuronide conjugation of hydroxylated metabolites, sulphate conjugation of cyclobutrifluram, cleavage of the amide bond to give the trifluoromethyl nicotinamide metabolite, hydrolysis of the amide bond and subsequent oxidative cleavage of the cyclobutane moiety to give an amino dichloro phenyl oxobutanoic acid metabolite (Phenyl cleaved metabolite E). **Feces:** Quantitative differences in fecal metabolites were noted between sexes and dose groups. SYN549104 (hydroxyl SYN549522) was the major component in feces following low dose administration and accounted for 9.8–14.3% of the AD. Metabolite B (hydroxyl glucuronide) was the major fecal component in high dose rats (22.8–40.9% of the AD). In the high-dose group, unchanged cyclobutrifluram accounted for 15.7–17.0% of the AD following dosing with the phenyl radiolabel, and 23–27.1% of the AD following dosing with the pyridinyl radiolabel. In the low-dose group, Metabolite A was detected equally (6.1–8.8% of the AD) in both sexes, regardless of radiolabel. However, in high-dose animals, it was only detected in ♀ rats administered the phenyl radiolabel (0.3% of the AD). Metabolite C was similar between the radiolabel positions but was detected at 0.8–1.6% AD in ♀ and 4.4–11.5% AD in ♂ and only detected in minor amounts (0.1% AD) in bile duct-cannulated ♀. SYN510275, pyridinyl specific metabolite was detected in feces of rats administered the pyridinyl radiolabel (≤4.6% AD) The metabolic steps prior to elimination in feces involved hydroxylation, glucuronide conjugation of hydroxylated metabolites, sulphate conjugation of cyclobutrifluram, and cleavage of the amide bond to give the trifluoromethyl nicotinamide metabolite SYN510275. **Bile:** Unchanged cyclobutrifluram was not detected in bile. Metabolite B was the major component regardless of sex, dose or radiolabel position and accounted for 38.2–56.6% of the AD for the phenyl radiolabel and 38.3–52.5% AD for the pyridinyl radiolabel. Differences in the amount of Metabolite C were noted between sexes (1.5% AD in ♂ and 5.7% AD in ♀).

Study type/ Animal/ PMRA #	Study results
	The metabolic steps prior to elimination in bile involved glucuronide conjugation of hydroxylated metabolites, sulphate conjugation of cyclobutrifluram, cysteine conjugation of hydroxylated metabolites, and cleavage of the amide bond to give the trifluoromethyl nicotinamide metabolite SYN510275.
Pharmacokinetics (oral gavage) Wistar rats PMRA# 3273129	Cyclobutrifluram radiolabeled at either the [Phenyl-U-^{14}C] or [Pyridinyl-2-^{14}C] position was administered as single dose of 5 or 500 mg/kg bw (gavage) or 1 mg/kg bw (i.v.). **Low oral dose:** The Cmax in plasma and blood for both radiolabels was observed at 0.5 to 12 hours post-dosing. AUC values in blood and plasma were similar between the sexes. The bioavailability estimate was similar between the sexes for the phenyl radiolabel (~120%) whereas it was slightly higher in ♂ (128/102% in ♂/♀) for the pyridinyl radiolabel. The half-life of elimination could not be estimated for most groups. **High oral dose:** The Cmax in blood and plasma ranged from 2 to 24 hours post-dosing. AUC values in blood and plasma were similar between the sexes. The bioavailability estimate was similar between the sexes for the phenyl radiolabel (~45%) whereas it was slightly higher in ♂ (43/36% in ♂/♀) for the pyridinyl radiolabel **Intravenous dose:** Blood concentrations were similar between the sexes. Initial theoretical concentrations declined to 1 hour post-dose and then plateaued to 24 hours. The half-life of elimination could not be estimated.
Tolerability and TK study - 7 Day Oral (oral gavage) and single dose IV Wistar rats PMRA# 3273177	SYN547386 (S-enantiomer of Cyclobutrifluram) was administered to both sexes at 0, 50, 250, 500, 1000 mg/kg bw/day (gavage) for 7 days or 1 mg/kg (i.v.) (♂ only). SYN547386: variable and inconsistent concentration levels. Cmax and total AUC systemic exposure were higher for ♀. Rapid clearance. Oral bioavailability in ♂ was less than 4%. Weight loss noted in ♀ at 1000 mg/kg bw/day with overall bwg lower and lower food intake. No difference in food intake for ♂ 500 mg/kg bw/day and higher, but lower bwg was evident.
7-Day Oral (oral gavage) Toxicokinetic Study (♀) Wistar rats PMRA# 3273175	SYN547386 (S-enantiomer of Cyclobutrifluram) was administered at 25, 50, 100, 250, 375 and 500 mg/kg bw/day for 7 days. SYN547386 and its metabolite were both detectable at all doses. No clinical signs of toxicity observed, or effects on bw or fc.

Study type/ Animal/ PMRA #	Study results
	Exposure to SYN547386 and its metabolite on Day 1 increased supra-proportionally between 25 to 100 mg/kg, but was subproportional at doses above 100 mg/kg. On Day 7, when compared with Day 1, exposure to SYN547386 was lower and increased subproportionally across all dose levels.
Acute Toxicity Studies	
Acute Oral Toxicity Sprague-Dawley rats PMRA# 3273132	LD_{50} > 5000 mg/kg bw (♀) No clinical signs of toxicity. **Low acute oral toxicity**
Acute Oral Toxicity Wistar rats PMRA# 3477761	LD_{50} > 2000 mg/kg bw (♀) Clinical signs 2-4 hrs after dosing: ↓ activity (1 ♀), hunched posture in (4 ♀), and piloerection (3 ♀). All cleared by Day 1. Study used to determine time to peak effect for acute neurotoxicity study. Time to peak effect ≈ 3 hours. **Low acute oral toxicity**
Acute Dermal Toxicity (Fixed Dose) Sprague-Dawley rats PMRA# 3273133	LD_{50} > 2000 mg/kg bw (♀) No clinical signs of toxicity. **Low acute dermal toxicity**
Acute Inhalation Toxicity (nose-only) Sprague-Dawley rats PMRA# 3273134	LC_{50} > 4.08 mg/L (corrected for purity) Irregular respiration and nasal discharge (1♂). All resolved by Day 6 **Low acute inhalation toxicity**
Eye Irritation New Zealand White rabbits PMRA# 3273138	MAS (24, 48, 72 hrs) = 0 MIS = 0 **Non-irritating to the eye**
Dermal Irritation New Zealand White rabbits PMRA# 3273135	MAS (24, 48 72 hrs) = 0 MIS = 0 No signs of erythema, edema, no clinical signs **Non-irritating to the skin**

Study type/ Animal/ PMRA #	Study results
Dermal Sensitization (LLNA) CBA/J mice PMRA# 3273139	Negative (SI < 3.0 in all groups) No clinical signs of toxicity or signs of dermal irritation. **Not a dermal sensitizer**
In vitro measurement of the Airway Irritation Potential of Cyclobutrifluram using the MucilAir™ Airway Model (non-guideline) Human airway epithelium PMRA# 3273150	**Study considered acceptable with limitations** Evaluation of irritation assessed by transepithelial electrical resistance (TEER), LDH release, resazurin metabolism (marker of cellular metabolism) and histology analysis No change in TEER or LDH release. No change in resazurin metabolism. No histology difference from control tissues compared to test chemical treated tissues. Limitation: study not subjected to quality assurance procedures
Short-Term Toxicity Studies	
28-day Oral Toxicity (diet) CD-1 mice PMRA# 3273141	**Study considered acceptable with limitations** NOAEL not established Effects at ≥ 62/63 mg/kg bw/day (♂/♀): ↑ spleen wt (♂/♀); ↑ thyroid wt, ↑ triglycerides, ↓ cholesterol (♂); ↑ extramedullary hemopoiesis in spleen (♀) Effects at ≥ 338/334 mg/kg bw/day (♂/♀): ↓ RBC, ↓ Hb, ↑ MCV, ↑ RDW, ↑ reticulocytes, ↑ liver wt (♂/♀); ↓ A/G ratio, ↑ hepatocellular hypertrophy, ↑ extramedullary haemopoiesis of the spleen (♂); ↑ adrenal wt, ↑ ALP, ↑ ALT (♀) Effects at ≥ 630/684 mg/kg bw/day (♂/♀): ↑ adrenal wt (♂); ↑ hepatocellular hypertrophy (♀) Effects at 1585/1771 mg/kg bw/day (♂/♀): ↑ GGT (♂/♀); ↓ abs. prostate wt, ↑ ALP (♂); ↓ eosinophils, ↓ glucose (♀) ↑ hepatic microsomal CYP-enzymes and UDP-GT activity towards T4 at ≥ 62/63 mg/kg bw/day (♂/♀) Toxicokinetic evaluation was conducted but results were highly variable and inconclusive. Limitation: small group sizes for assessment of hematology and clinical chemistry in ♀.

Study type/ Animal/ PMRA #	Study results
90-day Oral Toxicity (diet) CD-1 mice PMRA# 3273145	NOAEL = 17/22 mg/kg bw/day (♂/♀) LOAEL = 94/134 mg/kg bw/day (♂/♀) Effects at the LOAEL: ↓ Hb, ↓ MCHC, ↑ ALP, ↓ cholesterol, ↓ albumin, ↑ globulin, ↓ A/G ratio, ↑ neutrophils, ↑ triglycerides, ↑ liver wt, ↑ spleen wt, hepatocellular hypertrophy (♂/♀); ↑ WBC, splenic extramedullary haemopoiesis (♂); ↓ RBC, ↓ HCT, ↑ reticulocytes (♀)
28-day Oral Toxicity (diet) Wistar rats PMRA# 3273143	NOAEL not established LOAEL = 32/35 mg/kg bw/day (♂/♀) Effects at the LOAEL: ↑ thyroid follicular cell hypertrophy, ↑ hepatic microsomal total CYP content, ↑ CYP-dependent enzymes PROD, BROD, EROD, UDP-GT) (♂/♀); ↓ hemoglobin, ↑ inflammatory cell infiltrates in lamina propria of cecum (♀) Blood concentrations of cyclobutrifluram were generally undetectable by Day 2 in most animals. However, when quantifiable, concentration versus time profiles were highly variable. Quantifiable concentrations were a reflection of nocturnal eating behaviour. Generally, where evaluable, systemic exposure increased with increasing dose.
90-day Oral Toxicity (diet) Sprague-Dawley rats PMRA# 3273146, 3273148	NOAEL = 9.6/11 mg/kg bw/day (♂/♀) LOAEL = 51/59 mg/kg bw/day (♂/♀) Effects at the LOAEL: ↓ fc, ↓ fe, liver centrilobular hypertrophy, thyroid follicular cell hypertrophy (♂/♀); ↓ bw/ bwg, ↑ total protein, ↑ globulin, ↓ spleen wt (♂);↑ X- and Y-ambulation, ↑ fibrinogen, ↑ liver wt, ↑ adrenal wt (♀)
28-day oral toxicity (capsule) (non-guideline) Beagle dogs PMRA# 3273144	**Study considered acceptable with limitations** NOAEL not established Effects at ≥100 mg/kg bw/day: ↑ liver wt (♀) Effects at ≥300 mg/kg bw/day: ↓ bwg (week 1), ↑ ALP, hepatocellular hypertrophy (♂/♀); ↑ triglycerides, ↑ liver wt (♂); ↑ adrenal wt (♀) Effects at 600 mg/kg bw/day: ↓ bwg (♂/♀); ↑ gamma glutamyl transferase, ↑ adrenal wt (♂); bw loss (wk 1), ↑ triglycerides (♀) Limitation: small group size
90-day oral toxicity (Capsule)	NOAEL = 30/100 mg/kg bw/day (♂/♀) LOAEL = 100/300 mg/kg bw/day (♂/♀)

Study type/ Animal/ PMRA #	Study results
Beagle dogs PMRA# 3273149	Effects at the LOAEL: ↓ bwg, ↑ ALP, ↑ liver wt, ↓ albumin (♂/♀); ↑ hepatocellular hypertrophy (♀)
28-day dermal toxicity Wistar rats PMRA# 3273152	NOAEL = 300 mg/kg bw/day (♂/♀) LOAEL = 1000 mg/kg bw/day (♂/♀) Effects at the LOAEL: ↓ ALP, ↑ liver wt ↑ adrenal wt (♂/♀); ↑ creatinine, ↓ AST, adrenal vacuolation (♂); ↓ ALT, liver necrosis (♀)
28-day inhalation toxicity (nose-only) Sprague Dawley rats PMRA# 3518791	NOAEC = 40.2 mg/m^3 (8.6/9.2 mg/kg bw/day ♂/♀) LOAEC = 80.3 mg/m^3 (17/18 mg/kg bw/day ♂/♀) Effects at the LOAEC: ↓ bw, ↓ bwg, ↑ alveolar macrophage aggregation, bronchiole/alveolar wall smooth muscle cell hypertrophy, alveolar/alveolar duct wall thickening, and inflammatory cell infiltration (♂/♀); ↑ rel. testis wt, ↑ rel. brain wt, ↑ rel. heart wt (♂)
Chronic Toxicity/Oncogenicity Studies	
18-month oncogenicity (diet) CD-1 mice PMRA# 3273163	NOAEL = 14/16 mg/kg bw/day (♂/♀) LOAEL = 48/54 mg/kg bw/day (♂/♀) Effects at the LOAEL: ↑ adrenal wt (♂/♀); ↑ liver wt, hepatic hemangioma, hepatocellular carcinoma (♂); ↑ spleen wt, splenic extramedullary hematopoiesis (♀) Tumour incidences in ♂/♀ Hepatic hemangioma (%): 0, 0, 2, 4 / 0, 0, 0, 0 Hepatocellular carcinoma (%): 0, 2, 2, 8* / 0, 0, 0, 0 * p≤ 0.05 (Peto) Evidence of carcinogenicity – Hepatic hemangioma and hepatocellular carcinoma (♂)
2-year chronic toxicity/oncogenicity (diet) Wistar rats PMRA# 3273162	NOAEL = 6.8/9.0 mg kg bw/day (♂/♀) LOAEL = 26/33 mg/kg bw/day (♂/♀) Effects at the LOAEL: ↑ rel. liver wt (♂/♀); ↓ bw/bwg, ↓ fe, ↑ thyroid gland follicular cell carcinoma (♂); ↑ abs. liver wt, ↑ thyroid gland follicular cell adenoma (♀) Tumour incidences in ♂/♀ Follicular cell adenoma (%): 12, 15, 23, 8 / 0, 0, 0, 6* Follicular cell carcinoma (%): 0, 2, 2, 7 / 0, 0, 2, 0 * p≤ 0.05 (Peto)

Study type/ Animal/ PMRA #	Study results
	Evidence of carcinogenicity – Follicular cell adenoma (♀) and follicular cell carcinoma (♂)
Developmental/Reproductive Toxicity Studies	
2-generation reproductive toxicity (diet) Wistar rats PMRA# 3273172, 3273173, 3359487	Parental NOAEL = 9.0/11 mg/kg bw/day (♂/♀) Parental LOAEL = 43/53 mg/kg bw/day (♂/♀) Effects at the LOAEL: ↑ rel. liver wt (P♂,P♀) ↑ thyroid follicular cell hypertrophy (P,F1♂/P♀), ↑ thyroid wt (P,F1♂, P♀) Offspring NOAEL = 11 mg/kg bw/day Offspring LOAEL = 53 mg/kg bw/day Effects at the LOAEL: ↓ bw PND 21 (F1a), ↓bwg PND 1-21 (F1a), ↑ liver wt (♂/♀); ↓ bw PND 14 (F1a), ↑ mean age of balano-preputial separation (F1) (♂) Reproductive NOAEL = 9.0/53 mg/kg bw/day (♂/♀) Reproductive LOAEL = 43 mg/kg bw/day/not determined (♂/♀) Effects at the LOAEL: ↓ fertility index (F1♂) **No evidence of sensitivity of the young**
Developmental toxicity (oral gavage) – dose range-finding Wistar rat PMRA# 3273176	**Study considered acceptable with limitations** **NOAEL not established.** Maternal Effects at 250 mg/kg bw/day: ↓ bwg GD 6 to 8 No treatment-related developmental effects up to 250 mg/kg bw/day (assessment included viability, weight, sex, external, skeletal and visceral abnormalities). Toxicokinetics: Mean blood concentrations of cyclobutrifluram did not follow a dose response; mean blood concentrations of metabolite SYN549104 were more than 30 times higher than those for unchanged cyclobutrifluram and followed a dose response. Limitations: small group sizes, thyroid hormones not assessed.
Developmental toxicity (oral gavage) Wistar rat PMRA# 3273178, 3273174	**Study considered acceptable with limitations** Maternal NOAEL = 250 mg/kg bw/day (HDT) Maternal LOAEL not established Non-adverse effects at 250 mg/kg bw/day: ↓ bwg GD 6 to 8, ↑ TSH levels

Study type/ Animal/ PMRA #	Study results
	Developmental NOAEL = 250 mg/kg bw/day (HDT) Developmental LOAEL not established No treatment-related developmental effects (assessment included viability, weight, sex, external, skeletal and visceral abnormalities). **No evidence of sensitivity of the young** **No evidence of treatment-related malformations** Toxicokinetics: Mean blood concentrations of cyclobutrifluram in maternal animals increased with dose level in a non-proportionate manner; mean blood concentrations of metabolite SYN549104 were more than 20 times higher than those for unchanged cyclobutrifluram and increased with dose level. Thyroid hormone assessments, thyroid weights and microscopic examinations were conducted in maternal animals Limitation: dose level selection inadequate
Developmental toxicity (oral gavage) – dose range-finding New Zealand White rabbits PMRA# 3273180	**Study considered acceptable with limitations** **NOAEL not established** Maternal effects at ≥75 mg/kg bw/day: ↓ fc GD 16 to 18 and GD 6 to 28 Maternal Effects at 125 mg/kg bw/day: ↓ bwg GD 0 to 6 and thereafter, ↓ fc GD 5 to 6 and thereafter No treatment-related developmental effects (assessment included viability, weight, sex, external, skeletal and visceral abnormalities). Toxicokinetics: Mean blood concentrations of cyclobutrifluram were 8.42, 12.9, and 37.1 ng/mL for the 25, 75, and 125 mg/kg bw/day dose groups. Mean blood concentrations of metabolite SYN549104 were much higher for equivalent doses at 3830, 7340, and 12000 ng/mL at 25, 75, and 125 mg/kg bw/day, respectively. Limitation: small group sizes
Developmental toxicity (gavage)	Maternal NOAEL = 75 mg/kg bw/day Maternal LOAEL = 125 mg/kg bw/day

Study type/ Animal/ PMRA #	Study results
New Zealand White rabbits PMRA# 3273181	Effects at the LOAEL: bw loss GD 6-8 and 6-10, ↓ bwg (starting on GD 6 and continuing throughout study; highest magnitude occurring between GD 6 and 10), ↓ fc GD 6 to 8 and thereafter Developmental NOAEL = 125 mg/kg bw/day (HDT) Developmental LOAEL not established No treatment-related developmental effects (assessment included viability, weight, sex, external, skeletal and visceral abnormalities). **No evidence of sensitivity of the young** **No treatment-related malformations**
Genotoxicity Studies	
Bacterial Reverse Mutation assay *S.* Typhimurium TA98, TA100, TA1535, TA1537, and *E. coli* WP2.uvrA, WP2 PMRA# 3273153	Negative ± metabolic activation Tested up to a limit concentration.
Bacterial Reverse Mutation assay *S.* Typhimurium TA98, TA100, TA1535, TA1537, and *E. coli* WP2.uvrA, WP2 PMRA# 3273154	Negative ± metabolic activation Tested up to a limit concentration.
Bacterial Reverse Mutation assay *S.* Typhimurium TA98, TA100, TA1535, TA1537, and *E coli* WP2.uvrA, WP2 PMRA# 3273155	Negative ± metabolic activation Tested up to a limit concentration.

Study type/ Animal/ PMRA #	Study results
Cell Mutation assay (in vitro) Mouse Lymphoma L5178Y Cells at the TK$^{\pm}$ locus PMRA# 3273159	Negative ± metabolic activation Tested up to the limit of solubility.
Micronucleus Assay (in vitro) Human peripheral blood lymphocytes PMRA# 3273156	Negative ± metabolic activation Tested up to the limit of solubility.
Micronucleus Assay (in vitro) Human peripheral blood lymphocytes PMRA# 3273157	Negative ± metabolic activation Tested up to the limit of solubility or cytotoxic concentrations.
Micronucleus Assay (in vitro) Human peripheral blood lymphocytes PMRA# 3273158	Negative ± metabolic activation Tested up to the limit of solubility.
Micronucleus Assay (in vivo) (gavage) Wistar rats PMRA# 3273160	Negative No clinical signs of toxicity
Neurotoxicity Studies	
Acute oral neurotoxicity (gavage) Wistar rats PMRA# 3273183	NOAEL = 600 mg/kg bw (♂/♀) LOAEL = 2000 mg/kg bw (♂/♀) Effects at the LOAEL: ↑ activity count on Day 8 in FOB, ↓ motor activity on Day 1 (♂/♀); ↓ body temperature Day 1, ↓ landing footsplay on Day 8 (♀) **No evidence of selective neurotoxicity**

Study type/ Animal/ PMRA #	Study results
Single Dose (Time to Peak Effect) (gavage) (non-guideline) Wistar Rats PMRA# 3273184	Dose of 2000 mg/kg bw was considered suitable for dosing in the main acute neurotoxicity study. Time to peak effect was not determined.
Subchronic Neurotoxicity Study Waiver request PMRA# 3273186	Waiver request accepted based on the lack of evidence of overt neurotoxicity in the acute neurotoxicity toxicity study or the single dose time-to-peak-effect study, or in other studies across the database. Following acute oral gavage dosing in rats, changes in activity count, decreased motor activity, decreased landing foot splay and decreased body temperature were observed at the limit dose of testing. There was a lack of neurohistopathological effects in the submitted toxicology studies conducted in rats, mice, and dogs. In addition, cyclobutrifluram appears to have low exposure to the nervous system, as observed by its rapid excretion and very low concentrations in the brain and fat. There is also a lack of or limited evidence of neurotoxicity in related compounds.
Metabolite studies: SYN510260 (CA5542), 2-(trifluoromethyl)nicotinic acid); SYN510275	
Acute Oral Toxicity Up-and-Down Method Sprague-Dawley Rats PMRA# 3273187	LD_{50}> 5000 mg/kg bw (♀) No clinical signs of toxicity **Low acute oral toxicity**
Bovine Corneal Opacity and Permeability (BCOP) Test Bovine corneas PMRA# 3273190	Mean In vitro Irritation Score (IVIS) = 161 Final Opacity = 149 Final OD_{490} = 0.069 **Severely Irritating to the eye**
In Vitro Skin Corrosivity Test in the EPISKIN™ Model Reconstructed Human epidermis PMRA# 3273191	Mean cell viability = 91.9% **Non-corrosive to the skin**

Study type/ Animal/ PMRA #	Study results
In Vitro Skin Irritation Test in the EPISKIN™ Model Reconstructed Human epidermis PMRA# 3273192	Mean cell viability = 114.2% **Non-irritant to skin**
In Vitro Skin Sensitization Assay - Human-Cell Line Activation Test (h-CLAT) THP-1 cells PMRA# 3273194	**Positive** Conducted using OECD Test Guideline 442E (2018) and DB-ALM Protocol No. 158
Keratinosens Test an In Vitro Skin Sensitisation Assay KeratinoSens cell line (immortalized human adherent HaCaT keratinocytes) PMRA# 3273195	**Negative** No potential to activate Nrf2 transcription factor Conducted using OECD Test Guideline 442D
In Chemico Determination of the Skin Sensitization Potential of CA5542A using the Direct Peptide Reactivity Assay (DPRA) PMRA# 3273196	**Negative** Mean of SPCC and SPCL depletion = 0% No or minimal reactivity class when using Cysteine 1:10/Lysine 1:50 prediction model Conducted using OECD Test Guideline 442C
Bacterial Reverse Mutation assay *S.* Typhimurium TA98, TA100, TA1535, TA1537, and *E. coli* WP2 *uvrA* (pKM101) PMRA# 3273188	**Negative** Tested up to a limit concentration.

Study type/ Animal/ PMRA #	Study results
Bacterial Reverse Mutation Assay *S.* Typhimurium strains TA98, TA100, TA1535, TA1537, and *E. coli* strains WP2 *uvrA* (pKM101) and WP2 (pKM101) PMRA# 3273199	**Negative** Tested up to a limit concentration.
Micronucleus Assay (in vitro) Human peripheral blood lymphocytes PMRA# 3273189	**Negative** Tested up to concentration that did not perturb pH.
In vitro forward mutation assay in mammalian cells Chinese hamster ovary (CHO/ HGPRT) cells PMRA# 3273193	**Negative** Tested up to concentration that did not perturb pH and up to a concentration where precipitation was not observed by eye.
Micronucleus Assay (in vitro) Human peripheral blood lymphocytes PMRA# 3273198	**Negative** Tested up to the recommended limit concentration.
Other studies	
Immunotoxicity – waiver rationale PMRA# 3273131	Waiver rationale accepted based on lack of evidence in the available database demonstrating immunosuppressive effects, and evaluations of other compounds in the same class of chemistry that have no evidence of immunotoxicity.
2-, 7-, and 28-day oral toxicity investigating liver MOA (diet) (non-guideline) CD-1 mice	Administration of cyclobutrifluram was associated with elevation in alkaline phosphatase activity and increased liver weight. Administration of cyclobutrifluram at dietary concentrations of 120, 400 or 800 ppm was associated with a minor, but non dose or duration related, generalized increase in Ki67 stained proliferating hepatocytes at Day 8 and Day 29.

Study type/ Animal/ PMRA #	Study results
PMRA# 3273167	Biochemical analysis of hepatic microsomal enzyme activities demonstrated that cyclobutrifluram is an inducer of CYP2B, as assessed by PROD activity, which is a marker of activation of CAR in male CD-1 mice.
Metabolomics Assessment of Plasma and Liver Samples from a 28-day Dietary Liver Mode of Action Study (non-guideline) CD-1 mice (♂) PMRA# 3273168	Plasma and liver samples from animals tested in in the 2-, 7- and 28-day oral toxicity study investigating liver MOA (PMRA# 3273167) were used to conduct comprehensive hybrid (semi-targeted) polar and lipidomic metabolomics analyses to compare metabolomic profiles and differentially abundant metabolites (DAMs) in response to cyclobutrifluram, to those induced by PB, a positive control of CAR activation, relative to control. The biochemical changes induced by phenobarbital and cyclobutrifluram appeared to be similar. The full feature set showed that cyclobutrifluram has a much weaker effect on the liver than phenobarbital. There was a consistent lack of unique features associated with the cyclobutrifluram profile in both liver and plasma at all time points, which suggests a lack of concurrent mechanisms other than those associated with phenobarbital and thus with CAR activation. The phenobarbital effect DAMs reduced feature set shows strong similarity with the full feature set profiles, supporting that they are representative of the key biochemical changes and are in strong agreement with the literature reported effect profiles of phenobarbital. Up and down regulation of the phenobarbital effect DAMs was consistent with the cyclobutrifluram effect profiles, supporting cyclobutrifluram as a CAR activator.
Mouse Liver Toxicogenomics Study to Test the Dose-Dependency of Pathways Affected by Treatments (non-guideline) PMRA# 3273169	This study used plasma and liver samples from animals tested in the 2-,7-, and 28-day oral (diet) toxicity study investigating liver MOA (PMRA # 3273167) to conduct whole genome microarray (transcription profiling) analysis. These data were then used for pathway analysis using Ingenuity Pathway Analysis (IPA) software to assess the effects of cyclobutrifluram dose and exposure time on toxicologically relevant transcription pathways. Additionally, a correlation analysis was performed on gene expression signatures, for activity of CAR, aryl hydrocarbon receptor (AHR), and peroxisome proliferator activated receptor alpha (PPARa). CAR/RXR activation, AHR signaling and PXR/RXR activation pathways were significantly over-represented in the differentially expressed gene (DEG) lists across all treatment groups. Several CAR-regulated genes were also significantly induced in a dose- and time dependent fashion. The test item profile of overrepresented toxicity pathways was similar to that of the

Study type/ Animal/ PMRA #	Study results
	phenobarbital (PB) positive control. There were significant positive correlations between genes in the CAR signature and the cyclobutrifluram DEG lists at day 3 mid and high dose (dose-dependent), day 8 low dose and day 29 low dose treatments. There was a time-dependent positive correlation at the cyclobutrifluram low dose, reaching significance at day 8 and 29. There were significant positive correlations between the AHR signature and the cyclobutrifluram DEGs at day 3 and day 29 high dose. Key AHR-regulated genes Cyp1a1, Cyp1a2, Cyp1b1 and AhRR were not induced by cyclobutrifluram, indicating that AHR was not activated.
CAR3 transactivation assay with mouse, rat and human CAR (in vitro) (non-guideline) COS-1 cells PMRA# 3273170	Under the conditions of this assay, rat, mouse, and human cells exhibited statistically significant, dose-dependent CAR activation in response to cyclobutrifluram treatment. Rat demonstrated the highest activation relative to the DMSO control (up to ~12.7 fold), followed by mouse (up to ~5.1 fold), then human (up to ~1.9 fold).
In-Vitro Inhibition of Rat Thyroid peroxidase (TPO) (non-guideline) Rat thyroid microsomes from male Wistar rat thyroid glands PMRA# 3273171	Cyclobutrifluram was not found to be an inhibitor of rat TPO activity

Table 6 Toxicity profile of end-use products containing Cyclobutrifluram

Study type/Animal/PMRA #	Study results
Acute Toxicity Studies – A22011 Crop	
Acute oral toxicity (Up-and Down Method) Wistar rats PMRA# 3273071	LD_{50} > 5000 mg/kg bw (♀) No clinical signs of toxicity. **Low acute oral toxicity**
Acute dermal toxicity Wistar rats	LD_{50}> 2000 mg/kg bw (♂♀) No clinical signs of toxicity or signs of irritation.

Study type/Animal/PMRA #	Study results
PMRA# 3273072	**Low acute dermal toxicity**
Acute Inhalation toxicity (nose-only) Sprague-Dawley rats PMRA# 3273073	LC_{50} > 5.08 mg/L (♂♀) No clinical signs of toxicity. **Low acute inhalation toxicity**
Eye Irritation New Zealand White rabbits PMRA# 3273076	MAS (24, 48, 72 hrs) = 3.11 MIS = 18.67 at 1 hr **Minimally irritating to the eye**
Eye Irritation [In Vitro test in Isolated Chicken Eyes (ICE)] ROSS 308 chicken eyes PMRA# 3273077	Overall ICE Class = 2 × Class I, 1 × Class IV **Not classified as a severe irritant and not classified as a non-irritant according to OECD Test Guideline 438**
Dermal Irritation New Zealand White rabbits PMRA# 3273075	MAS (24, 48, 72 hrs) = 0 MIS = 0 **Non-irritating to the skin**
Dermal Irritation (In Vitro EpiSkin™ Model) Reconstructed human epidermis (EpiSkin™) PMRA# 3273074	Mean Relative Viability = 95.1% **Non-irritating to the skin according to OECD Test Guideline 439**
Dermal Sensitization (LLNA) CBA/J mice PMRA# 3273078	Negative SI < 3.0 at all concentrations **Not a dermal sensitizer**

Study type/Animal/PMRA #	Study results
Acute Toxicity Studies – A23156 Crop	
Acute oral toxicity (Up-and Down Method) Sprague-Dawley rats PMRA# 3273395	LD_{50}> 2000 mg/kg bw (♀) Clinical signs of toxicity included irregular respiration. **Low acute oral toxicity**
Acute dermal toxicity **Waiver Request** PMRA# 3273396	Waiver request accepted based on the results of the acute oral toxicity study with an LD_{50} greater than 2000 mg/kg bw in females. **Considered of low acute dermal toxicity**
Acute Inhalation toxicity (nose-only) Sprague-Dawley rats PMRA# 3273397	LC_{50} > 5.08 mg/L (♂/♀) Clinical signs of toxicity included irregular respiration. **Low acute inhalation toxicity**
Eye Irritation [In Vitro Isolated Chicken Eyes (ICE)] ROSS 308 chicken eyes PMRA# 3273402	Overall ICE Class = 1 × Class I, 1 × Class II, 1 × Class III **Not classified as a severe irritant and not classified as non-irritant according to OECD TG 438.**
Eye Irritation NZW Rabbits PMRA# 3273401	MAS (24, 48, 72 hrs) = 27.67 MIS = 31.3 at 48 hrs **Moderately irritating to the eye** By 24 hrs: all three treated eyes exhibited corneal opacity and conjunctivitis that decreased over time. All animals free of ocular irritation by day 7 or 14
Dermal Irritation (In Vitro Skin Irritation Test in the EPISKIN™ Model) PMRA# 3273398	Relative Viability value = 119.7% **Non-corrosive to the skin according to OECD TG 431**
Dermal Irritation [In Vitro Skin Irritation Test in the EpiDerm™ Model (EPI-200-SIT)] PMRA# 3273400	Mean relative viability = 2.9% (compared to –ve control) **Dermal irritant according to OECD TG 439**

Study type/Animal/PMRA #	Study results
Primary Skin Irritation NZW Rabbits PMRA# 3273399	MAS (24, 48, 72 hrs) = 0.67 MIS = 1.33 at 24 hrs **Slightly irritating to the skin**
Dermal Sensitization (LLNA) CBA/J mice PMRA# 3273403	Positive SI = 3.27 at the 100% concentration EC3 value = 82.9% **Potential dermal sensitizer**
Acute Toxicity Studies – VICTRATO and VICTRATO 2	
Acute oral toxicity (Up-and Down Method) Sprague Dawley rats PMRA# 3273340	LD_{50} > 5000 mg kg bw (♀) Clinical signs included hypoactivity, irregular respiration, ↓fecal volume, hunched posture, piloerection, and ataxia. **Low acute oral toxicity**
Acute dermal toxicity (Fixed dose method) Sprague-Dawley rats PMRA# 3273343	LD_{50} > 2000 mg/kg bw (♀) No clinical signs of toxicity or signs of dermal irritation. **Low acute dermal toxicity**
Acute Inhalation toxicity (nose-only) Sprague-Dawley rats PMRA# 3273345	LC_{50} > 5.06 mg/L (♂/♀) Clinical signs of toxicity included hypoactivity and anogenital staining. **Low acute inhalation toxicity**
Eye Irritation In Vitro Eye Irritation Test in Isolated Chicken Eyes (ICET) PMRA# 3273354	Mean Maximum corneal swelling at up to 240 min = 0.6% Mean Maximum corneal opacity change = 0.50 Mean fluorescein retention change = 3.00 **Not classified as a severe irritant and not classified as non-irritant according to OECD TG 438.**
Eye Irritation New Zealand Albino Rabbits PMRA# 3273353	MAS (24, 48, 72 hrs) = 1.11 MIS = 7.33 at 1 hr **Minimally irritating to the eye**

Study type/Animal/PMRA #	Study results
Dermal Irritation PMRA# 3273350	MAS (24, 48, 72 hrs) = 1.56 MIS = 3.33 at 1 hr **Mildly irritating to the skin**
Dermal Irritation In Vitro Skin Irritation Test in the EPISKIN™ Model Human epidermis PMRA# 3273348	Relative Viability = 100.3% **Non-irritant to skin according to OECD TG 431.**
Dermal Sensitization LLNA CBA/J mice PMRA# 3273356	Negative SI =2.69 at the 100% concentration **Not a dermal sensitizer**

Table 7 Summary of dermal absorption values for Cyclobutrifluram

Product	Scenario	Dermal absorption	Source study[1]
Soil-Directed Spray Products			
A22011 Crop and A23156 Crop	Mixer/loader	2%	Human in vitro (PMRA# 3273079)
	All other scenarios	6%	
Seed Treatment Products			
VICTRATO 2 and VICTRATO	Mixer/loader	1%	Human in vitro (PMRA# 3273359 and 3273360)
	All other scenarios	6%	

[1] Although a rat in vitro study was submitted to the PMRA (PMRA# 3579394), its results were not considered to derive the dermal absorption values for human exposure, as 1) the human in vitro study was considered to be sufficient to select dermal absorption values and 2) rat skin was shown to be more permeable than human skin, which results in unnecessary conservatism in estimating human dermal absorption.

Table 8 Comparison of mean percent recovery of cyclobutrifluram absorbed through skin in vitro after 8 hours exposure (measured 24 hours post exposure) to A22011B

Formulation used	**A22011B (A22011 Crop)**			**A22011B (A22011 Crop)**		
Study type	Human in vitro			Rat in vitro		
Dose group	Formulation Concentrate	High In-Use Dilution	Low In-Use Dilution	Formulation Concentrate	High In-Use Dilution	Low In-Use Dilution
Concentration (g/L)	450	1.5	0.15	450	1.5	0.15
Applied Dose (µg/cm^2)	4634/4880	15.71	1.55	4654	15.5	1.56
Absorbed dose[1]	0.36	2.29	4.67	4.21	5.02	13.72
Total Tape Strips (%)	1.11	1.50	1.29	9.60	0.59	3.22
Potentially absorbed dose[2] (including all tape strips) (%)	**1.48**	**3.79**	**5.96**	**13.80**	**5.61**	**16.94**
Total recovery (%)	**98.48**	**99.40**	**98.27**	**101.83**	**101.08**	**97.01**

[1] Absorbed dose = Sum of unexposed skin, exposed skin, receptor fluid, receptor chamber wash and receptor rinse

[2] Potentially absorbable dose = Sum of total skin (unexposed skin, exposed skin, and total tape strips), terminal receptor fluid, and receptor chamber wash and receptor rinse

Table 9 Comparison of mean percent recovery of cyclobutrifluram absorbed through human skin in vitro after 8 hours exposure (measured 24 hours post exposure) to A22417B (VICTRATO 2) and A22147C (VICTRATO)

Formulation used	**A22417B (VICTRATO 2)**		**A22417C (VICTRATO)**		
Study Type	In vitro		In vitro		
Dose Group	Formulation Concentrate	High In-Use Dilution	Formulation Concentrate	High In-Use Dilution	Low In-Use Dilution
Concentration (g/L)	500	25	500	25	2.5
Applied dose (µg/cm^2)	5040	256	5155	256	24.4
Absorbed (%)[1]	0.23	0.91	0.16	1.26	2.62
Total Tape Strips (%)	0.22	0.58	0.11	2.63	3.24
Potentially absorbed dose (including all tape strips) (%)[2]	**0.45**	**1.49**	**0.27**	**3.89**	**5.86**
Total Recovery (%)	**98.05**	**94.27**	**94.26**	**103.45**	**98.83**

[1] Absorbed dose = Sum of unexposed skin, exposed skin, receptor fluid, receptor chamber wash and receptor rinse

[2] Potentially absorbable dose = Sum of total skin (unexposed skin, exposed skin, and total tape strips), terminal receptor fluid, and receptor chamber wash and receptor rinse

Table 10 AHETF unit exposure estimates for mixer/loaders and applicators handling Cyclobutrifluram via A22011 crop and A23156 crop (µg/kg a.i. handled)

Exposure scenario & PPE		**Dermal**	**Dermal absorbed[1]**	**Inhalation[2]**
PPE: Single layer and chemical-resistant gloves				
Mixer/loader AHETF estimates				
A	Liquid, open mixing and loading Single-layer (SL) + chemical-resistant (CR) gloves	58.5	1.17	0.63
Applicator AHETF estimates				
B	Open-cab groundboom application SL + CR gloves	25.4	1.52	1.68
Mixer/loader + applicator AHETF estimates				
A+B	Liquid open mix/load + open-cab groundboom application SL + CR gloves	83.9	2.69	2.31

[1] Adjusted with dermal absorption factor of 2% for mixing/loading and 6% for all other activities
[2] Light inhalation rate

Table 11 Mixer/loader/applicator dermal and inhalation risk Assessment for Cyclobutrifluram on romaine lettuce treated with A22011 crop or A23156 crop

Exposure scenario[1]		Absorbed dermal unit exposure (µg/kg a.i.)[2]	Inhalation unit exposure (µg/kg a.i.)[2]	ATPD[3]	Rate (kg a.i./ha)	Dermal daily exposure (mg/kg bw/day)[4]	Inhalation daily exposure (mg/kg bw/day)[4]	Dermal MOE[5]	Inhalation MOE[5]
PPE: Single layer and chemical-resistant gloves (no gloves inside a close-cab tractor)									
A	M/L for soil drench or irrigation	1.17	0.63	140	0.100	2.05×10^{-4}	1.10×10^{-4}	4.40×10^{4}	7.80×10^{4}
A+B	M/L/A via Groundboom sprayer	2.69	2.31	26	0.100	8.76×10^{-5}	7.51×10^{-5}	1.03×10^{5}	1.15×10^{5}

1 M/L = Mixing/Loading, M/L/A= Mixing/Loading/Application
2 Unit exposure estimates based on AHETF (see Table 2).
3 ATPD = Area treated per day; Values for Romaine lettuce from the PMRA Standard Area Treated per Day table (2025-02-18).
4 Exposure = (Unit exposure × ATPD × Rate) / (80 kg bw × 1000 µg/mg)
5 MOE = Margin of exposure; Based on NOAEL of 9 mg/kg bw/day for dermal exposure and 8.6 mg/kg bw/day for inhalation exposure; Target MOE =100 for both dermal and inhalation exposures

Table 12 Postapplication worker exposure and risk estimate for Cyclobutrifluram on day 0 after the single application of A22011 crop or A23156 crop to romaine lettuce

Postapplication activity	Peak DFR (µg/cm²)[1]	Transfer coefficient (TC) (cm²/hr)[2]	Dermal exposure (mg/kg bw/day)[3]	MOE[4]	REI[5] (hours)
Hand set/handline irrigation	0.25	1750	0.0026	3429	12
Hand Harvesting		1100	0.0017	5455	
Transplanting, hand weeding, and scouting		230	0.0003	26087	

1 DFR = Dislodgeable foliar residue; Calculated using the standard 25% dislodgeable on the day of application and 10% dissipation per day
2 TC = Transfer coefficients; Obtained from PMRA Agricultural TCs Table (2024-10-29)
3 Dermal Exposure = (Peak DFR [µg/cm²] × TC [cm²/hr] × 8 hours × 6% [dermal absorption]) / (80 kg bw × 1000 µg/mg)
4 MOE = Margin of exposure; Based on a NOAEL of 9 mg/kg bw/day, Target MOE = 100
5 REI = Restricted-entry interval; Minimum REI is 12 hours to allow residues to dry, suspended particles to settle and vapours to dissipate.

Table 13 Commercial mixer/loader/treater/handlers exposure and risk estimates for VICTRATO and VICTRATO 2

Exposure scenario	PPE	Unit exposure (µg/kg a.i.)[1] µg/g a.i./100 kg seed for cleaner[6]		Seed treated (kg seed/ day)[2]	Rate (kg a.i./kg seed)[3] or g a.i./100 kg seed	Daily exposure (mg/kg bw/day)[4, 6]		Calculated MOE[5]	
		Dermal	Inhalation			Dermal	Inhalation	Dermal	Inhalation
Commercial Closed-Transfer Systems									
Treater	SL + CR gloves	2.56	3.72	63 000	0.0005	0.00101	0.00147	8929	5871
Bagger/ Sewer/ Stacker	SL + CR gloves	6.84	18.7	63 000	0.0005	0.00269	0.00736	3342	1168
Cleaner[5]	SL + CR gloves	7.62 µg/ g a.i./100 kg seed	24.1 µg/ g a.i./100 kg seed	N/A	50 g a.i./ 100 kg seed	0.00476	0.01506	1890	571
Commercial Open-Transfer Systems									
Treater	SL + CR gloves	2.65	2.47	63 000	0.0005	0.00104	0.00097	8625	8843

1 Dermally absorbed unit exposures (dermal or inhalation) from selected surrogate exposure studies (AH806 and AH803)
2 Commercial throughput values are from the PMRA's memo "Commercial seed treatment throughput values" (2013).
3 Application rate = 50 g a.i./100 kg = 0.0005 kg a.i./kg seed
4 Dermal or Inhalation Exposure = (dermal or inhalation unit exposure in µg a.i./kg a.i. handled per day × kg seed treated per day × application rate in kg/kg seed/ (80 kg bw × 1000 µg/mg)
5 Based on NOAEL=9 mg/kg bw/day for dermal and 8.6 mg/kg bw/day for inhalation; Target MOE =100 for both
6 For clean-up personnel unit exposures are normalized for application rate in g a.i./100 kg seed; Exposure (mg/kg bw/day) = Unit exposure (µg/g a.i./100 kg seed) × application rate (g a.i./100 kg seed)/(80 kg bw × 1000 µg/mg)

Table 14 On-farm mixer/loader/treater/planter risk assessment for VICTRATO and VICTRATO 2

Exposure scenario	PPE	Dermally absorbed unit exposure (µg/kg a.i.)[1]	Inhalation unit exposure (µg/kg a.i.)[1]	Through-put (kg seed /day)[2]	Rate (kg a.i./kg seed)[3]	Daily dermal exposure (mg/kg bw/ day)[4]	Daily inhalation exposure (mg/kg bw/ day)[4]	Dermal MOE[5]	Inhalation MOE[5]
Treater/ Planter	Single layer plus CR-gloves	24.4404	223.03	9000	0.0005	0.00137	0.0125	6546	686

1 Unit exposure from selected surrogate exposure study (AH610)
2 The amounts of seed treated/planted per day (kg seed/day) are from the PMRA's Seed Treated Planted Per Day-2018 table
3 Application rate of 50 g a.i./100 kg seed = 0.0005 kg a.i./kg seed
4 Dermal or Inhalation Exposure = (dermal or inhalation unit exposure × Throughput/day × Rate) / (80 kg bw × 1000 µg/mg)
5 Based on NOAEL= 9 mg/kg bw/day for dermal and 8.6 mg/kg bw/day for inhalation; Target MOE =100 for both.

Table 15 Exposure risk assessment for planting commercially treated soybeans with VICTRATO and VICTRATO 2

Exposure scenario	PPE	Dermal adjusted unit Exposure (µg/kg a.i.)[1]	Inhalation unit exposure (µg/kg a.i.)[1]	Through-put (kg seed/ day)[2]	Rate (kg a.i./ kg seed)[3]	Daily dermal exposure (mg/kg bw/ day)[4]	Daily inhalation exposure (mg/kg bw/ day)[4]	Dermal MOE[5]	Inhalation MOE[5]
Planter	single layer plus CR gloves, closed- cab planter	96.414	80.88	9000	0.0005	0.0054	0.0045	1660	1890

[1] Unit exposure from the selected surrogate exposure study (AH825)
[2] The amounts of seed treated/planted per day (kg seed/day) are from the PMRA's Seed Treated Planted Per Day-2018 table
[3] Application rate = 50 g ai/100 kg seed = 0.0005 kg/kg seed
[4] Exposure = (dermal or inhalation unit exposure in µg a.i./kg a.i. handled per day × kg seed treated per day × application rate in kg/kg seed) / (80 kg bw × 1000 µg/mg)
[5] Based on NOAEL = 9 mg/kg bw/day for dermal and 8.6 mg/kg bw/day for inhalation ; Target MOE = 100 for both.

Table 16 Integrated food residue chemistry summary

Nature of the residue in laying hen				**PMRA# 3273208**
Species and Numbers	6 laying hens (Shaver)			
Radiolabel positions	[phenyl-U-^{14}C]-SYN549522 (specific activity: 2.38 MBq/mg) and [pyridinyl-2-^{14}C]-SYN549522 (specific activity: 2.36 MBq/mg)			
Average doses	[^{14}C-phenyl]-label: 15.9 mg/kg feed [^{14}C-pyridinyl]-label: 15.5 mg/kg feed Corresponds to 1.06 mg/kg bw/day for both radiolabels			
Treatment Regimen	Once per day; gelatin capsule orally via dosing gun			
Study period	14 consecutive days			
Collection time	Eggs: 2/day (morning and evening), separated into whites and yolks Excreta and cage wash: 1/day			
Tissues collected	Liver, breast muscle, leg and thigh muscle, omental fat, subcutaneous fat with skin attached, and GI tract with contents.			
Interval from last dose to sacrifice	~12 hours on day 14			
Plateau of residues in eggs	Reached at the end of dosing. TRR in egg white (mean TRRs per 24 h period) plateaued at 0.201 ppm, averaging days 9–13, and 0.582 ppm, averaging days 10–13 for the phenyl and pyridinyl labels, respectively. TRR in egg yolk (mean TRRs per 24 h period) plateaued at 0.561 ppm averaging days 9–13, and 0.713 ppm averaging days 11–13 days for the phenyl and pyridinyl labels, respectively.			
Extraction solvents	Egg white, liver and composite muscle: Acetonitrile:water (4:1, v/v) and (1:1, v/v) Fat and egg yolk: as above including hexane			
Matrices	**[phenyl-U-^{14}C]**		**[pyridinyl-2-^{14}C]**	
	TRRs (ppm)	**% of Administered Dose**	**TRRs (ppm)**	**% of Administered Dose**
Excreta	7.998	82.1	NR	83.6
Cage Wash	NR	8.0	NR	6.8
Pooled Egg Yolk (Day 1–14)	0.561	0.3	0.707	0.4
Pooled Egg White (Day 1–14)	0.192	0.4	0.519	0.8
Liver	1.028	0.2	1.231	0.2
Fat	0.158	<0.01	0.222	<0.01
Muscle	0.059	<0.01	0.274	<0.01
Summary of major identified metabolites in hen matrices				
Radiolabel Position	**Major Metabolites**			
Metabolites Identified	**[phenyl-U-^{14}C**		**[pyridinyl-2-^{14}C]**	
Liver	-		SYN510275	

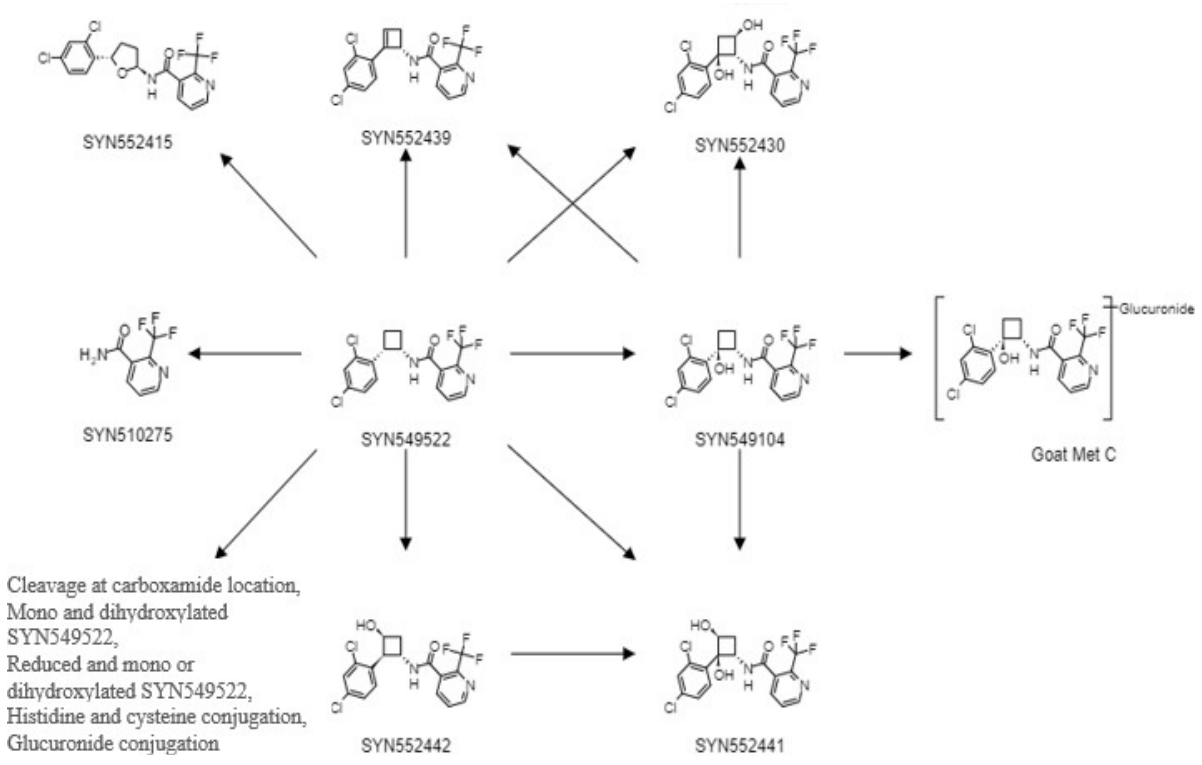
Fat (Omental + Skin with fat)	-	SYN510275
Muscle	SYN552430, SYN552441	SYN510275
Egg white	SYN549104, SYN552430, SYN552441, SYN552442	SYN510275, SYN549104
Egg yolk	SYN549104	SYN510275

Nature of the residue in lactating goat	**PMRA# 3273210**
Species and Numbers	2 lactating goats (Toggenburg × Saanen)
Radiolabel positions	[phenyl-U-^{14}C]-SYN549522 (specific activity: 2.50 MBq/mg) and [pyridinyl-2-^{14}C]-SYN549522 (specific activity: 2.20 MBq/mg)
Average doses	[^{14}C- phenyl]-label: 38.2 mg/kg feed (corresponding to 0.926 mg/kg bw/day) [^{14}C- pyridinyl]-label: 38.6 mg/kg feed (corresponding to 1.149 mg/kg bw/day)
Treatment Regimen	Gelatin capsule, once per day, orally, via a dosing gun
Study period	8 consecutive days
Collection times	Milk: 2/day (morning and evening); Urine, feces and cage wash: 1/day
Tissues collected	Liver, kidneys, muscle (flank, loin); fat (peritoneal [omental], perirenal, subcutaneous)
Interval from last dose to sacrifice	12 hours
Plateau of residues in milk	Reached at the end of dosing. Mean residues in milk achieved a plateau concentration of ~0.039 ppm (phenyl-label) and 0.290 ppm (pyridinyl-label) after 5 days and 6 days dosing, respectively.
Extraction solvents	All tissues: Twice with acetonitrile:water (4:1, v/v) followed by once with acetonitrile:water (1:1, v/v) Milk: Acetonitrile:hexane

Matrices	**[phenyl-U-^{14}C]**		**[pyridinyl-2-^{14}C]**	
	TRRs (ppm)	**% of Administered Dose**	**TRRs (ppm)**	**% of Administered Dose**
Urine	NR	39.4	NR	26.8
Feces	NR	41.5	NR	47.2
Cage Wash	NR	2.5	NR	6.8
Pooled Milk (Day 4–8)	0.1	1.047	1.0	3.051
Kidney	1.068	<0.1	2.863	0.1
Liver	3.980	0.9	8.512	1.6
Peritoneal Fat	0.214	<0.1	0.320	<0.1
Perirenal Fat	0.208	<0.1	0.326	<0.1
Subcutaneous Fat	0.172	<0.1	0.378	<0.1
Flank Muscle	0.125	<0.1	0.739	<0.1
Loin Muscle	0.060	<0.1	0.929	<0.1

Summary of Major Identified Metabolites in Goat Matrices		
Radiolabel Position	**Major Metabolites**	
Metabolites Identified	**[phenyl-U-^{14}C]**	**[pyridinyl-2-^{14}C]**
Muscle	Metabolite C, SYN549104, SYN552439	SYN510275
Fat	SYN552415, SYN552439	SYN510275, SYN552439
Kidney	Metabolite C	Metabolite C, SYN510275
Liver	-	SYN510275
Milk	Metabolite A, SYN549104	SYN510275

Proposed Metabolic Scheme in Livestock



*SYN549522 = cyclobutrifluram

Livestock feeding – Dairy Cattle

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/Dairy Cattle			
Whole milk	Cyclobutrifluram and the metabolite SYN510275, expressed as parent equivalents	0.002	0
Fat			0
Liver			0
Kidney			0
Muscle			0
Swine			
Fat	Cyclobutrifluram and the	0.002	0

Liver	metabolite SYN510275, expressed as parent equivalents		0
Kidney			0
Muscle			0
Note: Residues of cyclobutrifluram were not detected in any matrix. Residues of the SYN510275 metabolite were detected in all matrices.			
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	Cyclobutrifluram and the metabolite SYN510275, expressed as parent equivalents	0.003	0
Fat			0
Liver			0
Muscle			0
Note: Residues of cyclobutrifluram were not detected in any matrix. Residues of the SYN510275 metabolite were detected in all matrices.			

Nature of the residue in wheat [Seed treatment]			**PMRA# 3273202**
Radiolabel Positions	[phenyl-U-^{14}C]-cyclobutrifluram (specific activity: 2.50 MBq/mg) and [pyridinyl-2-^{14}C]-cyclobutrifluram (specific activity: 2.56 MBq/mg)		
Treatment			
Test Site	Seeds were sown at the rate of ~190 kg seed/ha in three rows per container (four containers per radiolabel), which were placed in separate greenhouses for the duration of the study (in other words, a different greenhouse for each radiolabel).		
Treatment	Seed treatment		
Total Rate	120.16 and 120.19 g a.i./ha (equivalent to 60.4 and 62.7 g a.i./100 kg seed) for the phenyl and the pyridinyl labels, respectively.		
Formulation	Solutions		
Harvest	Wheat forage: 48 days after the seed treatment and 40 days after sowing (BBCH22-30). Wheat hay: 63 days after the seed treatment and 55 days after sowing (BBCH41-49). Wheat straw and grain: 114 days after the seed treatment and 106 days after sowing (BBCH89, normal maturity).		
Extraction solvents	Wheat forage, hay and straw (both radiolabels); grain (pyridinyl label): three times with acetonitrile:Milli-Q water (8:2; v/v) and once with acetonitrile:Milli-Q water (1:1; v/v). Wheat grain (phenyl label): twice with acetonitrile:Milli-Q water (8:2; v/v) and once with acetonitrile:Milli-Q water 1:1 (v/v).		
Matrices	**PHI (days)**	**[phenyl-U-^{14}C]-label TRR (ppm)**	**[pyridinyl-2-^{14}C]-label TRR (ppm)**
Forage	48	0.740	0.696
Hay	63	1.470	1.650

Straw	114	4.236	3.758
Grain		0.024	0.054
Summary of major identified metabolites in wheat matrices			
Radiolabel Position	**Major Metabolites**		
Metabolites Identified	**[phenyl-U-^{14}C]-label**	**[pyridinyl-2-^{14}C]-label**	
Forage	Cyclobutrifluram	Cyclobutrifluram	
Hay	Cyclobutrifluram	Cyclobutrifluram	
Straw	Cyclobutrifluram, SYN549104, SYN552301, SYN552202	Cyclobutrifluram, SYN549104, SYN510275	
Grain	Cyclobutrifluram	SYN510260, TFA	
Nature of the residue in potatoes [At-plant in-furrow treatment]		**PMRA# 3273205**	
Radiolabel Position	[phenyl-U-^{14}C]-cyclobutrifluram (specific activity: 2.50 MBq/mg) and [pyridinyl-2-^{14}C]-cyclobutrifluram (specific activity: 2.56 MBq/mg)		
Treatment			
Test Site	Two polypropylene containers filled with commercially obtained sandy loam soil over a drainage layer into which seed potatoes were placed in two furrows of 10–15 cm deep as three potatoes per furrow for each label (in other words, six per label). The furrows and exposed potatoes were sprayed with formulated [phenyl-U-^{14}C]-cyclobutrifluram or [pyridinyl-2-^{14}C]-cyclobutrifluram. Following the application, the potatoes were allowed to dry and were covered with soil from top of the furrows. The second application was made 25 days later to the whole soil area of the same containers, which was allowed to dry, and the soil was mounded on top of the potatoes to ~7 cm high. For each application, the containers were enclosed in chambers made of a wooden frame and polythene film to act as greenhouses. There were separate greenhouses for each radiolabel for the duration of the study.		
Treatment	In-furrow potato seed piece treatment at planting and an application to the entire soil area in the container 25 days later.		
Total Rate	Phenyl label: 245.9 g a.i./ha followed by 249.6 g a.i./ha for a total of 495.5 g a.i./ha Pyridinyl label: 247.2 g a.i./ha followed by 244.9 g a.i./ha for a total of 492.1 g a.i./ha		
Formulation	Suspension concentrate		
Harvest	Immature foliage and tubers: 53 days after the second application (BBCH45 growth stage) Mature foliage and tubers: 81 days after the second application (BBCH49 growth stage)		
Extraction solvents	Immature tubers and mature foliage (both radiolabels): three times with acetonitrile: Milli-Q water (8:2, v/v) followed by once with acetonitrile:Milli-Q water (1:1, v/v). Mature tubers and immature foliage (both radiolabels): twice with acetonitrile:Milli-Q water (8:2, v/v) and once with acetonitrile:Milli-Q water (1:1, v/v).		

	Immature foliage: the aqueous acetonitrile extracts 1 and 2 were combined and re-extracted three more times with acetonitrile:Milli-Q water (1:1, 8:2 and 8:2, v/v), respectively. Mature foliage: the aqueous acetonitrile extracts 1 to 3 were combined, and a portion was partitioned three times with an equal volume of ether.

Matrices	**PHI (days)**	**[phenyl-U-^{14}C]-label**	**[pyridinyl-2-^{14}C]-label**
		TRR (ppm)	**TRR (ppm)**
Immature foliage	53	0.437	0.615
Immature tubers		0.025	0.034
Mature foliage	81	1.180	1.414
Mature tubers		0.027	0.039

Summary of major identified metabolites in potato matrices		
Radiolabel Position	**Major Metabolites**	
Metabolites Identified	**[phenyl-U-^{14}C]-label**	**[pyridinyl-2-^{14}C]-label**
Immature foliage	Cyclobutrifluram, SYN549104	Cyclobutrifluram, SYN549104, SYN510275
Immature tubers	Cyclobutrifluram	Cyclobutrifluram, SYN549104
Mature foliage	Cyclobutrifluram, SYN549104, SYN551636	Cyclobutrifluram, SYN549104, SYN551636, SYN510275
Mature tubers	Cyclobutrifluram, SYN549104	Cyclobutrifluram, SYN549104

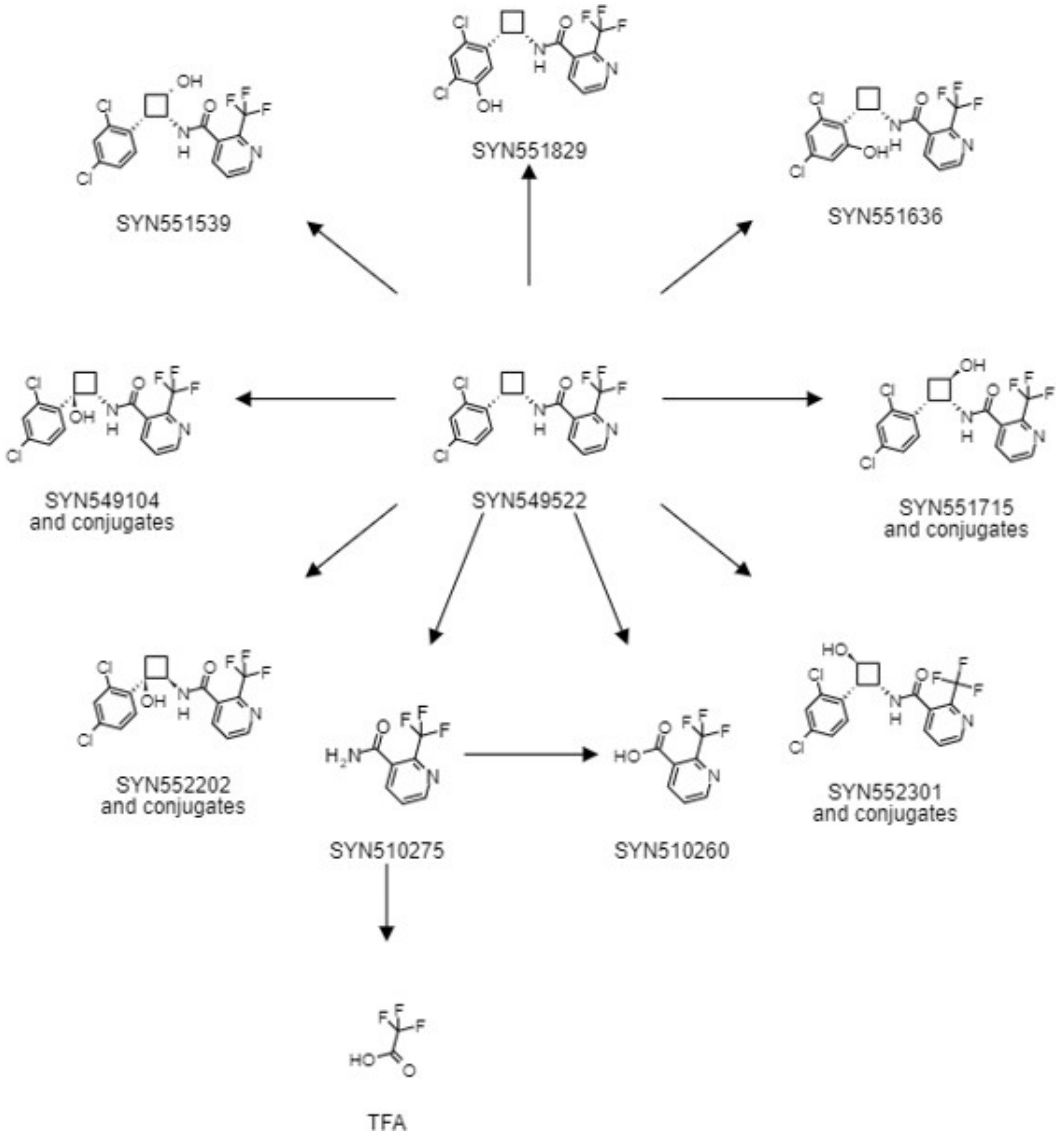
Nature of the residue in soybean [Seed treatment]	**PMRA # 3273206**
Radiolabel Position	[phenyl-U-^{14}C]-cyclobutrifluram (specific activity: 2.50 MBq/mg) and [pyridinyl-2-^{14}C]-cyclobutrifluram (specific activity: 2.56 MBq/mg)
Treatment	
Test Site	Soybean seed pretreated with [^{14}C]-cyclobutrifluram was sown in twelve polypropylene containers filled with commercially-obtained sandy loam soil over a drainage layer and grown in greenhouse conditions. Six containers were sown with seed pretreated with the phenyl-label, and the other six, with seed pretreated with the pyridinyl-label. For each radiolabel, three containers were sown at a lower rate and three others were sown at a higher rate. The containers for each radiolabelled form were placed in separated greenhouses for the duration of the study.
Treatment	Seed treatment
Total Rate	Phenyl-label: 48.0 g a.i./ha, equivalent to 71.9 g a.i./100 kg seed (0.12 mg ai/seed*) Pyridinyl-label: 48.6 g a.i./ha, equivalent to 71.3 g a.i./100 kg seed (0.12 mg ai/seed*) *Based on 6600 seeds/kg (Source: proposed product label, PMRA# 3277384).
Formulation	Solution
Harvest	Soybean forage: 63 days after seed treatment and 56 days after sowing (BBCH49-51). Soybean hay: 91 days after the seed treatment and 84 days after sowing

	(BBCH ~73). Samples were air dried for five days post-harvest. Soybean straw and grain: 127 days after the seed treatment and 120 days after sowing (BBCH89, at normal maturity).
Extraction solvents	Soybean forage, hay and straw (both radiolabels): three times with acetonitrile:Milli-Q water (8:2, v/v) and once with acetonitrile:Milli-Q water (1:1, v/v). Wheat grain (both radiolabels): an initial extraction with hexane followed by four extractions with aqueous acetonitrile, with the third extraction performed with aqueous acetonitrile 1:1 (v/v) rather than 8:2 (v/v).

Matrices	**PHI (days)**	**[phenyl-U-^{14}C]-label**	**[pyridinyl-2-^{14}C]-label**
		TRR (ppm)	**TRR (ppm)**
Forage	63	0.315	0.142
Hay	91	0.529	0.735
Straw	127	0.133	0.170
Grain		0.009	0.035

Summary of major identified metabolites in soybean matrices		
Radiolabel Position	**Major Metabolites**	
Metabolites Identified	**[phenyl-U-^{14}C]-label**	**[pyridinyl-2-^{14}C]-label**
Forage	Cyclobutrifluram	Cyclobutrifluram, SYN510275
Hay	Cyclobutrifluram	Cyclobutrifluram, SYN510275
Straw	Cyclobutrifluram	Cyclobutrifluram, SYN510275, TFA
Grain	Cyclobutrifluram, SYN549104	SYN510275

Proposed Metabolic Scheme in Plants



*SYN549522 = cyclobutrifluram; TFA = trifluoroacetic acid

Freezer storage stability in plant matrices				**PMRA # 3273200**
Tested Matrices	**Analytes**	**Tested Intervals**	**Temperature (°C)**	**Category**
Wheat grain	Cyclobutrifluram and metabolites SYN510275, SYN510260 and SYN549104	0-day, 1, 3, 6, 9 and 11 months	≤ -20°C	High-starch
Cucumber				High-water
Dry beans; soybean seed				High-protein
Soybean seed				High-oil
--	--		--	High-acid

Crop field trials and residue decline on romaine lettuce	**PMRA# 3273212**

Crop field trials were conducted in 2020 in the United States in North American growing regions 5 (2 trials) and 10 (6 trials) for a total of 8 trials. A suspension concentrate formulation of cyclobutrifluram was applied once as an at-plant soil drench after transplanting, a soil broadcast or a soil-directed spray after seed planting at rates of 97.4–106 g a.i./ha. No adjuvants were used at any field trial sites. At two trials, samples were collected at additional PHIs of 8–9 days and 3–4 days before normal crop harvest, and at 4–5 days and 8–11 days after normal crop harvest to assess residue decline.

In the decline trials, residues of cyclobutrifluram decreased with time at one trial, and were below the LOQ (in other words, <0.01 ppm) at the second trial.

Crop	**Total Application Rate (g a.i./ha)**	**PHI (days)**	**Analyte**	**Residue Levels (ppm)[1]**					
				n	**LAFT**	**HAFT**	**Median**	**Mean**	**SDEV**
Romaine lettuce	97.4 - 106	40-73	Cyclobutrifluram	8	<0.01	0.023	<0.01	<0.01	0.004

n = number of independent trials, LAFT = lowest average field trial, HAFT = highest average field trial, SDEV = standard deviation

[1] For computation, values <LOQ are assumed to be at the LOQ.

Crop field trials and residue decline on soybeans	**PMRA# 3273215 (North American trials); PMRA# 3589229 and 3589230 (Brazilian trials)**

Crop field trials were conducted in the United States (U.S.) in 2020 and in Brazil in 2019 and 2020. The U.S. trials were conducted in North American growing regions 2 (1 trial), 4 (1 trial) and 5 (9 trials), and the Brazilian trials (a total of 8) were conducted in 5 major soybean production regions for a total number of soybean trials of 19. Flowable concentrate (450 g a.i./L) or suspension concentrate (500 g a.i./L) formulations of cyclobutrifluram were applied to soybean seeds prior to planting at a rates of 0.145–0.166 mg a.i./seed (equivalent to 40.8–150.0 g a.i./ha) in the American trials, and at rates of 0.068–0.092, 0.102–0.138 and 0.14–0.18 mg a.i./seed (~31–32, 47–48 and 50–64 g a.i./ha, respectively), in the Brazilian trials. No adjuvants were used at any field trial sites.

Decline tests weren't conducted at either the U.S. or Brazilian trials and none are required since the application timing is prior to formation of edible commodity.

Crop	**Total Application Rate (mg a.i./seed)**	**PHI (days)**	**Analyte**	**Residue Levels (ppm)**					
				n	**LAFT**	**HAFT**	**Median**	**Mean**	**SDEV**
American Trials									
Soybean seed	0.145–0.166	122-160	Cyclobutrifluram	11	<0.01	<0.01	<0.01	<0.01	0.00
Brazilian Trials									
Soybean seed	0.07–0.09	105-146	Cyclobutrifluram	8	<0.01	<0.01	<0.01	<0.01	0.00

	0.102–0.138	105-146			<0.01	<0.01	<0.01	<0.01	0.00
	0.136–0.184	105-146			<0.01	<0.01	<0.01	<0.01	0.00

n = number of independent trials, LAFT = lowest average field trial, HAFT = highest average field trial, SDEV = standard deviation

Processed food and feed – Soybean seed	**PMRA # - N/A**
Processing studies for soybean seed were not conducted and are not required since residues of cyclobutrifluram were non quantifiable in soybean seed in field trials conducted at exaggerated rates compared to the proposed seed treatment rate, and because cyclobutrifluram is water soluble, and therefore, would not likely concentrate into oil during soybean processing.	

Confined accumulation in rotational crops – Spinach, radish and wheat (spring)	**PMRA# 3273218**
Radiolabel Position	[phenyl-U-^{14}C]-Cyclobutrifluram (specific activity: 2.59 MBq/mg) and [pyridinyl-2-^{14}C]-Cyclobutrifluram (specific activity: 2.20 MBq/mg)
Treatment	
Test Site	Nine containers were used for each radiolabel and were kept outdoors for 28 days prior to being moved into glasshouses two days before the first plantback interval (PBI) of 30 days and remained in greenhouse conditions for the remainder of the study. A separate greenhouse was used for each radiolabel.
Soil Type	Sandy loam
Treatment	Single bare soil application at 522.83 g a.i/ha (PH-label) or 522.90 g a.i./ha (PY-label), and aged for 30, 120 and 273 days after application (DAA).
Formulation	Not indicated
Extraction solvents	Samples were extracted sequentially using the IRATE (Improved Rapid Approach to Extraction) method: Subsamples with TRRs >0.01 ppm were extracted twice with acetonitrile:water 8:2 (v/v). Following the second extraction, if the %TRR was <10%, a third extraction was conducted using acetonitrile:water 1:1 (v/v). If the %TRR was >10%, a third extraction was made using acetonitrile:water 8:2 (v/v) followed by another extraction using acetonitrile:water 1:1 (v/v).

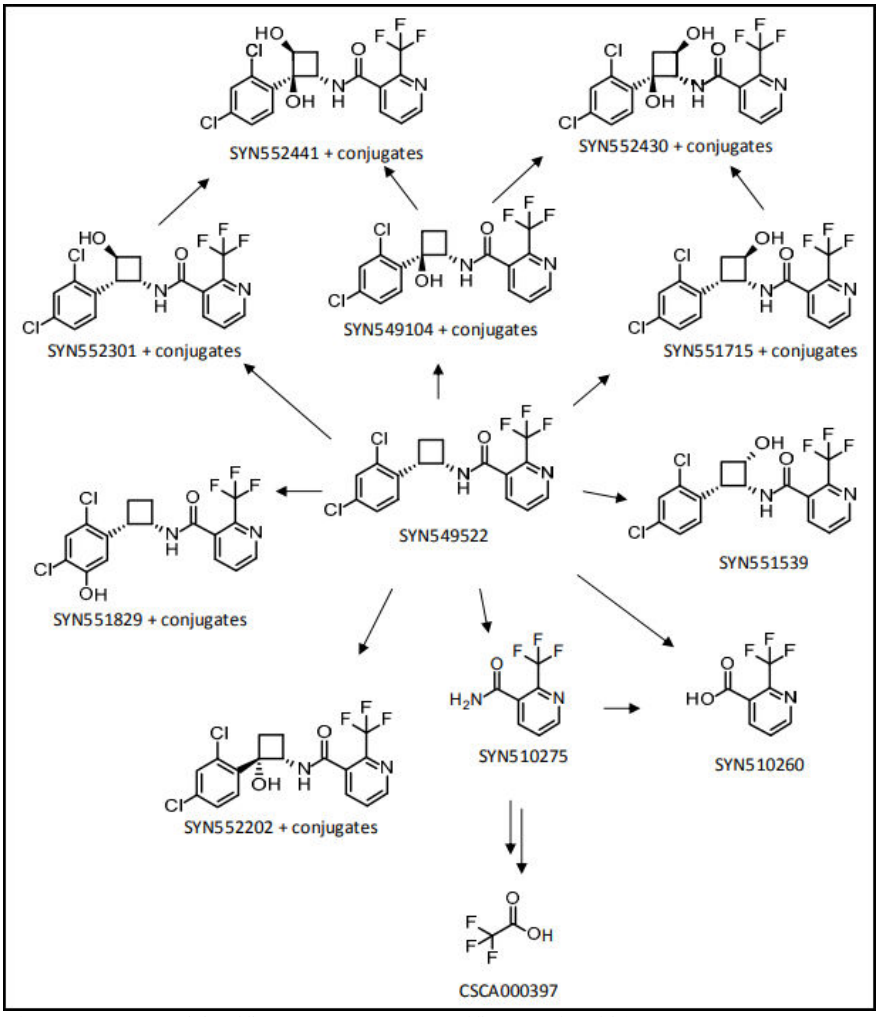
Matrices	**PBI (days)**	**[phenyl-U-^{14}C]-Cyclobutrifluram**	**[pyridinyl-2-^{14}C]-Cyclobutrifluram**
		TRR (ppm)	**TRR (ppm)**
Wheat forage	30	0.401	0.514
	120	0.829	0.922
	273	0.647	1.545
Wheat hay	30	3.249	4.319
	120	1.439	2.549
	273	2.036	4.546
Wheat straw	30	7.054	10.930
	120	6.292	6.773

	273	3.621	8.744
Wheat grain	30	0.109	0.245
	120	0.097	0.134
	273	0.058	0.204
Immature spinach	30	0.021	0.098
	120	0.084	0.359
	273	0.374	0.835
Mature spinach	30	0.150	0.392
	120	0.334	0.625
	273	0.265	1.007
Radish foliage	30	0.386	0.754
	120	0.240	0.605
	273	0.242	1.000
Radish roots	30	0.043	0.075
	120	0.024	0.045
	273	0.040	0.088

Summary of major identified metabolites in rotated crops

Plantback Intervals (PBI)	**1st Rotation (30-day PBI)**		**2nd Rotation (120-day PBI)**		**3rd Rotation (273-day PBI)**	
Metabolites Identified	**Major Metabolites**					
Radiolabel Position	**[phenyl-U-^{14}C]-**	**[pyridinyl-2-^{14}C]-**	**[phenyl-U-^{14}C]-**	**[pyridinyl-2-^{14}C]-**	**[phenyl-U-^{14}C]-**	**[pyridinyl-2-^{14}C]-**
Wheat forage	Cyclobutrifluram	Cyclobutrifluram SYN510275	Cyclobutrifluram SYN549104	Cyclobutrifluram SYN510275	Cyclobutrifluram	Cyclobutrifluram SYN510275 TFA
Wheat hay	Cyclobutrifluram SYN549104	Cyclobutrifluram SYN510275	Cyclobutrifluram SYN549104	Cyclobutrifluram SYN510275	Cyclobutrifluram	Cyclobutrifluram SYN510275
Wheat straw	Cyclobutrifluram SYN549104 SYN551829	Cyclobutrifluram SYN510275 SYN549104 SYN551829	Cyclobutrifluram SYN552202	Cyclobutrifluram SYN510275	Cyclobutrifluram SYN549104	Cyclobutrifluram SYN510275 SYN549104
Wheat grain	Cyclobutrifluram	Cyclobutrifluram SYN510275 SYN510260 TFA	Cyclobutrifluram	Cyclobutrifluram SYN510275 TFA	Cyclobutrifluram	Cyclobutrifluram TFA
Immature spinach	Cyclobutrifluram SYN549104	SYN510275 SYN551715 TFA	SYN549104	SYN510275 SYN549104 SYN551715 TFA	Cyclobutrifluram SYN549104 SYN552441 SYN552202	SYN510275 SYN549104 SYN551715 TFA
Mature spinach	Cyclobutrifluram SYN549104	SYN510275 SYN549104 TFA	SYN549104 SYN552441	SYN510275 SYN549104 TFA	SYN549104 SYN552441	SYN510275 SYN549104 TFA
Radish foliage	Cyclobutrifluram SYN549104 SYN552202	Cyclobutrifluram SYN510275	Cyclobutrifluram SYN549104 SYN552202	Cyclobutrifluram SYN510275	Cyclobutrifluram	Cyclobutrifluram SYN510275 TFA
Radish roots	Cyclobutrifluram SYN549104	Cyclobutrifluram SYN549104 SYN551715	Cyclobutrifluram SYN549104	Cyclobutrifluram SYN510275 SYN551715 TFA	Cyclobutrifluram	Cyclobutrifluram SYN510275 SYN551715 TFA

Proposed Metabolic Scheme in Rotational Crops



*SYN549522 = cyclobutrifluram; CSCA000397 = trifluoroacetic acid (TFA)

Residue data in field rotational crops	**PMRA# 3273220**

Twenty-seven trials (9 for radish, 9 for lettuce/spinach and 9 for winter/spring wheat) were conducted during the 2019–2020 growing season in North American growing region 5. One broadcast application was made to bare soil with a suspension concentrate formulation of cyclobutrifluram at rates of 1087–1147 g a.i./ha (11× proposed rate). No adjuvants were used at any 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 (ppm)**					
			n	**LAFT**	**HAFT**	**Median**	**Mean**	**SDEV**
Cyclobutrifluram								
Radish tops	1.09-1.13 (11x proposed rate)	27-31	9	0.023	0.141	0.029	0.064	0.066
		116-119		0.018	0.059	0.039	0.038	0.021
		354-371		0.012	0.028	0.025	0.022	0.009

Radish roots		27-31		<0.010	0.048	0.010	0.023	0.022
		116-119		<0.010	0.015	0.011	0.012	0.003
		354-371		0.013	0.041	0.029	0.027	0.014
Spinach/Lettuce		27-31		0.023	0.053	0.046	0.041	0.016
		116-119	9	0.013	0.036	0.025	0.025	0.012
		354-371		<0.010	0.024	0.013	0.016	0.007
Wheat forage		28-29		0.039	0.144	0.104	0.096	0.053
		120-127		0.026	0.061	0.061	0.049	0.020
		354-371		0.036	0.067	0.049	0.051	0.016
Wheat hay		28-29		0.043	0.328	0.046	0.139	0.163
		120-127		0.018	0.138	0.035	0.064	0.065
		354-371		0.037	0.090	0.047	0.058	0.028
Wheat straw		28-29	9	0.042	0.354	0.095	0.163	0.167
		120-127		0.019	0.211	0.103	0.111	0.096
		354-371		0.031	0.173	0.063	0.089	0.074
Wheat grain		28-29		<0.010	<0.010	0.010	0.010	N/A
		120-127		<0.010	<0.010	0.010	0.010	N/A
		354-371		<0.010	<0.010	0.010	0.010	N/A
SYN510275								
Radish tops		27-31		<0.020	0.377	0.111	0.169	0.185
		116-119		0.042	0.118	0.075	0.078	0.038
		354-371		0.036	0.059	0.047	0.047	0.011
Radish roots		27-31	9	<0.020	0.034	0.031	0.028	0.007
		116-119		<0.020	<0.020	0.020	0.020	N/A
		354-371		<0.020	<0.020	0.020	0.020	N/A
Spinach/Lettuce		27-31		<0.020	0.425	0.095	0.180	0.215
		116-119	9	0.033	0.201	0.079	0.104	0.087
		354-371		0.033	0.099	0.049	0.061	0.035
Wheat forage	1.09-1.13	28-29		0.027	0.372	0.123	0.174	0.178
		120-127		<0.020	0.085	0.023	0.043	0.036
		354-371		0.032	0.075	0.047	0.052	0.022
Wheat hay		28-29		0.031	0.408	0.044	0.161	0.214
		120-127		<0.024	0.163	0.026	0.071	0.080
		354-371		<0.020	0.139	0.022	0.060	0.068
Wheat straw		28-29	9	0.021	0.145	0.030	0.065	0.069
		120-127		<0.020	0.032	0.022	0.024	0.006
		354-371		<0.020	0.047	0.020	0.029	0.016
Wheat grain		28-29		<0.020	0.056	0.020	0.032	0.021
		120-127		<0.020	<0.020	0.020	0.020	N/A
		354-371		<0.020	<0.020	0.020	0.020	N/A
SYN510260								
Radish tops	1.09-1.13	27-31		<0.020	0.041	0.032	0.031	0.010
		116-119		<0.020	<0.020	0.020	0.020	N/A
		354-371	9	<0.020	<0.020	0.020	0.020	N/A
Radish roots		27-31		<0.020	<0.020	0.020	0.020	N/A

		116-119		<0.020	<0.020	0.020	0.020	N/A
		354-371		<0.020	<0.020	0.020	0.020	N/A
Spinach/Lettuce		27-31		<0.020	0.046	0.020	0.029	0.015
		116-119	9	<0.020	<0.020	0.020	0.020	N/A
		354-371		<0.020	<0.020	0.020	0.020	N/A
Wheat forage		28-29		<0.020	0.087	0.027	0.045	0.037
		120-127		<0.020	<0.020	0.020	0.020	N/A
		354-371		<0.020	<0.020	0.020	0.020	N/A
Wheat hay		28-29		<0.020	0.060	0.056	0.045	0.022
		120-127		<0.020	<0.020	0.020	0.020	N/A
		354-371		<0.020	<0.020	0.020	0.020	N/A
Wheat straw		28-29	9	<0.020	<0.020	0.020	0.020	N/A
		120-127		<0.020	<0.020	0.020	0.020	N/A
		354-371		<0.020	<0.020	0.020	0.020	N/A
Wheat grain		28-29		<0.020	0.103	0.026	0.050	0.047
		120-127		<0.020	<0.020	0.020	0.020	N/A
		354-371		<0.020	<0.020	0.020	0.020	N/A
SYN549104								
Radish tops		27-31		<0.010	0.041	0.010	0.020	0.018
		116-119		<0.010	0.023	0.011	0.015	0.007
		354-371		<0.010	<0.010	0.010	0.010	N/A
Radish roots		27-31	9	<0.010	<0.010	0.010	0.010	N/A
		116-119		<0.010	<0.010	0.010	0.010	N/A
		354-371		<0.010	<0.010	0.010	0.010	N/A
Spinach/Lettuce		27-31		<0.010	0.114	0.010	0.045	0.060
		116-119	9	<0.010	0.068	0.048	0.042	0.030
		354-371		<0.010	0.033	0.010	0.018	0.013
Wheat forage	1.09-1.13	28-29		<0.010	0.060	0.026	0.032	0.026
		120-127		<0.010	<0.010	0.010	0.010	N/A
		354-371		0.013	0.025	0.020	0.019	0.006
Wheat hay		28-29		0.015	0.230	0.074	0.106	0.111
		120-127		<0.011	0.068	0.014	0.031	0.032
		354-371		0.036	0.074	0.069	0.060	0.021
Wheat straw		28-29	9	0.018	0.230	0.056	0.101	0.113
		120-127		<0.010	0.060	0.020	0.030	0.027
		354-371		0.033	0.096	0.036	0.055	0.035
Wheat grain		28-29		<0.010	0.014	0.010	0.011	0.002
		120-127		<0.010	<0.010	0.010	0.010	N/A
		354-371		<0.010	<0.010	0.010	0.010	N/A

Values based on per-trial averages. For computation, values <LOQ are assumed to be at the LOQ.
n = number of independent field trials, LAFT = lowest average field trial, HAFT = highest average field trial, SDEV = standard deviation.

Once the results of the field accumulation study (shown above) were scaled down by a factor of 11× based on the concept of proportionality, plantback intervals of 0 days for labeled crops (soybean and Romaine lettuce), 120 days for cereals (Crop Group 15) and 365 days for all other crops can be supported.

Table 17 Food residue chemistry overview of metabolism studies and risk assessment

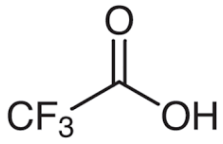
Plant studies			
Residue definition for enforcement **Primary crops (wheat [seed treatment], soybean [seed treatment], potato [at-plant in-furrow treatment])** **Rotational crops (wheat, radish and spinach/lettuce)**			Cyclobutrifluram
Residue definition for risk assessment	**Primary crops (wheat [seed treatment], soybean [seed treatment], potato [at-plant in-furrow treatment])**		Cyclobutrifluram, SYN510275, SYN510260 and SYN549104 (expressed as parent equivalents)
	Rotational crops (wheat, radish and spinach/lettuce)		Cyclobutrifluram, SYN510275, SYN510260, SYN549104 and trifluoroacetic acid [TFA] (expressed as parent equivalents)
Metabolic profile in diverse crops			Similar in soybean, wheat and potato
Animal studies			
Animals			**Ruminant and Poultry**
Residue definition for enforcement			Cyclobutrifluram and SYN510275 (expressed as parent equivalents)
Residue definition for risk assessment			
Metabolic profile in animals (goat, hen, rat)			The profile is similar in the investigated animals.
Fat soluble residue			No
Dietary risk from food and drinking water			
Basic acute dietary exposure analysis, 95th percentile	**Population**	**Estimated risk % of acute reference dose (ARfD)**	
		Food Alone	**Food and Drinking Water**

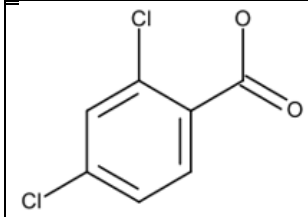
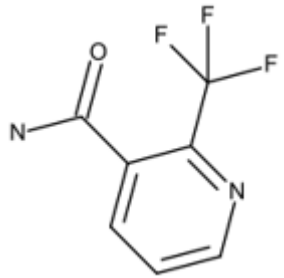
ARfD = 0.8 mg/kg bw for the total population **ARfD = 0.3 mg/kg bw for females 13-49 years** **Estimated acute drinking water concentration:** Combined residue of cyclobutrifluram, SYN 510275 ± trifluoroacetic acid (TFA) as the parent equivalent = **0.14 ppm**		**Primary Crops Only**	**Primary + Rotational Crops**	**Primary Crops Only**	**Primary + Rotational Crops**
	Infants < 1 year	0.16	0.19	3.23	3.26
	Children 1–2 years	0.27	0.30	1.46	1.50
	Children 3–5 years	0.15	0.19	1.14	1.16
	Children 6–12 years	0.10	0.12	0.88	0.90
	Youth 13–19 years	0.05	0.07	0.80	0.81
	Adults 20–49 years	0.04	0.05	0.93	0.94
	Adults 50+ years	0.03	0.04	0.81	0.82
	Females 13–49 years	0.10	0.14	2.50	0.59
	Total population	0.08	0.10	0.96	0.98

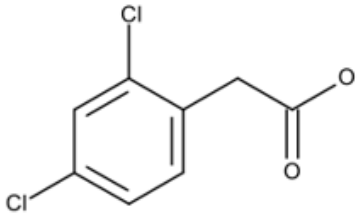
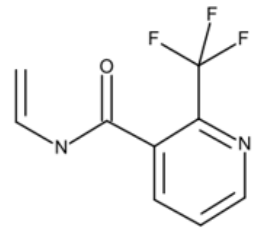
Basic chronic non-cancer and cancer dietary exposure analysis **ADI = 0.07 mg/kg bw/day** **Estimated chronic drinking water concentration (EECs):** Combined residues of cyclobutrifluram, SYN 510275 + trifluoroacetic acid (TFA) as the parent equivalent = **0.13 ppm**	**Population**	**Estimated risk % of acceptable daily intake (ADI)**					
		Food Alone		**Food and Drinking Water**			
				EEC: -TFA = 0.12 ppm		**EEC: +TFA = 0.13 ppm**	
		Primary Crops Only	**Primary + Rotational Crops**	**Primary Crops Only**	**Primary + Rotational Crops**	**Primary Crops Only**	**Primary + Rotational Crops**
	Infants < 1 year	0.4	0.6	13.3	13.6	14.4	14.7
	Children 1–2 years	1.4	1.8	6.2	6.5	6.6	6.9
	Children 3–5 years	0.8	1.1	4.7	5.0	5.0	5.3
	Children 6–12 years	0.5	0.6	3.4	3.5	3.6	3.8

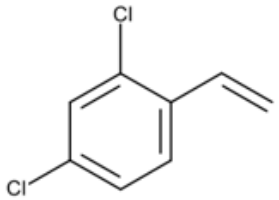
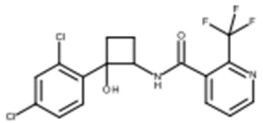
Combined residues of cyclobutrifluram and SYN 510275 (- TFA) as the parent equivalent = **0.12 ppm**	Youth 13–19 years	0.2	0.3	2.7	2.8	2.9	3.0
	Adults 20–49 years	0.2	0.3	3.6	3.7	3.9	4.0
	Adults 50+ years	0.2	0.2	3.5	3.6	3.8	3.9
	Females 13–49 years	0.2	0.3	3.6	3.6	3.8	7.23.9
	Total population	0.3	0.4	3.7	3.8	4.0	4.1

Table 18 Summary of the transformation products of cyclobutrifluram in the environment

Transformation product (TP)	Study Details	Comments
Major TPs		
Trifluoroacetic acid (TFA)  Produced on pyridinyl label only.	Hydrolysis – N/A Phototransformation in soil – N/A Aqueous phototransformation – N/A Aerobic biotransformation in soil – 10.6% AR Anaerobic biotransformation in soil – N/A Aerobic aquatic biotransformation – N/A Terrestrial field dissipation (TFD) – N/A Intact Soil cores – 3.0% AR K_{oc} – N/A	Major TP for aerobic biotransformation in soil. Aerobic soil biotransformation: Slightly exceeds 10% AR of the extracted material from one of five soils (Gartenacker) in aerobic soil study (pyridinyl label only). Concentration appears to have been increasing over course of study, although increasing trend is not definitive. It is likely that TFA accounts for some portion (<3%) of the % AR in the traps for all soils. Not detected in the extracts for any other soil or study. Soil cores: Supplementary study (pyridinyl label only; PMRA #3273224) conducted in glasshouses under irradiated aerobic conditions. Low levels detected in soil under all study conditions.
CGA177291	Hydrolysis – N/A Phototransformation in soil – 14.1% AR	Major TP for phototransformation in soil. Not produced during non-irradiated

Transformation product (TP)	Study Details	Comments
 2,4-dichloro-benzoic acid (DCBA) $C_7H_4Cl_2O_2$ MW: 191.0 g/mol Produced on phenyl label only.	Aqueous phototransformation – N/A Aerobic biotransformation in soil – NA Anaerobic biotransformation in soil – N/A Aerobic aquatic biotransformation – N/A TFD(1) – 3.5% AR Intact Soil cores – N/A K_{oc} – N/A	biotransformation studies in the laboratory. Maximum detected on Day 101 in the Ontario TFD study (~3.5%). Not detected in the Washington TFD study.
SYN510275  2-trifluoromethyl-nicotinamide $C_7H_5F_3N_2O$ MW: 190.12 g/mol Produced on pyridinyl label only.	Hydrolysis – N/A Phototransformation in soil – 47.8% AR Aqueous phototransformation – 29.2% AR Aerobic biotransformation in soil – NA Anaerobic biotransformation in soil – N/A Aerobic aquatic biotransformation – N/A TFD(1) – 2.6% AR Intact Soil cores(2) – 19.1% AR K_{oc}(3) – 1.9 to 10.9 (mean 5.58)	Major TP for phototransformation in soil and water. Laboratory studies indicate large amounts may form over time under continuous irradiation. Applicant conducted aerobic soil biotransformation and mobility studies using non-labelled test item. Non-extracted residues, volatiles, and transformation products were not monitored in aerobic soil. Aerobic soil biotransformation: Representative half-life/SFO values ranged from 53–246 days. Moderately persistent to persistent in soil under aerobic conditions. Soil cores: Major TP during supplementary study (pyridinyl label only; PMRA #3273224) conducted in glasshouses under irradiated aerobic conditions.

Transformation product (TP)	Study Details	Comments
		Maximum detected on Day 28 in the Ontario TFD study is ~2.6% (DT_{50} = 456 days). Maximum detected on Day 14 and 28 in the Washington TFD study is ~0.5%. Very high mobility in soil based on the K_{oc} values.
EXC8199  2,4-dichlorophenylacetic acid $C_8H_6Cl_2O_2$ MW: 205.0 g/mol Produced on phenyl label only.	Hydrolysis – N/A Phototransformation in soil – 11.6% AR Aqueous phototransformation – N/A Aerobic biotransformation in soil – NA Anaerobic biotransformation in soil – N/A Aerobic aquatic biotransformation – N/A TFD(1) – N/A Intact Soil cores – N/A K_{oc} – N/A	Major TP for phototransformation in soil. Not produced during non-irradiated biotransformation studies in the laboratory. Not detected in both TFD studies (Ontario and Washington).
SYN551231 	Hydrolysis – N/A Phototransformation in soil – N/A Aqueous phototransformation – 34.3% AR Aerobic biotransformation in soil – NA Anaerobic biotransformation in soil – N/A Aerobic aquatic biotransformation – N/A TFD – N/A Intact Soil cores – N/A	Major TP for phototransformation in water. Not produced during non-irradiated biotransformation studies in the laboratory.

Transformation product (TP)	Study Details	Comments
$C_9H_7F_3N_2O$ Produced on pyridinyl label only.	K_{oc} – N/A	
SYN551241  $C_8H_6Cl_2$ Produced on phenyl label only.	Hydrolysis – N/A Phototransformation in soil – N/A Aqueous phototransformation – 52.1% AR Aerobic biotransformation in soil – NA Anaerobic biotransformation in soil – N/A Aerobic aquatic biotransformation – N/A TFD – N/A Intact Soil cores – N/A K_{oc} – N/A	Major TP formed for phototransformation in water. Not produced during non-irradiated biotransformation studies in the laboratory. Volatile TP that was not trapped effectively during definitive test. Maximum 52.1% AR identified at the end of 5-day supplementary test.
Minor TP		
SYN549104  Produced on pyridinyl label only.	Hydrolysis – N/A Phototransformation in soil – N/A Aqueous phototransformation – N/A Aerobic biotransformation in soil – N/A Anaerobic biotransformation in soil – N/A Aerobic aquatic biotransformation – N/A TFD[(1)] – 0.4% AR Intact Soil cores[(2)] – 3.0% AR K_{oc} [(3)] – 31.3 to 82.0 (mean 53.6)	Chemical structure nearly identical to parent and appears to be hydrated form. Not detected in any laboratory studies where parent was the test item. Soil cores: Supplementary study (pyridinyl label only; PMRA #3273224) conducted in glasshouses under irradiated aerobic conditions. Low levels detected in soil under all study conditions. Detected at low levels (~0.1%) over duration of study in Ontario. Maximum detected on Day 28

Transformation product (TP)	Study Details	Comments
		in the Washington TFD study is ~0.4%. Applicant conducted aerobic soil biotransformation and mobility studies using non-labelled test item. Non-extracted residues, volatiles, and transformation products were not monitored in aerobic soil. Aerobic soil biotransformation: Representative half-life/SFO values ranged from 26.0–154.5 days. High to very high mobility in soil based on the K_{oc} values.

1 Soil samples in both TFD studies (PMRA# 3273232 and 3273237) were analysed for residues of cyclobutrifluram and its four TPs, SYN549104, SYN510275, CGA177291, and EXC8199.

2 This study (PMRA# 3273224) is classified as "Acceptable with Limitations" as it is a non-guideline study which intended to assess soil biotransformation in the presence of simulated natural sunlight following seed treatment and soil drench treatment. The endpoints are not intended for use during the quantitative risk assessment or when characterising persistence.

3 This study (PMRA #3273252) is classified as "Acceptable with Limitations" and partially satisfies the guideline requirements for a study on adsorption and desorption in soil. No sufficient data were available to calculate desorption parameters. The PMRA calculated adsorption parameters are used in risk assessment.

Table 19 Fate and behaviour of cyclobutrifluram and its transformation products in the environment

Property	Test substance	Medium	Value	Kinetic model	Major transformation products (maximum occurrence)[(1)]	Comments	PMRA#
Abiotic transformation							
Hydrolysis	Cyclobutrifluram (SYN549522)	pH 4 buffer, 50°C pH 4 buffer, 60°C pH 4 buffer, 70°C pH 7 buffer, 50°C pH 7 buffer, 60°C pH 7 buffer, 70°C pH 9 buffer, 50°C pH 9 buffer, 60°C pH 9 buffer, 70°C	Stable	N/A	N/A	Hydrolysis is not a major transformation process for cyclobutrifluram	3273256
Phototransformation on soil	Cyclobutrifluram (SYN549522)	Artificial sunlight	t_R/DT_{50} = 14.7 days	SFO	SYN510275 (47.8%); CGA177291 (14.1%); EXC8199 (11.6%)	Relatively fast transformation under photolytic conditions.	3273227
		Natural summer sunlight at 30-50°N	t_R/DT_{50} = 29.6 days				
Phototransformation in water	Cyclobutrifluram (SYN549522)	pH 7 buffer, 25°C	t_R/DT_{50} (natural summer sunlight equivalent at 30-50ºN) = 11-24 days	SFO	SYN551241 (52.1%); SYN510275 (29.2%); SYN551231 (34.3%)	Relatively fast transformation under photolytic conditions.	3273259
Phototransformation in air	A phototransformation in air study was not submitted for cyclobutrifluram and its major TPs. Persistence in air was estimated using the AOPWIN (v1.92) model. See details in Appendix I, Table 29.						

Property	Test substance	Medium	Value	Kinetic model	Major transformation products (maximum occurrence)[1]	Comments	PMRA#
Biotransformation							
Biotransformation in aerobic soil[2]	Cyclobutrifluram (SYN549522)	18 Acres (sandy clay loam, pH 5.5, 1.89% organic carbon (OC))	t_R/DT_{50} = 618.6 days	SFO	TFA (10.6%)	Moderately persistent to persistent in soil under aerobic conditions.	3273223
		East Anglia (sandy loam, pH 7.3, 2.12% OC)	t_R = 512.94 days DT_{50} = 444.6 days	DFOP			
		Sarpy (loam, pH 6.7, 2.07% OC)	t_R/DT_{50} = 986.2 days	SFO			
		Capay (clay loam, pH 7.2, 0.85% OC)	t_R/DT_{50} = 1097 days	SFO			
		Gartenacker (loam, pH 7.2, 2.25% OC)	t_R/DT_{50} = 245.5 days	SFO			
	Cyclobutrifluram (SYN549522)	Gartenacker (silt loam, pH 7.2, 2.2% OC)	t_R/DT_{50} = 150 days	SFO	N/A		3273225
	Cyclobutrifluram (SYN549522)	Intact 18 Acres soil core (sandy clay loam, pH 6.2, 1.8% OC)	Treated seed: t_R/DT_{50} = 51.5 days	SFO	SYN510275 (19.1%)		3273224[5]
			Blank seed[4]: t_R/DT_{50} = 130.2 days	SFO			

Property	Test substance	Medium	Value	Kinetic model	Major transformation products (maximum occurrence)[1]	Comments	PMRA#
		Intact Agrissolo soil core (clay loam, pH 5.4, 2.4% OC)	Treated seed: t_R/DT_{50} = 93.0 days	SFO			
			Blank seed[4]: t_R/DT_{50} = 120.6 days	SFO			
	SYN510275	18 Acres (sandy clay loam (pH 5.3, 1.9% OC)	t_R/DT_{50} = 70.7 days	SFO	N/A	Moderately persistent to persistent in soil under aerobic conditions.	3273229
		East Anglia (sandy loam, pH 7.0, 2.3% OC)	t_R/DT_{50} = 53.1 days	SFO			
		Sarpy (silt loam, pH 6.3, 2.1% OC)	t_R = 154 days DT_{50} = 60.2 days	IORE			
		Capay (clay, pH 7.0, 0.9% OC)	t_R/DT_{50} = 246 days	SFO			
		Gartenacker (silt loam, pH 7.2, 1.8% OC)	t_R/DT_{50} = 70.5 days	SFO			
	SYN549104	18 Acres (sandy clay loam, pH 5.3, 1.9% OC)	t_R/DT_{50} = 34.5 days	SFO	N/A	Slightly to moderately persistent in soil under aerobic conditions.	3273230
		East Anglia (sandy loam, pH 7.0, 2.3% OC)	t_R = 154.5 days	DFOP			

Property	Test substance	Medium	Value	Kinetic model	Major transformation products (maximum occurrence)[1]	Comments	PMRA#
			DT_{50} = 88.1 days				
		Sarpy (silt loam, pH 6.3, 2.1% OC)	t_R/DT_{50} = 29.9 days	SFO			
		Capay (loam, pH 7.0, 0.9% OC)	t_R/DT_{50} = 56.3 days	SFO			
		Gartenacker (silt loam, pH 7.2, 1.8% OC)	t_R/DT_{50} = 26.0 days	SFO			
Biotransformation in anaerobic soil	Cyclobutrifluram (SYN549522)	18 Acres (sandy loam, pH 6.0, 1.9% OC)	t_R/DT_{50} = 917 days	SFO	N/A	Persistent in soil under anaerobic conditions.	3273226
		East Anglia (sandy loam, pH 7.0, 2.2% OC)	t_R/DT_{50} = 335 days	SFO			
		Sarpy (silt loam, pH 6.3, 2.1% OC)	t_R/DT_{50} = 320 days	SFO			
		Capay (clay loam, pH 6.8, 1.1% OC)	t_R/DT_{50} = 438 days	SFO			
		Gartenacker (silt loam, pH 7.2, 2.2% OC)	t_R/DT_{50} = 669 days	SFO			
Biotransformation in aerobic aquatic	Cyclobutrifluram (SYN549522)	Calwich Abbey – Water (pH 7-8.4, total	t_R = 45.1 days	DFOP	N/A	Non-persistent to slightly persistent in	3273260

Property	Test substance	Medium	Value	Kinetic model	Major transformation products (maximum occurrence)[1]	Comments	PMRA#
systems[3]		organic carbon (TOC 3.7 ppm))	DT_{50} = 10.5 days			aqueous component of aquatic systems under aerobic conditions; persistent in water/sediment systems under aerobic conditions. No major TPs were formed in aerobic water/sediment systems. Aerobic aquatic degradation is not expected to be a major transformation route for cyclobutriflura m as it appears to be stable in water/sediment test systems. This appears to be driven by its partition to	
		Calwich Abbey – Total system	t_R/DT_{50} = 780 days	SFO			
		Golden Lake – Water (pH 7.42-8.8, 16.3 ppm TOC)	t_R = 235 days DT_{50} = 29.3 days	DFOP			
		Golden Lake – Total system	t_R/DT_{50} = 728 days	SFO			

Property	Test substance	Medium	Value	Kinetic model	Major transformation products (maximum occurrence)[1]	Comments	PMRA#
						sediment and persistence therein with little transformation.	
Biotransformation in anaerobic aquatic systems	Cyclobutrifluram (SYN549522)	Calwich Abbey – Water (pH 8.3, TOC 2.53 ppm)	t_R = 93.6 days DT_{50} = 15.2 days	DFOP	N/A	Slightly persistent to moderately persistent in aqueous component of aquatic systems under anaerobic conditions; persistent in water/sediment systems under anaerobic conditions. No major TPs were formed in anaerobic water/sediment systems. Anaerobic aquatic degradation is not expected to be a major	3273262
		Calwich Abbey – Total system	t_R/DT_{50} = 676 days	SFO			
		Golden Lake – Water (pH 8.3, TOC 14.78 ppm)	t_R = 161 days DT_{50} = 82.8 days	DFOP			
		Golden Lake – Total system	t_R/DT_{50} = 1230 days	SFO			

Property	Test substance	Medium	Value	Kinetic model	Major transformation products (maximum occurrence)[(1)]	Comments	PMRA#
						transformation route for cyclobutrifluram as it appears to be stable in water/sediment test systems. This appears to be driven by its partition to sediment and persistence therein with little transformation.	
Bioaccumulation							
Bioconcentration in fish (*Lepomis macrochirus*)	Cyclobutrifluram (SYN549522)	Fish	BCF_{KLG} = 42	N/A	N/A	Reduced by 44% during the first day of depuration and continued up to 97% after 14 days. Cyclobutrifluram has limited potential to bioaccumulate in fish.	3273308

Property	Test substance	Medium	Value	Kinetic model	Major transformation products (maximum occurrence)[1]	Comments	PMRA#
Mobility							
Adsorption / desorption in soil	Cyclobutrifluram (SYN549522)	Japanese volcanic ash (sandy loam, pH 4.8, 1.9% OC)	K_{oc} = 224 mL/g K_d = 4.3 mL/g	N/A	N/A	Cyclobutrifluram has medium mobility in soil based on the K_{oc} values.	3273248
		St. Triphon (clay loam, pH 7.4, 3.7% OC)	K_{oc} = 242 mL/g K_d = 9.0 mL/g				
		Hepler (silt loam, pH 5.4, 3.0% OC)	K_{oc} = 349 mL/g K_d = 10.5 mL/g				
	Cyclobutrifluram (SYN549522)	Seven Springs (sand, pH 5.1, 0.58% OC)	K_{oc} = 643 mL/g K_d = 3.7 mL/g	N/A	N/A	Cyclobutrifluram has low to medium mobility in soil based on the K_{oc} values.	3273250
		18 Acres (sandy clay loam, pH 5.5, 1.89% OC)	K_{oc} = 405 mL/g K_d = 7.7 mL/g				
		Sarpy (loam, pH 6.7, 2.08% OC)	K_{oc} = 338 mL/g				

Property	Test substance	Medium	Value	Kinetic model	Major transformation products (maximum occurrence)[1]	Comments	PMRA#
			K_d = 7.0 mL/g				
		Gartenacker (loam, pH 7.2, 2.26% OC)	K_{oc} = 301 mL/g K_d = 6.8 mL/g				
		Capay (clay loam, pH 7.2, 0.86% OC)	K_{oc} = 465 mL/g K_d = 4.0 mL/g				
		East Anglia (sandy loam, pH 7.3, 2.13% OC)	K_{oc} = 306 mL/g K_d = 6.5 mL/g				
	SYN510275	Seven Springs (loamy sand, pH 5.2, 0.56% OC)	K_{oc} = 6.5 mL/g K_d = 0.04 mL/g	N/A	N/A	SYN510275 has very high mobility in soil based on the K_{oc} values.	3273252
		18 Acres (sandy clay loam, pH 5.3, 1.9% OC)	K_{oc} = 3.5 mL/g K_d = 0.1 mL/g				
		Sarpy (loam, pH 6.3,	K_{oc} = 5.1 mL/g				

Property	Test substance	Medium	Value	Kinetic model	Major transformation products (maximum occurrence)[1]	Comments	PMRA#
		2.1% OC)	K_d = 0.1 mL/g				
		Gartenacker (loam, pH 7.2, 1.8% OC)	K_{oc} = 1.9 mL/g K_d = 0.03 mL/g				
		Capay (clay loam, pH 7.0, 0.9% OC)	K_{oc} = 10.9 mL/g K_d = 0.1 mL/g				
	SYN549104	Seven Springs (loamy sand, pH 5.2, 0.56% OC)	K_{oc} = 43.8 mL/g K_d = 0.25 mL/g	N/A	N/A	SYN549104 has high to very high mobility in soil based on the K_{oc} values.	3273254
		18 Acres (sandy clay loam, pH 5.3, 1.9% OC)	K_{oc} = 62.8 mL/g K_d = 1.2 mL/g				
		Sarpy (silt loam, pH 6.3, 2.1% OC)	K_{oc} = 48.3 mL/g K_d = 1.0 mL/g				

Property	Test substance	Medium	Value	Kinetic model	Major transformation products (maximum occurrence)[1]	Comments	PMRA#
		Gartenacker (silt loam, pH 7.2, 1.8% OC)	K_{oc} = 31.3 mL/g K_d = 0.6 mL/g				
		Capay (clay, pH 7.0, 0.9% OC)	K_{oc} = 82 mL/g K_d = 0.7 mL/g				
Soil leaching	Study not submitted, or required.						
Volatilization	Study not submitted, or required.						
Field studies							
Field dissipation	Cyclobutrifluram SC (A22011B); Formulation (450 g a.i./L)	Ontario bare soil plot (Loam, pH 7.1, 0.17-1.3% OC)	DT_{50} (cyclobutrifluram) = 25.4 days	IORE	N/A	Cyclobutrifluram residues were mainly detected in the 0-40 cm soil depth interval. SYN510275 residues were mainly detected in the 0-100 cm soil depth interval.	3273237
			DT_{50} (SYN510275) = 456 days	SFO			

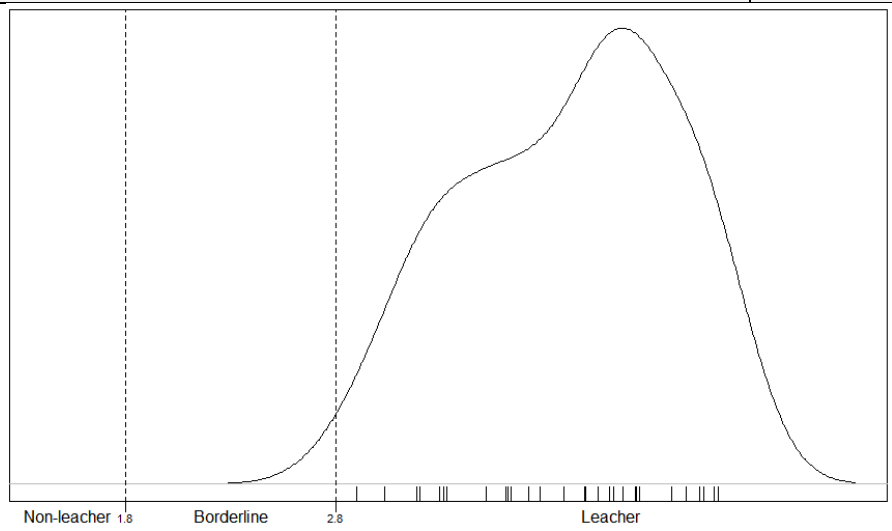
Property	Test substance	Medium	Value	Kinetic model	Major transformation products (maximum occurrence)[(1)]	Comments	PMRA#
		Washington potato soil plot (Loamy fine sand, pH 8.3, 0.14-0.36% OC)	DT_{50} (cyclobutrifluram) = 36.0 days	SFO	N/A	Cyclobutrifluram residues were detected in the 10-20 cm and 20-40 cm segments by Day 7, and in the 40-60 cm, 60-80 cm, and 80-100 cm segments by Days 63, 90, and 180, respectively.	3273232
		Washington bare soil plot (Loamy fine sand, pH 8.3, 0.14-0.36% OC)	DT_{50} (cyclobutrifluram) = 32.5 days	SFO		Cyclobutrifluram residues were detected in the 10-20 cm segment by Day 7, in the 20-40 cm segments by Day 28, and in the 40-60 cm, 60-80 cm, 80-100 cm segments by Day 63.	
Field leaching	Study not submitted, or required						

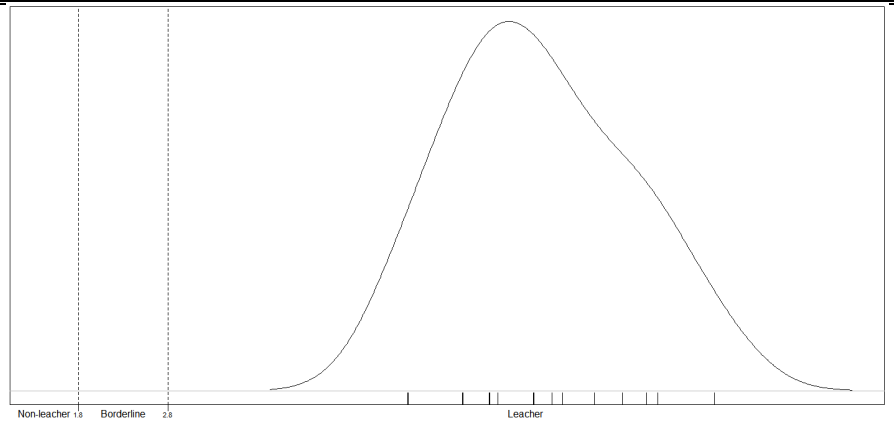
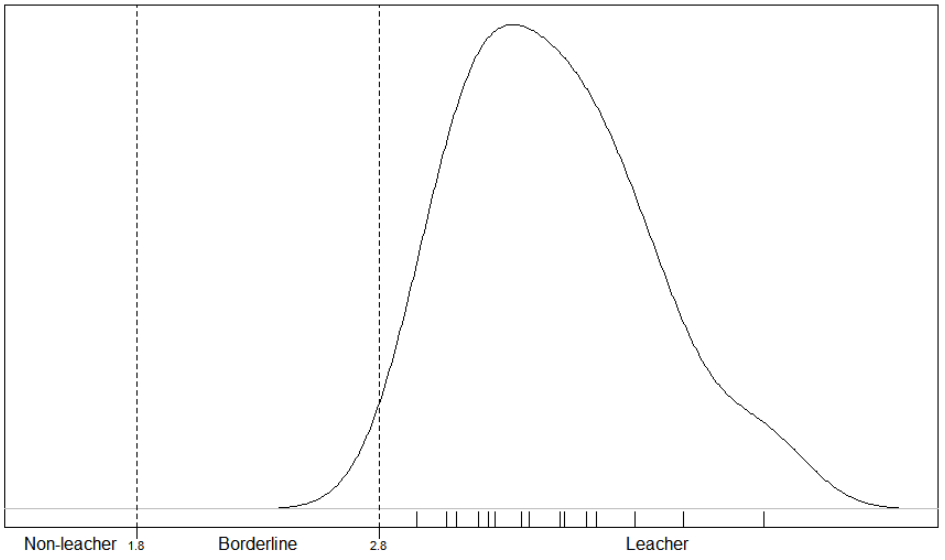
1 There were insufficient data to calculate degradation kinetics for all major TPs.

2. The 90% upper confidence bound on the mean of the t_R values in aerobic soil for cyclobutrifluram and SYN510275 are 832 and 175 days, respectively. These values were used to calculate estimated environmental concentrations (EECs) in soil for the risk assessment.
3. Only two representative aerobic aquatic half-lives were available for cyclobutrifluram. As such, the maximum value of 780 days was used for cyclobutrifluram to calculate estimated environmental concentrations (EECs) in water for the risk assessment. The aerobic aquatic half-live for SYN510275 is not available.
4. Blank seed refers to the glass beads treated with labelled cyclobutrifluram (SYN549522) during the aerobic degradation study in soil (PMRA# 3273224).
5. This study (PMRA #3273224) is classified as "Acceptable with Limitations" as it is a non-guideline study which intended to assess soil biotransformation in the presence of simulated natural sunlight following seed treatment and soil drench treatment. The endpoints are not intended for use during the quantitative risk assessment or when characterising persistence.

Table 20 Leaching assessment of cyclobutrifluram residues

Leaching criteria of Cohen et al. (1984)[1]				
Criteria	**Test Item**			**Leaching Criteria Met?**
	Cyclobutrifluram	**SYN510275[2]**	**SYN549104**	
Solubility in water >30 mg/L	19 mg/L in pure water (TGAI)	N/A	N/A	SYN549522 - No
K_d (mL/g): <5 and usually <1 or 2	4.3 to 10.5 (mean 7.9); and 3.73 to 7.66 (mean 5.96)	0.03 to 0.11 (mean 0.07)	0.25 to 1.19 (mean of 0.75)	SYN549522 - No SYN510275 - Yes SYN549104 - Yes
K_{oc} <300	224.2 to 348.8 (mean 271.8); and 301 to 643 (mean 410)	1.93 to 10.9 (mean 5.58)	31.3 to 82.0 (mean 53.7)	SYN549522 - Yes SYN510275 - Yes SYN549104 - Yes
Henry's law constant (atm m^3/mol): $<10^{-2}$	7.3×10^{-5} Pa.m^3/mole at 20°C (7.2×10^{-10} atm m^3/mol)	N/A	N/A	SYN549522 - Yes
pK_a: Negatively charged (either fully or partially) at ambient pH	No pKa was observed in the pH range of 2 to 12.0 by spectrophotometric analysis of a solution of Cyclobutrifluram in water.	N/A	N/A	SYN549522 - No

Leaching criteria of Cohen et al. (1984)[1]				
Criteria	**Test Item**			**Leaching Criteria Met?**
	Cyclobutrifluram	**SYN510275[2]**	**SYN549104**	
Hydrolysis half-life: >20 weeks (>140 days)	Hydrolytically stable at pH 4, pH 7, and pH 9 at temperatures of 50, 60, and 70°C.	N/A	N/A	SYN549522 - No
Soil phototransformation half-life: >1 week (>7 days)	14.7 days under artificial sunlight, which is equivalent to 29.6 days under natural sunlight at 30°N to 50°N).	N/A	N/A	SYN549522 – Yes
Half-life in soil: >2 to 3 weeks (>14 to 21 days)	DT_{50} = 51.5 to 1097 days in aerobic soil. DT_{50} = 320 to 917 days in anaerobic soil.	DT_{50} = 53.1 to 246 days in aerobic soil.	DT_{50} = 26.0 to 88.1 days in aerobic soil.	SYN549522 - Yes SYN510275 – Yes SYN549104 – Yes
Groundwater Ubiquity Score (GUS) Assessment[3]				
Test item	**GUS Plot**			**Notes**
Cyclobutrifluram				Leacher

Leaching criteria of Cohen et al. (1984)[1]				
Criteria	**Test Item**			**Leaching Criteria Met?**
	Cyclobutrifluram	**SYN510275[2]**	**SYN549104**	
SYN510275				Leacher
SYN549104				Leacher

1 Cohen et al. (1984). Potential pesticide contamination of groundwater from agricultural uses. In: R.F. Kruger and J.D., Seibor, eds. Treatment and disposal of pesticide wastes. American Chemistry Society Symposium Series No. 259, American Chemical Society: Washington, DC.
2. Information for TPs other than SYN510275 and SYN549104 is not available.
3. Gustafson, D.I. 1989. Groundwater ubiquity score: A simple method for assessing pesticide leachability. Environmental Toxicology and Chemistry 8:339-357.

Table 21 Estimated environmental concentrations (EECs) and estimated daily dietary exposure (EDEs) for cyclobutrifluram in the environment

Substance	EEC/EDE		Method of calculation	Notes
Soil: Screening Level Risk Assessment				
Cyclobutrifluram	100 g a.i./ha		Based on one single application of cyclobutrifluram to soil at the rate of 100 g a.i./ha per year.	EECs in g a.i./ha were used to evaluate risks to beneficial arthropods and non-target terrestrial plants (seedling emergence). EECs in mg a.i./kg dw soil were used to evaluate risks to earthworms.
	0.044 mg a.i./kg dw soil		EEC of cyclobutrifluram in soil was calculated based on one single application of cyclobutrifluram to soil at the rate of 100 g a.i./ha per year, and assuming a soil bulk density of 1.5 g/cm^3 and a soil depth of 15 cm.	
Water: Screening Level Risk Assessment (EEC in mg/L)				
Water depth:	**15 cm**	**80 cm**		
Cyclobutrifluram	100 g a.i./ha		Based on one single application of cyclobutrifluram to soil at the rate of 100 g a.i./ha per year.	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.
	0.067	0.013	EECs of cyclobutrifluram in surface water was calculated considering a direct overspray of cyclobutrifluram to a one-hectare wetland with depths of 15 and 80 cm at the above application rate (100 g a.i./ha per year) to water.	
SYN510275	0.033	0.006	EECs of the major TP in surface water were calculated as described above for cyclobutrifluram, but using the maximum application rate (1 × 100 g a.i./ha per year) and assuming 100% transformation of the parent to the TP on a molar basis. Dissipation of the parent was not considered.	
Plant Surfaces: Screening Level and Refined Risk Assessments				
Cyclobutrifluram	100 g a.i./ha		On-field EEC: calculated based on one single application of cyclobutrifluram to plant surfaces at the rate of 100 g a.i./ha per year.	Used to evaluate on-field risks to beneficial arthropods

Substance	EEC/EDE	Method of calculation	Notes
			and non-target terrestrial plants.
EEC for Bees: Soil-Applied end-use products (Direct contact exposure)			
Cyclobutrifluram	0.24 µg a.i./bee	Estimated contact exposure (µg a.i./bee) for bees from the uses of soil-applied end-use products are calculated using the following formulas: 2.4 µg a.i./bee/1 kg a.i./ha × maximum yearly application rate (0.10 kg a.i./ha).	Used to evaluate risks associated with soil-applied end-use products to pollinators (bees).
EDEs for Bees: Soil-Applied end-use products (Oral exposure to pollen and/or nectar)			
Cyclobutrifluram	0.034 µg a.i./bee/day (adult) 0.014 µg a.i./bee/day (larvae)	EDEs for bees for soil-applied end-use products (µg a.i./bee) are calculated using the following formulas: application rate of 100 g a.i./ha (0.100 kg a.i./ha) × adjustment factor • Adult adjustment factor was calculated as the food consumption of 0.292 g/bee per day × (Briggs EEC)(1) • 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 × (Briggs EEC)(1)	Used to evaluate risks associated with soil-applied end-use products to pollinators (bees).
EDEs for Bees: Seed Treatment end-use products (Oral exposure to pollen and/or nectar)			
Cyclobutrifluram	0.292 µg a.i./bee/day (adult) 0.124 µg a.i./bee (larvae)	EDEs for bees for seed treatment end-use products (µg a.i./bee) are calculated using the following formulas: (default residue level of 1 µg a.i./g) × consumption rate (0.292 g/day for adult bee, 0.124 g/day for larvae).	Used to evaluate risks associated with seed treatment end-use products to pollinators (bees).

See Tables 25 and 26 for the EDEs for food items/treated seeds for birds and mammals.

(1) The method for estimating dietary exposures to bees resulting from soil treatments is based on an empirically based model developed by Briggs et al. (1982 and 1983), with modifications (referred to here as "the Briggs' Model"). This model relates the Log K_{ow} of a chemical to its concentration in plant shoots, which can be used as a surrogate for concentrations in nectar and in pollen). In using the Briggs' model, the approach is to use **Equation 1**, with the 95th percentile TSCF value that is specific to an assessed pesticide's Log K_{ow} (calculated using **Equation 2**). It is assumed that the resulting value is equivalent to pesticide concentrations in pollen and nectar of crops receiving soil treatments of the pesticide.

Equation 1. $C_{stem} = [10^{(0.95*\text{Log } Kow-2.05)} + 0.82] * TSCF * [\rho / (\theta + \rho * K_{oc} * f_{oc})] * C_{soil}$

Where:
C_{stem} = concentration in stems (µg a.i./g plant)

C_{soil} = concentration in soil (µg a.i./g soil)
f_{oc} = fraction of organic carbon in soil
θ = soil-water content by volume (cm^3/cm^3)
ρ = soil bulk density (g-dw/cm^3)
K_{oc} = soil organic carbon-water partitioning coefficient (cm^3/g-oc or L/kg-oc)
TSCF = Transpiration Stream Concentration Factor

Equation 2. $TSCF=-0.0648 * (\text{Log } K_{ow})^2 +0.241 * \text{Log } K_{ow} + 0.5822$

Table 22 Toxicity of Cyclobutrifluram to Non-Target Species

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity(1)	PMRA#
Terrestrial Organisms					
Invertebrates					
Earthworm (*Eisenia andrei*)	14-d Acute	Cyclobutrifluram	LC_{50} >1000 mg a.i./kg soil dw NOEC = 500 mg a.i./kg soil dw	N/A(2)	3273347
	56-d Chronic		28-d NOEC (survival, growth) >1000 mg test item/kg soil dw NOEC (reproduction) = 171 mg a.i./kg soil dw EC_{50} (reproduction) = 536 mg a.i./kg soil dw	N/A(2)	3273355
	56-d Chronic	Cyclobutrifluram SC (A22011B); Formulation (450 a.i./L)	28-d NOEC (survival, growth) >1000 mg test item/kg soil dw (381 mg a.i./kg soil dw) NOEC (reproduction) =	N/A(2)	3273349

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity[1]	PMRA#
			309 mg test item/kg soil dw (118 mg a.i./kg soil dw) EC_{50} (reproduction) = 668 mg test item/kg soil dw (225 mg a.i./kg soil dw)		
	56-d Chronic	Cyclobutrifluram FS (A22417C); Formulation (500 g a.i./L)	28-d NOEC (survival, growth) >1000 mg test item/kg soil dw (414 mg a.i./kg soil dw) NOEC (reproduction) = 171 mg test item/kg soil dw (71 mg a.i./kg soil dw) EC_{50} (reproduction) = 639 mg test item/kg soil dw (265 mg a.i./kg soil dw)	N/A[2]	3273352
Honey bee (*Apis mellifera* L.)	48-h Oral	Cyclobutrifluram	LD_{50} >72.2 µg a.i./bee	Practically non-toxic	3273332
	48-h Contact		LD_{50} >200 µg a.i./bee		
	3-d Brood (single exposure)		LC_{50} >909 mg a.i./kg larval diet (LD_{50} >30.0 µg a.i./larva)	Practically non-toxic	3273337
			NOEC = 303 mg a.i./kg larval diet (NOED = 10.0 µg a.i./larva)	N/A	
	10-d Chronic dietary		NOEC = 400 mg a.i./kg sucrose solution (NOEDD = 6.11 µg	No adverse effects up to the highest	3273335

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity(1)	PMRA#
			a.i./bee/d)	concentration tested.	
	22-d Chronic dietary (repeated exposure)		NOEC ≥160 mg a.i./kg diet (NOED ≥24.6 µg a.i./larva/development period; or NOEDD ≥6.15 µg a.i./larva/d)	No adverse effects up to the highest concentration tested.	3273338
Parasitic arthropod (*Aphidius rhopalosiphi*)	13-d Contact (glass plate)	Cyclobutrifluram SC (A22011B); Formulation (450 a.i./L)	48-h LR_{50} >672 g a.i./ha 48-h NOER (mortality) = 672 g a.i./ha ER_{50} >672 g a.i./ha NOER (reproduction) = 672 g a.i./ha	No adverse effects up to the highest concentration tested.	3273341
Predatory arthropod (*Typhlodromus pyri*)	14-d Contact (glass plate)	Cyclobutrifluram SC (A22011B); Formulation (450 a.i./L)	7-d LR_{50} >672 g a.i./ha 7-d NOER (mortality) = 672 g a.i./ha ER_{50} >672 g a.i./ha NOER (reproduction) <168 g a.i./ha	No adverse effects at the highest concentration tested, but reproduction effect was observed at lower concentrations tested.	3273342
Predatory arthropod (*Hypoaspis aculeifer*)	14-d Contact (glass vessel)	Cyclobutrifluram FS (A22417C); Formulation (500 g a.i./L)	14-d LC_{50} >414 mg a.i./kg soil dw 14-d NOER (mortality) = 414 mg a.i./kg soil dw EC_{50}: >414 mg a.i./kg soil	No adverse effects up to the highest concentration tested.	3273344

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity(1)	PMRA#
			dw NOER (reproduction) = 414 mg a.i./kg soil dw		
Birds					
Bobwhite quail (*Colinus viginianus (L.)*)	14-d Acute oral	Cyclobutrifluram	LD_{50} >2000 mg a.i./kg bw	Practically non-toxic	3273264
	5-d Dietary		LC_{50} >5620 mg a.i./kg diet (LD_{50} >1264 mg a.i./kg bw/d) NOEC (bw) = 5260 mg a.i./kg diet (NOED = 1264 mg a.i./kg bw/day)	Practically non-toxic	3273271
	Reproduction		NOEC ≥2013 mg a.i./kg diet (NOED ≥173 mg a.i./kg bw/d)	No adverse effects up to the highest concentration tested.	3273277
Mallard duck (*Anas platyrhynchos*)	14-d Acute oral	Cyclobutrifluram	LD_{50} >2000 mg a.i./kg bw	Practically nontoxic	3273268
	5-d Dietary		LC_{50} ≥5620 mg a.i./kg diet (LD_{50} ≥2612 mg a.i./kg bw/d) NOEC (bw) = 562 mg a.i./kg diet (NOED = 229 mg a.i./kg bw/day)	Practically non-toxic	3273272

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity[1]	PMRA#
	Reproduction		NOEC ≥2013 mg a.i./kg diet (NOED ≥286 mg a.i./kg bw/day)	No adverse effects up to the highest concentration tested.	3273274
Canary (*Serinus canaria*)	14-d Acute oral	Cyclobutrifluram	LD_{50} >2000 mg a.i./kg bw	Practically non-toxic	3273266
Mammals					
Rat (*Rattus norvegicus*)	Acute	Cyclobutrifluram	LD_{50} >5000 mg a.i./kg bw/d LD_{50} >2000 mg a.i./kg bw/d	Practically non-toxic	3273132 3477761
	2-Generation dietary reproductive toxicity		Chronic NOAEL (male P) = 700 mg a.i./kg diet (430 mg a.i./kg bw/d) Chronic NOAEL (male F1) = 700 mg a.i./kg diet (53.0 mg a.i./kg bw/d) Chronic NOAEL (female P) = 700 mg a.i./kg diet (53.0 mg a.i./kg bw/d)	N/A[2]	3273172/ 3273173
Vascular Plants					
Monocotyledonae: *Allium cepa*, *Avena sativa*, *Lolium perenne*, *Zea mays*	Seedling emergence	Cyclobutrifluram SC (A22011B); Formulation (450	ER_{25}/ ER_{50} (all species) >910 g a.i./ha NOER (*Lolium perenne*	N/A[2]	3273294

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity[1]	PMRA#
Dicotyledonae: *Beta vulgaris*, *Brassica napus*, *Cucumis sativus*, *Glycine max*, *Lactuca sativa*, *Lycopersicon esculentum*		a.i./L)	only) = 303 g a.i./ha NOER (all remaining species) = 910 g a.i./ha		
	21-d Vegetative vigour (all species)		ER_{25}/ ER_{50} >910 g a.i./ha NOER = 910 g a.i./ha	No adverse effects up to the highest concentration tested.	3273292
Aquatic Organisms					
Freshwater Aquatic Invertebrates					
Water flea (*Daphnia magna*)	48-h Acute (Static)	Cyclobutrifluram	EC_{50} >27 mg a.i./L	At most slightly toxic	3273313
		SYN510275 (major TP of cyclobutrifluram)	EC_{50} >100 mg/L	Practically non-toxic	3273311
	21-d Chronic (Static-renewal)	Cyclobutrifluram	NOEC (growth) = 2.6 mg a.i./L	N/A[2]	3273315
Marine/estuarine Aquatic Invertebrates					
Mysid shrimp (*Americamysis bahia*)	96-h Acute (Static)	Cyclobutrifluram	LC_{50} >8.0 mg a.i./L	At most moderately toxic	3273279
	28-d Chronic (Flow-through)		NOEC = 1.3 mg a.i./L	N/A[2]	3273289
Eastern oyster (*Crassostrea virginica*)	96-h Acute (Flow-through)		IC_{50} = 0.33 mg a.i./L	Highly toxic	3273287
Freshwater Benthic Invertebrates					
Midge (*Chironomus dilutus*)	10-d Chronic (Intermittent-renewal)	Cyclobutrifluram	LC_{50} >36 mg a.i./kg sediment dw NOEC (growth/survival) = 20 mg a.i./kg sediment dw	N/A[2]	3273326

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity[1]	PMRA#
			Pore water LC_{50} >4.1 mg a.i./L Pore water NOEC (growth/survival) = 2.0 mg a.i./L		
Freshwater amphipod (*Hyalella azteca*)			LC_{50} >73 mg a.i./kg sediment dw NOEC (growth/survival) = 73 mg a.i./kg sediment dw Pore water LC_{50} >7.7 mg a.i./L Pore water NOEC (growth/survival) = 7.7 mg a.i./L	N/A[2]	3273324
Marine/estuarine Benthic Invertebrates					
Estuarine amphipod (*Leptocheirus plumulosus*)	10-d Chronic (Intermittent-renewal)	Cyclobutrifluram	LC_{50} >62 mg a.i./kg sediment dw NOEC = 62 mg a.i./kg sediment dw Pore water LC_{50} >4.5 mg a.i./L Pore water NOEC = 4.5 mg a.i./L	N/A[2]	3273280
Freshwater Fish					
Rainbow trout (*Oncorhynchus mykiss*)	96-h Acute (Static)	Cyclobutrifluram	LC_{50} = 13 mg a.i./L	Slightly toxic	3273298
Carp			LC_{50} >19 mg a.i./L	At most slightly	3273300

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity[1]	PMRA#
(*Cyprinus carpio*)				toxic	
Fathead minnow (*Pimephales promelas*)	96-h Acute (Static)	Cyclobutrifluram	LC_{50} = 11 mg a.i./L	Slightly toxic	3273303
		SYN510275 (major TP of cyclobutrifluram)	LC_{50} >100 mg/L	Practically non-toxic	3273304
	32-d Early-life stage	Cyclobutrifluram	NOEC (growth) = 1.9 mg a.i./L	N/A[2]	3273306
Marine/estuarine Fish					
Sheepshead minnow (*Cyprinodon variegatus*)	96-h Acute (Static)	Cyclobutrifluram	LC_{50} >18 mg a.i./L	At most slightly toxic	3273285
	34-d Early-life stage		NOEC (growth) = 0.43 mg a.i./L	N/A[2]	3273282
Freshwater Algae					
Freshwater alga (*Rhaphidocelis subcapitata*)	96-h Acute (Static)	Cyclobutrifluram	72-h EC_{50} (AUC)[3] = 6.5 mg a.i./L 72-h EC_{50} (growth rate) = 9.5 mg a.i./L 72-h EC_{50} (yield) = 6.7 mg a.i./L 72-h NOEC = 3.6 mg a.i./L 96-h EC_{50} (AUC) = 7 mg a.i./L 96-h EC_{50} (growth rate) = 14 mg a.i./L 96-h EC_{50} (yield) = 6.4 mg a.i./L 96-h NOEC = 3.6 mg a.i./L	Moderately toxic	3273323
		SYN510275 (major TP of	72/96-h EC_{50} (AUC, growth rate, yield) >100	Practically non-toxic	3273316

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity[1]	PMRA#
		cyclobutrifluram)	mg a.i./L 72/96-h NOEC = 100 mg a.i./L		
Diatom (*Naviculla pelliculosa*)		Cyclobutrifluram	72/96-h EC_{50} (AUC, growth rate, yield) >17 mg a.i./L 72/96-h NOEC = 17 mg a.i./L	At most slightly toxic	3273320
Cyanobacterium Bluegreen alga (*Anabaena flos-aquae*)		Cyclobutrifluram	72/96-h EC_{50} (AUC, growth rate, yield) >24 mg a.i./L 72/96-h NOEC = 24 mg a.i./L	At most slightly toxic	3273318
Marine/estuarine Algae					
Diatom (*Skeletonema costatum*)	96-h Acute (Static)	Cyclobutrifluram	72/96-h EC_{50} (AUC, growth rate, yield) >13 mg a.i./L 72/96-h NOEC = 10 mg a.i./L	At most slightly toxic	3273291
Freshwater Aquatic Plants					
Duckweed (*Lemna gibba*)	7-d Growth inhibition (Static-renewal)	Cyclobutrifluram	EC_{50} (yield, frond density-based) = 11 mg a.i./L EC_{50} (yield, frond weight-based) = 13 mg a.i./L EC_{50} (growth rate, frond density/weight-based) >16 mg a.i./L	Slightly toxic	3273330

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity(1)	PMRA#
			NOEC (frond density-based) = 0.57 mg a.i./L NOEC (frond weight-based) = 3.6 mg a.i./L		

1 USEPA classification, where applicable
2 No hazard/toxicity classification criteria is available for this endpoint.
3 AUC = area under the growth curve

Table 23 Screening level risk assessment for non-target terrestrial organisms (with the exception of bees, birds and mammals)

Organism	Exposure	Test substance	EEC(1)	Endpoint value	UF	Effects metric	RQ(2)	LOC	LOC exceeded?
Invertebrates									
Earthworm (*Eisenia andrei*)	14-d Acute	Cyclobutrifluram	0.044 mg a.i./kg soil dw	LC_{50} > 1000 mg a.i./kg soil dw	2	> 500 mg a.i./kg soil dw	≤ 0.0001	1	No
	56-d Chronic	Cyclobutrifluram	0.044 mg a.i./kg soil dw	NOEC = 171 mg a.i./kg dw soil	1	= 171 mg a.i./kg dw soil	0.0003	1	No
	56-d Chronic	Cyclobutrifluram SC (A22011B) Formulation	0.044 mg a.i./kg soil dw	NOEC = 118 mg a.i./kg dw soil	1	= 118 mg a.i./kg dw soil	0.0004	1	No
	56-d Chronic	Cyclobutrifluram FS (A22011B) Formulation	0.044 mg a.i./kg soil dw	NOEC = 71 mg a.i./kg dw soil	1	= 71 mg a.i./kg dw soil	0.0006	1	No
Predatory arthropod (*Typhlodromus pyri*)	14-d contact (glass plate)	Cyclobutrifluram SC (A22011B) Formulation	100 g a.i./ha	LR_{50} > 672 g a.i./ha	1	> 672 g a.i./ha	< 0.1488	2(3)	No
			100 g a.i./ha	ER_{50} > 672 g a.i./ha	1	> 672 g a.i./ha	< 0.1488	2(3)	No

Organism	Exposure	Test substance	EEC[1]	Endpoint value	UF	Effects metric	RQ[2]	LOC	LOC exceeded?
Predatory mite (*Hypoaspis aculeifer*)	14-d contact (glass plate)	Cyclobutrifluram FS (A22011B) Formulation	0.044 mg a.i./kg dw soil	LR_{50} > 414 mg a.i./kg soil dw	1	> 414 mg a.i./kg soil dw	< 0.0001	2[3]	No
			0.044 mg a.i./kg dw soil	ER_{50} > 414 mg a.i./kg soil dw	1	> 414 mg a.i./kg soil dw	< 0.0001	2[3]	No
Parasitic arthropod (*Aphidius rhopalosiphi*)	14-d contact (glass plate)	Cyclobutrifluram SC (A22011B) Formulation	100 g a.i./ha	LR_{50} > 672 g a.i./ha	1	> 672 g a.i./ha	< 0.1488	2[3]	No
			100 g a.i./ha	ER_{50} > 672 g a.i./ha	1	> 672 g a.i./ha	< 0.1488	2[3]	No
Vascular plants									
Vascular plants (ten species)[4]	Seedling emergence	Cyclobutrifluram	100 g a.i./ha	ER_{25} > 910 g a.i./ha	1	> 910 g a.i./ha	< 0.1	1	No
	21d-Vegetative vigour		100 g a.i./ha	ER_{50} > 910 g a.i./ha	2	> 455 g a.i./ha	< 0.2	1	No

1. See Table 21 for a description of how the EECs were calculated.
2. 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.
3. A LOC of 2 is used for spray applications on glass plates for *T. pyri*, *Hypoaspis aculeifer*, and *A. rhopalosiphi*, based on an extensive empirical comparison of the risk quotients and known acceptable effects from field and semi-field studies for the two indicator species. Significant ecological effects of pest control products on non-target arthropod populations are not expected at a risk quotient of 2 or less.
4. The ten species are Monocotyledonae: *Allium cepa*, *Avena sativa*, *Lolium perenne*, *Zea mays*; and Dicotyledonae*: Beta vulgaris*, *Brassica napus*, *Cucumis sativus*, *Glycine max*, *Lactuca sativa*, *Lycopersicon esculentum*.

Table 24 Screening level risk assessment for bees

Organism	Exposure	Test substance	EEC/EDE[1]	Endpoint value	UF	Effects metric	RQ[2]	LOC[3]	LOC Exceeded?
Soil-Applied end-use products: Direct contact and oral exposure to pollen and/or nectar *via* plant surfaces									
Honey bee (*Apis mellifera* L.)	48-h Contact	Cyclobutrifluram	0.24 µg a.i./bee	LD_{50} > 200 µg a.i./bee	1	> 200 µg a.i./bee	< 0.0012	0.4	No
	48-h Oral		2.862 µg a.i./bee	LD_{50} > 72.2 µg a.i./bee	1	> 72.2 µg a.i./bee	< 0.0396	0.4	No
	10-d Chronic dietary		2.862 µg a.i./bee	NOEDD = 6.11 µg a.i./bee/day	1	= 6.11 µg a.i./bee/day	0.4683	1	No
	Larval (3-d brood / single exposure)		1.215 µg a.i./larva	LD_{50} > 30.0 µg a.i./larva	1	> 30.0 µg a.i./larva	< 0.0405	0.4	No
	Larval (22-d chronic dietary / repeated exposure)		1.215 µg a.i./larva/day	NOEDD ≥ 6.15 µg a.i./larva/day	1	≥ 6.15 µg a.i./larva/day	≤ 0.1976	1	No
Soil-Applied end-use products: Oral exposure to pollen and/or nectar *via* soil									
Honey bee (*Apis mellifera* L.)	48-h Oral	Cyclobutrifluram	0.034 µg a.i./bee	LD_{50} > 72.2 µg a.i./bee	1	> 72.2 µg a.i./bee	< 0.0005	0.4	No
	10-d Chronic dietary		0.034 µg a.i./bee/day	NOEDD = 6.11 µg a.i./bee/day	1	= 6.11 µg a.i./bee/day	0.0056	1	No
	Larval (3-d brood / single exposure)		0.014 µg a.i./larva	LD_{50} > 30.0 µg a.i./larva	1	> 30.0 µg a.i./larva	< 0.0005	0.4	No
					1			1	No

Organism	Exposure	Test substance	EEC/EDE[1]	Endpoint value	UF	Effects metric	RQ[2]	LOC[3]	LOC Exceeded?
	Larval (22-d chronic dietary / repeated exposure)		0.014 µg a.i./larva/day	NOEDD ≥ 6.15 µg a.i./larva/day		≥ 6.15 µg a.i./larva/day	≤ 0.0024		
Seed Treatment end-use products: Oral exposure to pollen and/or nectar									
Honey bee (*Apis mellifera* L.)	48-h Oral	Cyclobutrifluram	0.292 µg a.i./bee	LD_{50} > 72.2 µg a.i./bee	1	> 72.2 µg a.i./bee	< 0.0040	0.4	No
	10-d Chronic dietary		0.292 µg a.i./bee/day	NOEDD = 6.11 µg a.i./bee/day	1	= 6.11 µg a.i./bee/day	0.0478	1	No
	Larval (3-d brood / single exposure)		0.124 µg a.i./larva	LD_{50} > 30.0 µg a.i./larva	1	> 30.0 µg a.i./larva	< 0.0041	0.4	No
	Larval (22-d chronic dietary / repeated exposure)		0.124 µg a.i./larva/day	NOEDD ≥ 6.15 µg a.i./larva/day	1	≥ 6.15 µg a.i./larva/day	≤ 0.0202	1	No

1 See Table 21 for a description of how the EEC/EDEs were calculated.
2 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.
3 LOC for bees is set at 0.4 for acute exposure, 1 for chronic exposure.

Table 25 Screening level risk assessment for birds and mammals for soil-applied end-use products

Organism	Effects metric (mg a.i./kg bw/d)[1]	Feeding guild (food item)	EDE (mg a.i./kg bw/d)[2]	RQ[3]	LOC	LOC exceeded?
Small bird (0.02 kg)						
Acute	200.00	Insectivore	8.14	0.04	1	No
Reproduction	173.00	Insectivore	8.14	0.05	1	No
Medium-sized bird (0.1 kg)						
Acute	200.00	Insectivore	6.35	0.03	1	No
Reproduction	173.00	Insectivore	6.35	0.04	1	No
Large-sized bird (1 kg)						
Acute	200.00	Herbivore (short grass)	4.10	0.02	1	No
Reproduction	173.00	Herbivore (short grass)	4.10	0.02	1	No
Small mammal (0.015 kg)						
Acute	500.00	Insectivore	4.68	0.01	1	No
Reproduction	43.10	Insectivore	4.68	0.11	1	No
Medium-sized mammal (0.035 kg)						
Acute	500.00	Herbivore (short grass)	9.08	0.02	1	No
Reproduction	43.10	Herbivore (short grass)	9.08	0.21	1	No
Large-sized mammal (1 kg)						
Acute	500.00	Herbivore (short grass)	4.85	0.01	1	No
Reproduction	43.10	Herbivore (short grass)	4.85	0.11	1	No

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

2 EDE = Estimated daily 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 soil-applied end-use products (A22011 Crop and A23156 Crop) for birds and mammals were calculated based on 1 × 100 g a.i./ha per year.

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 26 Screening level risk assessment for birds and mammals for seed treatment end-use products

Organism	Effects metric(mg a.i./kg bw/d)[1]	EDE (mg ai/kg bw/d)[2], [3]	RQ[4]	LOC	LOC exceeded?
Small-sized bird (0.02 kg)					
Acute	200.00	126.97	0.6	1	No
Reproduction	173.00	126.97	0.7	1	No
Medium-sized bird (0.10 kg)					
Acute	200.00	99.74	0.5	1	No
Reproduction	173.00	99.74	0.6	1	No
Large-sized bird (1.00 kg)					
Acute	200.00	29.08	0.1	1	No
Reproduction	173.00	29.08	0.2	1	No
Small-sized mammals (0.015 kg)					
Acute	500.00	72.56	0.1	1	No
Reproduction	43.10	72.56	**1.7**	1	**Yes**
Medium-sized mammals (0.035 kg)					
Acute	500.00	62.40	0.1	1	No
Reproduction	43.10	62.40	**1.5**	1	**Yes**
Large-sized mammals (1.00 kg)					
Acute	500.00	34.36	0.1	1	No
Reproduction	43.10	34.36	0.8	1	No

1 Uncertainty factors of 0.1 and 1 were applied to the acute oral and reproduction endpoints, respectively.

2 EDE = Estimated daily 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) $^{0.822}$

3 The EECs for consumption of treated seeds were calculated based on a converted rate of 63 g a.i./ha, which was derived from the maximum application seeding rate 50 g a.i./100 kg seed. The conversion was calculated using the following formula: Application Rate (g a.i./ha) = Seeding Rate (kg seed/ha) × Seed Treatment Rate (g a.i./ kg seed).

The seeding rate of soybean, which is the listed crop for seed treatment with cyclobutrifluram, is calculated using the following formula: Seeding Rate (kg seed/ha) = Desired Plant population (# plants /m^2) × 1000 Kernel weight (g) ÷ Seedling Survival Rate (0.90) ÷ 100), where:

Desired Plant Population per square metre (# plants/m^2) = 50

1000 kernel weight (grams) equivalent to weight of seeds (g/1000 seeds) = 100 – 200

Seeds per kilogram (on average) (# seeds/kg) = 5000 – 10 000

4 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 27 Refined risk assessment for small-sized and medium-sized mammals for seed treatment end-use products

Effects Metric (mg a.i./kg bw/d)(1)		EDE (mg ai/kg bw/d)(2), (3)	RQ	Number of seeds needed to reach endpoint		Area required (m^2)			
						No Drilling		Precision drilling(4)	
				min	max	min	max	min	max
Small mammals (0.015 kg)									
Acute	200.00	72.56	0.1	82.50	111.00	1.19	2.63	238.10	526.32
Reproduction	43.00	72.56	**1.7**	7.10	9.55	0.10	0.23	20.48	45.26
Medium mammals (0.035 kg)									
Acute	200.00	62.40	0.1	192.50	259.00	2.78	6.14	555.56	1228.07
Reproduction	43.00	62.40	**1.5**	16.56	22.27	0.24	0.53	47.78	105.61

1 Uncertainty factors of 0.1 and 1 were applied to the acute oral and reproduction endpoints, respectively.
2 EDE = Estimated daily dietary exposure; is calculated using the following formula: (FIR/bw) × EEC, where:

FIR: Food Ingestion Rate (Nagy, 1987). For mammals, the "all mammals" equation was used: FIR (g dry weight/day) = 0.235 (bw in g) $^{0.822}$

3 The EECs from consumption of treated seeds was calculated based on a converted rate of 63 g a.i./ha per year, which was derived from the maximum application seeding rate 50 g a.i./100 kg seed. The conversion is calculated using the following formula: Application Rate (g a.i./ha) = Seeding Rate (kg seed/ha) × Seed Treatment Rate (g a.i./ kg seed). The seeding rate of soybean, which is the listed crop for seed treatment with cyclobutrifluram, was calculated using the following formula: Seeding Rate (kg seed/ha) = Desired Plant population (# plants /m^2) × 1,000 Kernel weight (g) ÷ Seedling Survival Rate (0.90) ÷ 100), where:

Desired Plant Population per square metre (# plants/m^2) = 50
1000 kernel weight (grams) equivalent to weight of seeds (g/1000 seeds) = 100 – 200
Seeds per kilogram (on average) (# seeds/kg) = 5000 – 10 000

4 The percentage of seeds remaining on the soil surface in field headlands was assumed to be dependent on the seeding method and the time of year in which seeding occurs (de Snoo and Luttik 2004). The following parameters for drilling practices were used: standard drilling – spring: 3.3%; standard drilling – fall: 9.2%; precision drilling: 0.5%.
5 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 28 Screening level risk assessment for non-target aquatic organisms

Organism	Exposure	Test substance	EEC[1]	Endpoint value[2]	UF	Effects metric	RQ[3]	LOC	LOC exceeded ?
Freshwater organisms									
Water flea (*Daphnia magna*)	48-h Acute (Static)	Cyclobutrifluram	0.0125 mg a.i./L	EC_{50} > 27 mg a.i./L	2	> 13.5 mg a.i./L	< 0.001	1	No
		SYN510275	0.006 mg/L	EC_{50} > 100 mg/L	2	> 50.0 mg/L	< 0.0001	1	No
	21-d Chronic (Static-renewal)	Cyclobutrifluram	0.0125 mg a.i./L	NOEC = 2.6 mg a.i./L	1	= 2.6 mg a.i./L	0.005	1	No
Amphipod (*Hyalella azteca*)	10-d Sediment (Intermittent-renewal)	Cyclobutrifluram	0.0125 mg a.i./L	NOEC = 7.7 mg a.i./L	1	= 7.7 mg a.i./L	0.002	1	No
Midge (*Chironomus dilutus*)	10-d Sediment (Intermittent-renewal)	Cyclobutrifluram	0.0125 mg a.i./L	NOEC = 2.0 mg a.i./L	1	= 2.0 mg a.i./L	0.006	1	No
Rainbow trout (*Oncorhynchus mykiss*)	96-h Acute (Static)	Cyclobutrifluram	0.0125 mg a.i./L	LC_{50} = 13 mg a.i./L	10	= 1.3 mg a.i./L	0.010	1	No
Common carp (*Cyprinus carpio*)	96h-Acute (Static)	Cyclobutrifluram	0.0125 mg a.i./L	LC_{50} > 19 mg a.i./L	10	> 1.9 mg a.i./L	< 0.007	1	No
Fathead minnow (*Pimephales promelas*)	96-h Acute (Static)	Cyclobutrifluram	0.0125 mg a.i./L	LC_{50} = 11 mg a.i./L	10	= 1.1 mg a.i./L	0.011	1	No
	96-h Acute (Static)	SYN510275	0.006 mg/L	LC_{50} > 100 mg/L	10	> 10 mg/L	< 0.001	1	No
	32-d Early life stage	Cyclobutrifluram	0.0125 mg a.i./L	NOEC = 1.9 mg a.i./L	1	= 1.9 mg a.i./L	0.007	1	No
Amphibians (fish endpoints	96-h Acute (Static; fathead	Cyclobutrifluram	0.0667 mg a.i./L	LC_{50} = 11 mg a.i./L	10	= 1.1 mg a.i./L	0.061	1	No

Organism	Exposure	Test substance	EEC[(1)]	Endpoint value[(2)]	UF	Effects metric	RQ[(3)]	LOC	LOC exceeded ?
used as a surrogate)	minnow surrogate)								
	32-d Early-life stage (fathead minnow surrogate)	Cyclobutrifluram	0.0667 mg a.i./L	NOEC = 1.9 mg a.i./L	1	= 1.9 mg a.i./L	0.035	1	No
Freshwater algae (*Anabaena flos-aquae*)	96-h Acute (Static)	Cyclobutrifluram	0.0125 mg a.i./L	EC_{50} > 24 mg a.i./L	2	> 12.0 mg a.i./L	< 0.001	1	No
Freshwater diatom (*Navicula pelliculosa*)	96-h Acute (Static)	Cyclobutrifluram	0.0125 mg a.i./L	EC_{50} >17 mg a.i./L	2	> 8.5 mg a.i./L	< 0.001	1	No
Freshwater algae (*Rhaphidocelis subcapitata*)	96-h Acute (Static)	Cyclobutrifluram	0.0125 mg a.i./L	EC_{50} = 6.4 mg a.i./L	2	= 3.2 mg a.i./L	0.004	1	No
	96-h Acute (Static)	SYN510275	0.006 mg/L	EC_{50} > 100 mg/L	2	> 50.0 mg/L	< 0.0001	1	No
Vascular plants (*Lemna gibba*)	7-d Growth inhibition (Static-renewal)	Cyclobutrifluram	0.0125 mg a.i./L	EC_{50} = 11 mg a.i./L	2	= 5.5 mg a.i./L	0.002	1	No
Marine organisms									
Saltwater mysid (*Americamysis bahia*)	96-h Acute (Static)	Cyclobutrifluram	0.0125 mg a.i./L	LC_{50} > 8.0 mg a.i./L	2	> 4.0 mg a.i./L	< 0.003	1	No
	28-d Chronic (Flow-through)	Cyclobutrifluram	0.0125 mg a.i./L	NOEC = 1.3 mg a.i./L	1	= 1.3 mg a.i./L	0.010	1	No
Eastern oyster (*Crassostrea virginica*)	96-h Acute (Flow-through)	Cyclobutrifluram	0.0125 mg a.i./L	IC_{50} = 0.33 mg a.i./L	2	= 0.165 mg a.i./L	0.076	1	No

Organism	Exposure	Test substance	EEC[1]	Endpoint value[2]	UF	Effects metric	RQ[3]	LOC	LOC exceeded ?
Amphipod (*Leptocheirus plumulosus*)	10-d Sediment (Intermittent-renewal)	Cyclobutrifluram	0.0125 mg a.i./L	NOEC = 4.5 mg a.i./L	1	= 4.5 mg a.i./L	0.003	1	No
Sheepshead minnow (*Cyprinodon variegatus*)	96-h Acute (Static)	Cyclobutrifluram	0.0125 mg a.i./L	LC_{50} > 18 mg a.i./L	10	> 1.8 mg a.i./L	< 0.007	1	No
	34-d Early life stage	Cyclobutrifluram	0.0125 mg a.i./L	NOEC = 0.43 mg a.i./L	1	= 0.43 mg a.i./L	0.029	1	No
Marine diatom (*Skeletonema costatum*)	96-h Acute (Static)	Cyclobutrifluram	0.0125 mg a.i./L	EC_{50} > 13 mg a.i./L	2	> 6.5 mg a.i./L	< 0.002	1	No

1 See Table 21 for a description of how the EECs were calculated.
2 The most sensitive acute endpoint (for example, EC_{50}/LC_{50}) was used when multiple values were available for a species.
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 29 Toxic substances management policy considerations-comparison to TSMP track 1 criteria

TSMP track 1 criterion	TSMP Track 1 criterion value		Cyclobutrifluram	SYN510275 (major TP)	TFA, CGA177291, EXC8199, SYN551231, SYN551241 (major TPs); SYN549104 (minor TP)
CEPA toxic or CEPA toxic equivalent[1]	Yes		Yes	Yes	Yes
Predominantly anthropogenic[2]	Yes		Yes	Yes	Yes
Persistence[3]:	Soil	Half-life ≥ 182 days	Yes, DT_{50} values range from 150 to 1097 days (aerobic soil) and 320 to 917 days (anaerobic soil)	No, DT_{50} values range from 53.1 to 246 days (aerobic soil)	Not available for major TPs SYN549104: No, DT_{50} values range from 26.0 to 88.1 days (aerobic soil)
	Water	Half-life ≥ 182 days	Yes, DT_{50} values range from 728 and 780 days (aerobic whole	Not available	Not available
	Sedime	Half-life			

TSMP track 1 criterion	TSMP Track 1 criterion value		Cyclobutrifluram	SYN510275 (major TP)	TFA, CGA177291, EXC8199, SYN551231, SYN551241 (major TPs); SYN549104 (minor TP)
	nt	≥ 365 days	systems) and 676 to 1230 days (anaerobic whole systems)		
	Air	Half-life ≥ 2 days, or evidence of atmospheric transport to remote regions such as the Arctic	Not determined. The AOPWIN (v1.92) model is not suited for predicting the atmospheric half-life of cyclobutrifluram given the large fraction expected to be sorbed to airborne particles.	Yes, the AOPWIN (v1.92) predicted half-life in the gas phase in the atmosphere is 210 days based on the hydroxyl (OH) radical reaction (1.5×10^6 molecules OH/cm^3) during 12 hours of daylight.	TFA, CGA177291, EXC8199: Yes, the AOPWIN (v1.92) predicted half-life in the gas phase in the atmosphere is as follows based on the hydroxyl (OH) radical reaction (1.5×10^6 molecules OH/cm^3) during 12 hours of daylight. TFA: 20.6 days CGA177291: 12.2 days EXC8199: 4.83 days SYN551231, SYN551241: No, the AOPWIN (v1.92) predicted half-life in the gas phase in the atmosphere is as follows based on the hydroxyl (OH) radical reaction (1.5×10^6 molecules OH/cm^3) during 12 hours of daylight. SYN551231: 0.676 days SYN551241: 0.393 days SYN549104: Not determined. The AOPWIN (v1.92) model is not suited for predicting the atmospheric half-life of SYN549104 given the large fraction expected to be sorbed to airborne particles.
Bioaccumulation[4]	Log K_{OW} ≥ 5		No, log K_{OW} = 3.2	No: KOWWIN (v1.68) predicted	TFA: No, KOWWIN (v1.68) predicted log K_{OW} = 0.5

TSMP track 1 criterion	TSMP Track 1 criterion value	Cyclobutrifluram	SYN510275 (major TP)	TFA, CGA177291, EXC8199, SYN551231, SYN551241 (major TPs); SYN549104 (minor TP)
			log K_{OW} = -0.22	CGA177291: No, KOWWIN (v1.68) predicted log K_{OW} = 2.82 EXC8199: No, KOWWIN (v1.68) predicted log K_{OW} = 2.72 SYN551231: No, KOWWIN (v1.68) predicted log K_{OW} = 1.33 SYN551241: No, KOWWIN (v1.68) predicted log K_{OW} = 4.18 SYN549104: No, KOWWIN (v1.68) predicted log K_{OW} = 3.69
	BCF ≥ 5000	No, BCF = 42	Not required	Not required
	BAF ≥ 5000	Not available	Not available	Not available
Is the chemical a TSMP Track 1 substance (all four criteria must be met)?		No, does not meet all of TSMP Track 1 criteria.	No, does not meet all of TSMP Track 1 criteria.	No, do not meet all of 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.

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

Cyclobutrifluram is an active ingredient that is concurrently being registered in Canada and the United States for use as a seed treatment on soybean seed and as an at-plant in-furrow treatment on Romaine lettuce. The MRLs proposed for cyclobutrifluram in Canada are different from the corresponding proposed tolerances to be promulgated in the United States.

Once established, the U.S. tolerances for cyclobutrifluram will be listed in the Electronic Code of Federal Regulations, 40 CFR Part 180, by pesticide.

Currently, there are no Codex MRLs[10] listed for cyclobutrifluram in or on any commodity on the Codex Alimentarius Pesticide Index website.

Table 1 compares the MRLs proposed for cyclobutrifluram in Canada with corresponding U.S. tolerances and Codex MRLs.

Table 1 Comparison of Proposed Canadian MRLs, U.S. Tolerances and Codex MRLs (where different)

Food Commodity	Proposed Canadian MRLs (ppm)	Proposed U.S. Tolerances (ppm)	Codex MRL (ppm)
Soybean	0.01 in/on Dry soybean seed	0.03 in/on Soybean seed	Not established
Romaine lettuce	0.03 in/on Leaf lettuce	0.06 in/on Lettuce, leaf	
Eggs; Fat, meat and meat byproducts of cattle, goats, hogs, horses, poultry and sheep; milk	0.02	None	

For cyclobutrifluram, the differences between the proposed Canadian MRLs and the U.S. tolerances are due to the difference in the residue definition for enforcement in plants; in Canada, the residue definition is cyclobutrifluram *per se*, while in the U.S., the residue definition is cyclobutrifluram and the metabolite SYN510275.

[10] 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
3334682	2022, Confidential Business Information Cyclobutrifluram Technical (SYN549522) 2.11.2, DACO: 2.11.2 CBI
3334683	2022, Confidential Business Information Cyclobutrifluram Technical (SYN549522) 2.13.2, DACO: 2.13.2 CBI
3334684	2022, Confidential Business Information Cyclobutrifluram Technical (SYN549522) 2.13.3, DACO: 2.13.3 CBI
3446825	2023, Confidential Business Information Cyclobutrifluram, DACO: 2.11.3, 2.12, 2.13.2 CBI
3451837	2023, Confidential Business Information Cyclobutrifluram - Reg. No. Pending, DACO: 2.13.2 CBI
3273055	2021, A22011B - Manufacturing Process Description and Supporting Data, DACO: 0.8.11,0.8.12,0.9.1, 3.1.1, 3.1.2, 3.1.3, 3.1.4, 3.2.1, 3.2.2, 3.2.3, 3.3.1, 3.3.2, 3.4.1, 3.4.2, 3.5.4, Document H, Document J, IIIA 1.1, IIIA 1.2.1, IIIA 1.2.3, IIIA 1.3, IIIA 1.4.2, IIIA 1.4.3.3, IIIA 1.4.4, IIIA 1.4.5.1, IIIA 1.4.5.2, IIIA 1.5, IIIA 5.2.1, IIIA 5.2.2, IIIA 5.2.4 CBI
3273057	2021, A22011B - Physical and Chemical Properties, DACO: 12.7, 3.5.1, 3.5.10, 3.5.11, 3.5.12, 3.5.13, 3.5.14, 3.5.15, 3.5.2, 3.5.3, 3.5.4, 3.5.5, 3.5.6, 3.5.7, 3.5.8, 3.5.9,5.2,Document M, IIIA 1.5, IIIA 2.1, IIIA 2.11, IIIA 2.12, IIIA 2.13, IIIA 2.14, IIIA 2.2.1, IIIA 2.2.2, IIIA 2.3.1, IIIA 2.3.2, IIIA 2.3.3, IIIA 2.4.1, IIIA 2.4.2, IIIA 2.5.1, IIIA 2.5.2, IIIA 2.6.1, IIIA 2.6.2, IIIA 2.7.1, IIIA 2.7.2, IIIA 2.7.3, IIIA 2.7.4, IIIA 2.7.5, IIIA 2.7.6, IIIA 4.1.1, IIIA 4.1.3
3273263	2021, A22417C - Manufacturing Process Description and Supporting Data, DACO: 0.8.11,0.8.12,0.9.1, 3.1.1, 3.1.2, 3.1.3, 3.1.4, 3.2.1, 3.2.2, 3.2.3, 3.3.1, 3.3.2, 3.4.1, 3.4.2, 3.5.4,Document H, Document J, IIIA 1.1, IIIA 1.2.1, IIIA 1.2.3, IIIA 1.3, IIIA 1.4.2, IIIA 1.4.3.3, IIIA 1.4.4, IIIA 1.4.5.1, IIIA 1.4.5.2, IIIA 1.5, IIIA 5.2.1, IIIA 5.2.2, IIIA 5.2.4 CBI
3273270	2021, A22417C - Physical and Chemical Properties, DACO: 12.7, 3.5.1, 3.5.10, 3.5.11, 3.5.12, 3.5.13, 3.5.14, 3.5.15, 3.5.2, 3.5.3, 3.5.4, 3.5.5, 3.5.6, 3.5.7, 3.5.8, 3.5.9,5.2,Document M, IIIA 1.5, IIIA 2.1, IIIA 2.11, IIIA 2.12, IIIA 2.13, IIIA 2.14, IIIA 2.2.1, IIIA 2.2.2, IIIA 2.3.1, IIIA 2.3.2, IIIA 2.3.3, IIIA 2.4.1, IIIA 2.4.2, IIIA 2.5.1, IIIA 2.5.2, IIIA 2.6.1, IIIA 2.6.2, IIIA 2.7.1, IIIA 2.7.2, IIIA 2.7.3, IIIA 2.7.4, IIIA 2.7.5, IIIA 2.7.6, IIIA 4.1.1, IIIA 4.1.3
3273380	2021, A23156A - Manufacturing Process Description and Supporting Data, DACO: 0.8.11,0.8.12,0.9.1, 3.1.1, 3.1.2, 3.1.3, 3.1.4, 3.2.1, 3.2.2, 3.2.3, 3.3.1, 3.3.2, 3.4.1, 3.4.2, 3.5.4,Document H, Document J, IIIA 1.1, IIIA 1.2.1, IIIA 1.2.3, IIIA 1.3, IIIA 1.4.2, IIIA 1.4.3.3, IIIA 1.4.4, IIIA 1.4.5.1, IIIA 1.4.5.2, IIIA 1.5, IIIA 5.2.1, IIIA 5.2.2, IIIA 5.2.4 CBI

3273383 2021, A23156A - Physical and Chemical Properties, DACO: 12.7, 3.5.1, 3.5.10, 3.5.11, 3.5.12, 3.5.13, 3.5.14, 3.5.15, 3.5.2, 3.5.3, 3.5.4, 3.5.5, 3.5.6, 3.5.7, 3.5.8, 3.5.9,5.2,Document M, IIIA 1.5, IIIA 2.1, IIIA 2.11, IIIA 2.12, IIIA 2.13, IIIA 2.14, IIIA 2.2.1, IIIA 2.2.2, IIIA 2.3.1, IIIA 2.3.2, IIIA 2.3.3, IIIA 2.4.1, IIIA 2.4.2, IIIA 2.5.1, IIIA 2.5.2, IIIA 2.6.1, IIIA 2.6.2, IIIA 2.7.1, IIIA 2.7.2, IIIA 2.7.3, IIIA 2.7.4, IIIA 2.7.5, IIIA 2.7.6, IIIA 4.1.1, IIIA 4.1.3

3273095 2021, Cyclobutrifluram Technical (SYN549522) - Manufacturing Process Description and Supporting Data, DACO: 0.8.11,0.8.12,0.9.1,2.1,2.11.1,2.11.2,2.11.3,2.11.4,2.12.1,2.12.2,2.13.1,2.13.2,2.13.3, 2.13.4,2.14.12,2.15,2.2,2.3,2.3.1,2.4,2.5,2.6,2.7,2.8,2.9,Document H, Document J,IIA 1.1,IIA 1.10.2,IIA 1.11.1,IIA 1.11.2,IIA 1.2,IIA 1.3,IIA 1.4,IIA 1.5.1,IIA 1.5.2,IIA 1.6,IIA 1.7,IIA 1.8.1,IIA 1.8.2,IIA 1.9.1,IIA 1.9.2,IIA 2.5.1.1,IIA 2.5.1.2,IIA 2.5.1.3,IIA 2.5.1.4,IIA 2.5.1.5,IIA 2.5.1.6,IIA 2.5.2,IIA 4.1.3,IIA 4.2.1,IIA 4.2.3 CBI

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2.0 Human and animal health

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3273074	2018, SYN549522 SC (A22011B) - In Vitro Skin Irritation Test in the EPISKIN Model, DACO: 4.6.5,IIIA 7.1.4
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4.0 Value

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B. Additional information considered

i) Published information

1.0 Human and animal health

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ii) Unpublished information

2.0 Environment

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