Proposed Registration Decision PRD2025-11

Isocycloseram, VANECTO COCKROACH GEL BAIT, EQUENTO and A23128 ST

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Overview

Proposed Registration Decision for Isocycloseram

Health Canada's Pest Management Regulatory Agency (PMRA), under the authority of the *Pest Control Products Act*, is proposing registration for the sale and use of Isocycloseram Technical, VANECTO COCKROACH GEL BAIT, EQUENTO and A23128 ST, containing the active ingredient isocycloseram. VANECTO COCKROACH GEL BAIT is for the control of cockroaches in commercial, industrial and residential buildings and other listed structures. EQUENTO is a seed treatment product for the control of insect pests on wheat, oat, barley, rye and triticale. A23128 ST, also containing active ingredients difenoconazole, sedaxane, metalaxyl-M (and S-isomer) and fludioxonil, is another seed treatment product for the control of insect pests and the control or suppression of seed-borne and soil-borne diseases on wheat, oat, barley, rye and triticale.

Difenoconazole is currently registered for the control of a wide range of fungal diseases on diverse field crops, fruits and vegetables, and turf as a foliar spray, post-harvest spray and as a seed treatment. For details, see Proposed Re-evaluation Decision PRVD2021-06, *Difenoconazole and Its Associated End-use Products*, and Re-evaluation Decision RVD2022-05, *Difenoconazole and Its Associated End-use Products*.

Sedaxane is currently registered for the control or suppression of soil- and seed-borne diseases of seedlings and mature plants. For details, see Proposed Registration Decision PRD2015-03, *Sedaxane*, and Registration Decision RD2015-10, *Sedaxane*.

Metalaxyl-M is currently registered for the control of plant diseases caused by water-mould fungi in field and greenhouse food and feed crops (including seed treatment) as well as nursery outdoor and greenhouse non-food crops (including conifers, ornamentals and turf). For details, see Proposed Re-evaluation Decision PRVD2007-10, *Metalaxyl-and Metalaxyl-M*, and Re-evaluation Decision RVD2008-03, *Metalaxyl-and Metalaxyl-M*.

Fludioxonil is currently registered as a seed treatment, a foliar spray and a post-harvest dip to control fungal pathogens on a large number of crops. For details, see Proposed Re-evaluation Decision PRVD2016-03, *Fludioxonil*, and Re-evaluation Decision RVD2018-04, *Fludioxonil and Its Associated End-use Products*.

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 isocycloseram, VANECTO COCKROACH GEL BAIT, EQUENTO and A23128 ST.

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 Canada.ca.

Before making a final registration decision on isocycloseram, VANECTO COCKROACH GEL BAIT, EQUENTO and A23128 ST, Health Canada's PMRA will consider any written comments received from the public directly related to the proposed decision in this consultation document.[3] Health Canada will then publish a Registration Decision[4] on isocycloseram, VANECTO COCKROACH GEL BAIT, EQUENTO and A23128 ST, 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 isocycloseram?

Isocycloseram is a new conventional chemical insecticide that targets the nervous system of insects and mites on contact and through ingestion. It is effective against agricultural pests when applied as a seed treatment. When formulated as a gel bait, it is effective against cockroaches in and around commercial, industrial and residential structures.

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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*.

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

Health considerations

Can approved uses of isocycloseram affect human health?

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

Potential exposure to isocycloseram may occur through the diet (food and drinking water), when handling and applying the end-use products, when coming into contact with treated surfaces, or when handling and planting treated seed. 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, Isocycloseram Technical, was of low acute toxicity by the oral, dermal and inhalation routes of exposure. Isocycloseram was non-irritating to the eyes and skin but caused an allergic skin reaction. Consequently, the hazard statement “POTENTIAL SKIN SENSITIZER” is required on the label.

The end-use product, VANECTO COCKROACH GEL BAIT, containing isocycloseram, was of low acute toxicity by the oral route of exposure. It was also classified as being of low acute toxicity by the dermal and inhalation routes. In laboratory animals, it was minimally irritating to the eyes and skin and did not cause an allergic skin reaction.

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

The end-use product, A23128 ST, containing isocycloseram, sedaxane, difenoconazole, metalaxyl-M (and S-isomer), and fludioxonil, was of low acute toxicity by the oral and inhalation routes of exposure. It was also classified as being of low acute toxicity via the dermal route. In laboratory animals, it was minimally irritating to the eyes and skin and did not cause an allergic skin reaction.

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 isocycloseram 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, altered fetal development, and reduced survival of the

young. There was no evidence to suggest that isocycloseram damaged genetic material. An increase in ovarian tumours in female mice and testicular tumours in male rats could not clearly be attributed to treatment with isocycloseram. There was an indication that the young were more sensitive than the adult animal. The risk assessment protects against the effects noted above and other potential effects by ensuring that the level of exposure to humans is well below the lowest dose level at which these effects occurred in animal tests.

Occupational risks from handling VANECTO COCKROACH GEL BAIT

Occupational risks are not of health concern when VANECTO COCKROACH GEL BAIT is used according to the proposed label directions, which include protective measures.

Pest control operators (PCOs) applying VANECTO COCKROACH GEL BAIT can come in direct contact with isocycloseram residues on the skin. Therefore, the label specifies that for VANECTO COCKROACH GEL BAIT, workers must wear a long-sleeved shirt, long pants, chemical-resistant gloves, socks and shoes during application, clean-up and repair. For PCOs re-entering areas treated with VANECTO COCKROACH GEL BAIT, exposure and risk is considered negligible given the short exposure durations and limited dermal contact with treated surfaces.

Taking into consideration the label statements, and the duration of exposure for handlers, the risks from exposure to VANECTO COCKROACH GEL BAIT are not of health concern when the end-use product is used according to the proposed label directions.

Occupational risks from handling EQUENTO and A23128 ST

Occupational risks are not of health concern when EQUENTO and A23128 ST are used according to the proposed label directions, which include protective measures.

Workers in commercial facilities (and mobile treaters) mixing, loading, calibrating and treating cereal seeds (wheat (spring/winter/durum), barley, oats, rye, and triticale) with EQUENTO and A23128 ST, and those involved in cleaning, repair, bagging, sewing and stacking bags of treated seed and driving a forklift can come in direct contact with isocycloseram residues on the skin and through inhalation. Therefore, these workers must wear the personal protective equipment and comply with the engineering controls specified in Appendix I, Tables 1a and 1b.

Farmers treating and planting cereal seeds and farmers planting commercially treated cereal seeds may also come in direct contact with isocycloseram through direct skin contact or inhalation. Therefore, farmers must also wear the personal protective equipment and comply with the engineering controls specified in Appendix I, Tables 1a and 1b.

Taking into consideration the label statements and the durations of exposure for all workers, the risks from exposure to EQUENTO and A23128 ST are not of health concern when they are used according to the proposed label directions.

Health risks in residential and other non-occupational environments

VANECTO COCKROACH GEL BAIT

Risks in residential and other non-occupational environments are not of health concern when VANECTO COCKROACH GEL BAIT is used according to the proposed label directions.

EQUENTO and A23128 ST

EQUENTO and A23128 ST are not domestic class products and are not permitted for use in residential settings or other non-occupational environments. Therefore, risks in residential and other non-occupational environments are not of health concern when used according to the proposed label directions.

Health Risks to bystanders

VANECTO COCKROACH GEL BAIT

Bystander risks are not of health concern when VANECTO COCKROACH GEL BAIT is used according to the proposed label directions.

EQUENTO and A23128 ST

Bystander risks are not of health concern when EQUENTO and A23128 ST are used according to the proposed label directions and when spray drift restrictions are observed.

Residue in food and drinking water

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

Aggregate acute dietary (food plus drinking water) intake estimates indicated that all population subgroups including females 13–49 years of age are exposed to less than 10% of the acute reference doses, and therefore are not of health concern.

Aggregate chronic dietary (food plus drinking water) intake estimates indicated that the general population and all population subgroups are exposed to less than 8% of the acceptable daily intake (ADI), and therefore are not of health concern.

The *Food and Drugs Act* prohibits the sale of adulterated food, that is, food containing a pesticide residue that exceeds the established maximum residue limit (MRL). Pesticide MRLs are established for *Food and Drugs Act* purposes through the evaluation of scientific data under the *Pest Control Products Act*. Given that dietary risks from the consumption of foods are shown to be acceptable when isocycloseram is used according to the supported label directions, MRLs are being proposed as a result of this assessment (refer to PMRL2025-21, *Isocycloseram*).

MRLs for isocycloseram determined from the residue trials conducted throughout Canada and the United States can be found in the Science Evaluation of this document.

One of the isocycloseram products proposed for use as a seed treatment on small grain cereals is also formulated with the active ingredients difenoconazole, fludioxonil, sedaxane, and metalaxyl-M (and S-isomer). These active ingredients are already registered for these uses in Canada, and residues in treated commodities will be covered under the existing MRLs for each active ingredient.

Environmental considerations

What happens when isocycloseram is introduced into the environment?

When isocycloseram is used according to the label directions, the risks to the environment are acceptable for use as a structural cockroach bait and as a seed treatment.

The use of isocycloseram as a cockroach bait is expected to result in limited environmental exposure. Isocycloseram enters the environment when it is applied as a seed treatment. Isocycloseram may remain in soil for long periods of time. Isocycloseram has limited ability to move downward in the soil; however, given that it may remain in the soil for long periods of time, isocycloseram may reach groundwater. Isocycloseram has the potential to runoff into aquatic habitats. In water, isocycloseram is expected to move to sediment, where it remains for short to long periods of time depending on the type of water/sediment system and environmental conditions. Isocycloseram is not expected to build-up in the tissues of plants or animals.

When used in accordance with the label directions as a cockroach bait or seed treatment, isocycloseram poses acceptable risk to terrestrial and aquatic organisms when required risk-reduction measures are applied.

Value considerations

What is the value of VANECTO COCKROACH GEL BAIT?

VANECTO COCKROACH GEL BAIT provides a new mode of action for use in controlling cockroaches indoors or outdoors via spot, crack and crevice or void space applications.

Cockroaches can infest commercial, industrial and residential areas. VANECTO COCKROACH GEL BAIT has been demonstrated to provide control of cockroaches and will provide a new mode of action for cockroach management, which may reduce the risk of resistance development.

What is the value of EQUENTO and A23128 ST?

The seed treatment products EQUENTO and A23128 ST control wireworms, European chafer and June beetles on wheat, oat, barley, rye and triticale seedlings. Both products provide a new mode of action for June beetles.

Wireworm, European chafer and June beetle infestations can reduce the plant stand of small grain cereal crops by destroying seedlings and, under high pest pressure, may result in crop

failure. EQUENTO and A23128 ST reduced soil infestations of these pests by over 80% and significantly, and often strongly, increased plant stand, vigour and yield. A23128 ST also contains a suite of four fungicides (difenoconazole, sedaxane, metalaxyl-M (and S-isomer) and fludioxonil) that protect seedlings from common seed- and soil-borne diseases.

Measures to minimize risk

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

The key risk-reduction measures being proposed on the labels of Isocycloseram Technical, VANECTO COCKROACH GEL BAIT, EQUENTO, and A23128 ST to address the potential risks identified in this assessment are as follows.

Key risk-reduction measures for VANECTO COCKROACH GEL BAIT

Human health

To reduce the potential exposure of workers to isocycloseram through direct skin contact or inhalation, workers applying VANECTO COCKROACH GEL BAIT must wear a long-sleeved shirt, long pants, chemical-resistant gloves, socks and shoes during application, clean-up and repair. The label also requires that VANECTO COCKROACH GEL BAIT only be applied by individuals holding an appropriate pesticide applicator certificate or license recognized by the provincial/territorial pesticide regulatory agency where the application occurs. In addition, the label states that care should be taken to avoid the pesticide exiting the void, and any residue deposits on non-target surfaces must be removed by the applicator.

Environment

- Precautionary label statements indicating toxicity to aquatic organisms.

Key risk-reduction measures for EQUENTO and A23128 ST

Human health

To reduce the potential exposure to isocycloseram through direct skin contact or inhalation of sprays, the EQUENTO and A23128 ST labels specify that workers in commercial facilities (and mobile treaters) mixing, loading, calibrating and treating cereal seeds (wheat (spring/winter/durum), barley, oats, rye, and triticale), and those involved in cleaning, repair, bagging, sewing and stacking bags of treated seed and driving a forklift must wear the personal protective equipment and comply with the engineering controls specified in Appendix I, Tables 1a and 1b.

Farmers treating and planting cereal seeds and farmers planting commercially treated cereal seeds may also come into contact with isocycloseram through direct skin contact or inhalation. Therefore, farmers must also wear the personal protective equipment and comply with the engineering controls specified in Appendix I, Tables 1a and 1b.

Furthermore, a standard label statement to protect against drift during application is present on the labels.

Environment

- Precautionary label statements indicating toxicity to aquatic organisms, bees, birds and small-sized mammals.
- Label statements indicating that any spilled or exposed seeds must be incorporated into the soil or otherwise cleaned-up from the soil surface.
- Best management practice label statements to reduce runoff entering sensitive aquatic habitats.
- Best management practice label statements to minimize bee exposure to dust during planting of treated seed.
- Precautionary label statements to indicate leaching to groundwater is possible.

Next steps

Before making a final registration decision on isocycloseram, VANECTO COCKROACH GEL BAIT, EQUENTO and A23128 ST, 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 (9 October 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 Publications (contact information on the cover page of this document). 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

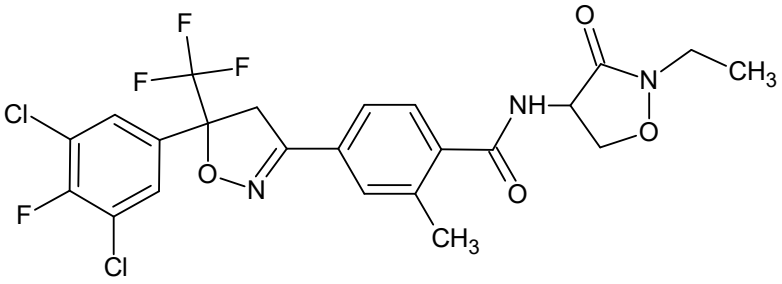
When Health Canada makes its registration decision, it will publish a Registration Decision on isocycloseram, VANECTO COCKROACH GEL BAIT, EQUENTO and A23128 ST (based on the Science Evaluation of this consultation document). In addition, the test data referenced in this consultation document will be available for public inspection, upon application, in the PMRA's Reading Room. For more information, please contact the PMRA's Pest Management Information Service.

Science evaluation

Isocycloseram, VANECTO COCKROACH GEL BAIT, EQUENTO and A23128 ST

1.0 The active ingredient, its properties and uses

1.1 Identity of the active ingredient

Active substance	Isocycloseram
Function	Insecticide
Chemical name	
1. International Union of Pure and Applied Chemistry (IUPAC)	mixture comprised of 80–100% 4-[(5*S*)-5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl]-*N*-[(4*R*)-2-ethyl-3-oxoisoxazolidin-4-yl]-2-methylbenzamide and 20–0% of the (5*R*,4*R*), (5*R*,4*S*) and (5*S*,4*S*) isomers
2. Chemical Abstracts Service (CAS)	4-[5-(3,5-dichloro-4-fluorophenyl)-4,5-dihydro-5-(trifluoromethyl)-3-isoxazolyl]-*N*-(2-ethyl-3-oxo-4-isoxazolidinyl)-2-methylbenzamide
CAS number	2061933-85-3
Molecular formula	$C_{23}H_{19}Cl_2F_4N_3O_4$
Molecular weight	548.3
Structural formula	
Purity of the active ingredient	98 %

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

Technical product—Isocycloseram Technical

Property	Result
Colour and physical state	White crystalline solid
Odour	Sweetish
Melting range	135.3°C
Boiling point or range	Not required for a solid
Density	1.53 g/cm^3 at 20°C
Vapour pressure	<6.2 × 10^{-6} Pa at 25°C
Ultraviolet (UV)-visible spectrum	1) Methanol (neutral solution) λ_{max} (nm) — ε (L/(mol cm)) 265 — 2.50 × 10^4 2) Methanol (acidic solution) λ_{max} (nm) — ε (L/(mol cm)) 265 — 2.26 × 10^4 3) Methanol (basic solution) λ_{max} (nm) — ε (L/(mol cm)) 265 — 2.24 × 10^4 No absorption observed above 340 nm
Solubility in water at 20°C	1.2 mg/L
Solubility in organic solvents at 25°C	Solvent — Solubility (g/L) dichloromethane — 400 acetone — 270 ethyl acetate — 190 methanol — 75 toluene — 33 n-hexane — 39 n-octanol — 17
n-Octanol-water partition coefficient (K_{ow})	log K_{ow} = 4.9 at 20°C
Dissociation constant (pK_a)	No dissociable protons in the pH range of 2–12
Stability (temperature, metal)	Stable when stored in contact with metals (Fe and Al) and metal salts (Fe(II) acetate and Al(III)acetate) at 40°C for 14 days

End-use product—VANECTO COCKROACH GEL BAIT

Property	Result
Colour	Beige
Odour	Sweetish
Physical state	Solid (paste)
Formulation type	PA (paste)
Label concentration	Isocycloseram 1.0 %
Container material and description	Plastic syringe (1 to 1000 g)
Density	1.134 g/cm^3 at 20°C
pH of 1% dispersion in water	5.24
Oxidizing or reducing action	Not an oxidizing substance. Incompatible with strong oxidizers.
Storage stability	Stable in commercial packaging for 14 days at 54°C
Corrosion characteristics	Not corrosive to commercial packaging
Explodability	Not an explosive substance

End-use product—EQUENTO

Property	Result
Colour	Red
Odour	Sweetish
Physical state	Liquid
Formulation type	SU (suspension)
Label concentration	Isocycloseram 100 g/L
Container material and description	Plastic jug or tote, 1 to 1050 L
Density	1.074 g/cm^3 at 20°C
pH of 1% dispersion in water	5.1
Oxidizing or reducing action	Not an oxidizing substance. Incompatible with strong oxidizers.
Storage stability	Stable in commercial packaging for 14 days at 54°C
Corrosion characteristics	Not corrosive to commercial packaging
Explodability	Not an explosive substance

End-use product—A23128 ST

Property	Result
Colour	Red
Odour	Aromatic

Property	Result
Physical state	Liquid
Formulation type	SU (suspension)
Label concentration	Difenoconazole 36.8 g/L Isocycloseram 15.4 g/L Sedaxane 15.4 g/L Metalaxyl-M (and S isomer) 9.2 g/L Fludioxonil 7.6 g/L
Container material and description	Plastic jug or tote (1 to 1050 L)
Density	1.045 g/cm^3 at 20°C
pH of 1% dispersion in water	6.68
Oxidizing or reducing action	Not an oxidizing substance. Incompatible with strong oxidizers.
Storage stability	Stable in commercial packaging for 14 days at 54°C
Corrosion characteristics	Not corrosive to commercial packaging
Explodability	Not an explosive substance

1.3 Directions for use

VANECTO COCKROACH GEL BAIT

VANECTO COCKROACH GEL BAIT is a paste containing 1.0% isocycloseram and is applied in commercial, industrial and residential areas as a crack and crevice, spot or void application at 1–3 spots (0.5 g–1.5 g product, 0.005–0.015 g a.i.) per m^2 of treated area for light to moderate infestations of cockroaches, or at 3–4 spots (1.5–2.0 g product, 0.015–0.02 g a.i.) per m^2 for heavy infestations of cockroaches. The product is to be re-applied as the bait is consumed or spoiled if the pest problem persists or re-occurs. For indoor applications, the product is to be applied along cracks and crevices or into voids where cockroaches may find harborage. For outdoor applications to the exterior surfaces of buildings and other structures, the product is to be applied at pest entry sites or to other structures acting as a cockroach harborage within 1 m of a building or structure.

EQUENTO and A23128 ST

EQUENTO and A23128 ST are seed treatments applied to seed with commercial or on-farm seed treatment equipment prior to planting.

EQUENTO is a suspension formulation containing 100 g/L isocycloseram. It is applied to wheat, oat, barley, rye and triticale seed at a rate range of 25–75 mL product (2.5 g–7.5 g a.i.) per 100 kg seed for use against wireworms and at 50–75 mL product (5.0 g–7.5 g a.i.) per 100 kg seed for use against European chafers and June beetles. The higher rate is used when high pest pressures are anticipated.

A23128 ST is a suspension formulation containing 15.4 g/L isocycloseram (ICS) as well as the fungicides difenoconazole (DFZ, 36.8 g/L), sedaxane (SDX, 15.4 g/L), metalaxyl-M (and S-isomer) (MFN, 9.2 g/L) and fludioxonil (FLD, 7.6 g/L). A23128 ST is applied to wheat, oat, barley, rye and triticale seed at a rate of 325 mL product (5 g ICS + 12 g DFZ + 5 g SDX + 3 g MFN + 2.5 g FLD) per 100 kg seed to control moderate wireworm, European chafer and June beetle infestations and to control or suppress a suite of common seed- and soil-borne seedling diseases. When high wireworm, European chafer and/or June beetle pest pressures are anticipated, 325 mL of A23128 ST (5.0 g ICS) per 100 kg seed may be tank mixed with 25 mL of EQUENTO (2.5 g ICS) per 100 kg seed to provide a total of 7.5 g ICS per 100 kg seed.

1.4 Mode of action

Isocycloseram is an Insecticide Resistance Action Committee (IRAC) Mode of Action Group 30 insecticide and miticide that blocks inhibitory neurotransmission by binding to gamma-aminobutyric acid (GABA) receptors, resulting in lethal hyperexcitation. Isocycloseram is effective on contact and through ingestion. It does not have systemic activity in plants.

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 Methods for formulation analysis

The methods provided for the analysis of the active ingredients in the formulations have been validated and assessed to be acceptable for use as enforcement analytical methods.

2.3 Methods for residue analysis

High-performance liquid chromatography methods with tandem mass spectrometry (HPLC-MS/MS) were developed and proposed for data generation and enforcement purposes. These methods fulfilled the requirements with regards to selectivity, accuracy and precision at the respective method limit of quantitation. Acceptable recoveries (70–120%) were obtained in environmental media. Methods for residue analysis in environmental media are summarized in Appendix I, Table 2a.

High performance liquid chromatography methods with tandem mass spectrometric detection (HPLC-MS/MS; QuEChERS multiresidue method (EN15662:2009 in plant and animal matrices)) were developed and proposed for enforcement purposes. Several data gathering methods were used to quantify residues of isocycloseram in animal matrices, plant crop matrices, and processed fractions. 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. Adequate extraction efficiencies were demonstrated using radiolabeled samples from primary crop

metabolism studies (mustard greens, soybeans, tomatoes, and paddy rice), confined rotational crop studies (immature lettuce, wheat forage and straw, radish root and leaves), laying hen matrices (liver, muscle, fat, and egg yolk) and lactating goat matrices (liver, kidney, and milk) analyzed with the enforcement method. Methods for residue analysis in plant and animal matrices are summarized in Appendix I, Table 2b.

3.0 Impact on human and animal health

3.1 Hazard assessment

3.1.1 Toxicology summary

Isocycloseram, also identified as SYN547407, is an isoxazoline insecticide. The pesticidal mode of action (MOA) of isocycloseram involves modulation of the gamma-aminobutyric acid (GABA)-gated chloride channel by allosterically blocking the GABA-activated chloride channel, causing hyperexcitation and convulsions in insects.

A detailed review of the toxicology database for isocycloseram was conducted. The database is complete, consisting of the full array of toxicity studies currently required for hazard assessment purposes. Additional studies included an in vitro airway irritation study, genotoxicity studies on a metabolite of isocycloseram and a repeat-dose oral (dietary) toxicity study designed to compare the relative toxicities of the four main isomers of isocycloseram. 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 relevant scientific information found in the published literature. Overall, the scientific quality of the data is acceptable and the database is considered adequate to characterize the potential health hazards associated with isocycloseram.

The absorption, distribution, metabolism, and excretion profile of isocycloseram was investigated in rats. The toxicokinetic profile of isocycloseram following repeat gavage, dietary or capsule dosing in rats, mice, rabbits and dogs was also determined. In addition, intravenous (i.v.) administration of radiolabeled isocycloseram and subsequent measurement in blood and excreta was used to establish oral bioavailability or oral absorption in rats.

Following the administration of a single low or high oral gavage dose of isocycloseram radiolabeled at the methylphenyl ring, halophenyl ring, or oxoisoxazolidinyl ring, studies in bile duct-cannulated (BDC) and intact rats showed that isocycloseram was quickly and extensively absorbed following the administration of a single low or high oral dose. Following a single low dose, the oral absorption was approximately 96–100%, suggesting absorption was complete. Absorption decreased slightly to 88% after a single high dose. In both sexes of BDC rats, absorption at 72 hours following a single low or high dose was estimated to be approximately 67% and 52%, respectively, of the administered dose (AD) based on the sum of radioactivity quantified in bile, urine, tissues (excluding the gastrointestinal tract), and carcass. Oral and i.v. dosing gave similar area under the curve (AUC) values, with unchanged isocycloseram accounting for less than 3.5% of the dose in excreta of intact or BDC rats.

The time to peak plasma concentration was 6 to 8 hours at the low dose and 4 to 12 hours at the high dose following the administration of isocycloseram radiolabeled at the methylphenyl ring. Isocycloseram was widely distributed, with the highest residues found in the kidney, liver, and adrenal glands. The pattern of tissue distribution was similar between sexes for both dose levels, irrespective of radiolabel position; however, time to peak tissue levels varied, with maximum levels occurring 8 and 4 hours following the administration of the low- and high-dose levels, respectively.

Elimination of orally administered isocycloseram was fairly rapid following administration of all radiolabels, with the majority being eliminated in the feces for intact rats or in the bile for BDC rats. Excretion patterns were similar between sexes, irrespective of dose or radiolabel.

Isocycloseram was extensively metabolized in rats and the metabolite profile was similar between sexes, irrespective of dose level, single or repeat dose, or radiolabel position. Unchanged isocycloseram was a minor component in the feces. In intact rats given the methylphenyl radiolabel, SYN549436 was the largest circulating metabolite in the plasma accounting for approximately 57-80% of the total radioactivity in both sexes and was excreted into feces via the bile, with approximately 2–4% of the AD in bile. The glucuronide conjugate of SYN549436 additionally accounted for up to 6% of the AD in bile. Other metabolites accounting for more than 5% of the AD in bile were SYN549543 and SYN549432 glucuronide. The major metabolic reactions of isocycloseram involve de-ethylation and subsequent opening of the oxazolidinone ring with hydrolysis of the amide group, opening of the isoxazole ring, oxidative defluorination, cleavage of the isoxazole and oxazolidinone ring with oxidative defluorination, reduction of the cleaved isoxazole ring, loss of the oxazolidinone ring followed by cleavage of the isoxazole ring, and glucuronic acid conjugation.

A study was conducted to assess in vitro metabolism of isocycloseram radiolabeled on the methylphenyl, halophenyl, and oxoisoxazolidinyl rings in rat and human liver microsomes following incubation for 60 minutes. A total of 10 metabolites were detected, with similar metabolites identified following dosing with all three radiolabels suggesting that cleavage between the different rings likely did not occur. Metabolism was considered moderate, with unchanged isocycloseram accounting for 79–80% and 86–87% of the radioactive residues in the cultures using human and rat liver microsomes, respectively. The same major metabolite was observed in both the human and rat liver microsomes. Overall, it was concluded that isocycloseram was metabolized in both the human and rat liver microsomes and the metabolic composition was similar in both species.

Plasma levels of isocycloseram were measured in repeat-dose oral toxicity studies in mice, rats, and dogs. In mice, blood concentrations generally increased in a dose-proportional manner with no consistent differences in concentration between sexes following 28 days of dosing. Following 90 days of dosing in mice, concentrations in males were lower on days 28 and 85 relative to day 2, while concentrations in females were consistent throughout the various timepoints. Blood concentrations also increased with increasing dose in rats following 28 and 90 days of dosing, with results from the 28-day oral study in rats showing higher concentrations in females than in males, and peak concentrations occurring at day 9 or day 16, depending on sex and dose level. Results of the 90-day oral study in rats showed concentrations generally increasing in a greater

than proportional manner between the low- and mid-dose but becoming more proportional between the mid- and high-dose in both sexes. Following repeated dosing for 90 days in rats, concentrations were generally comparable between day 2 and day 28 and lower on day 85 in males, while the results in females demonstrated comparable concentrations on days 2 and 85 and higher concentrations on day 28. In dogs treated for 28 days, concentrations were generally comparable between days 1 and 28 in both sexes, with time to peak concentration being shorter on day 28 when compared to day 1. The results of the 90-day oral study in dogs showed a proportional increase in blood concentration with increasing dose, and no difference between sexes. However, concentrations increased up to two hours post-dosing, followed by a bi-phasic decline up to eight hours with a subsequent increase in concentration up to 24 hours. Overall, it was demonstrated that there was systemic exposure to isocycloseram in mice, rats, and dogs.

In acute toxicity studies, the technical grade active ingredient, Isocycloseram Technical, was of low acute toxicity via the oral, dermal, and inhalation routes of exposure in rats. It was non-irritating to the eyes and skin of rabbits, and was positive for skin sensitization when tested in mice using the Local Lymph Node Assay (LLNA).

The end-use product, VANECTO COCKROACH GEL BAIT, containing isocycloseram, was of low acute toxicity via the oral route of exposure in rats and was considered to be of low acute toxicity via the dermal and inhalation routes. It was minimally irritating to the eyes and skin of rabbits, and was negative for skin sensitization when tested in mice using the LLNA.

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

The end-use product, A23128 ST, containing isocycloseram, sedaxane, difenoconazole, metalaxyl-M (and S-isomer), and fludioxonil, was of low acute toxicity via the oral and inhalation routes of exposure in rats, and was considered to be of low acute toxicity via the dermal route. It was minimally irritating to the eyes and skin of rabbits, and was negative for skin sensitization when tested in mice using the LLNA.

Repeat-dose oral toxicity studies with isocycloseram were available in mice and rats via the dietary route, and in dogs via capsule. In these studies, dogs and rats appeared to be the most sensitive species, followed by the mouse. Following repeated oral exposure with isocycloseram, the liver (mouse, rat, dog), adrenals (mouse, rat) and small intestine (mouse, rat) were identified as the primary target organs of toxicity with effects on the spleen (mouse), hematopoietic system (mouse, rat), and testes and epididymides (rat) also observed. Liver effects included increased weight, hepatocellular hypertrophy, elevated liver enzymes, vacuolation, and macroscopic observations. Effects on the adrenals included increased weight, hypertrophy, and vacuolation. In mice, the spleen showed signs of extramedullary hematopoiesis, increased erythropoiesis, increased cellularity and increased weight.

The hematopoietic system appeared to be affected in mice and rats as seen by altered hematological parameters. In rats, tubular degeneration was evident in the testes and cellular debris and decreased sperm were noted in the epididymis. The Leydig cell tumours in rats and ovarian luteomas in mice that were observed following long-term oral dosing were considered to have an equivocal relationship to treatment and are discussed further below.

There was no evidence to suggest increased toxicity with extended duration of dosing in the rat and mouse studies. However, males appeared to be more sensitive to treatment than females following repeated oral dosing in rats.

Following short-term dermal exposure of rats to isocycloseram for 28 days, increased adrenal weight, adrenal vacuolation, altered hematological parameters and vacuolation of the small intestine were observed.

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

There was equivocal evidence of tumourigenicity in female mice for ovarian luteomas and in male rats for Leydig cell adenomas. The slightly elevated incidences of these tumours in high-dose animals were not statistically significantly different from the control incidence. There was no progression to malignant tumours, and the findings were only observed in a single sex and of one species. Additionally, there was no evidence of pre-neoplastic lesions or other effects in the ovary in the mouse. Based on these considerations, these tumours were considered to have an equivocal relationship to treatment.

A limited number of genotoxicity studies were provided for one isocycloseram metabolite, SYN548569 (CA5697A), which included a bacterial reverse mutation assay and an in vivo micronucleus assay in the mouse, both which produced negative results. Additionally, although an in vitro micronucleus assay in human lymphocytes using metabolite SYN548569 showed positive results both in the presence and absence of metabolic activation, the in vivo micronucleus assay produced negative results and therefore, metabolite SYN548569 was considered overall to be negative for mutagenicity.

In an enhanced 1-generation reproductive oral (gavage) toxicity study in rats, systemic toxicity observed in parental animals was generally consistent with findings reported in other repeat-dose oral toxicity studies in rats. This included vacuolation of the liver and increased adrenal weights, as well as effects reflective of reproductive toxicity at the same dose level, including decreased weights of the testes and epididymis and other effects on the testes (testicular tubular degeneration) and epididymides (decreased sperm). There were no effects observed in the offspring, suggesting that there was no increased sensitivity of the young animal when compared to the adult animal.

In a 2-generation reproductive oral (dietary) toxicity study in rats, systemic toxicity observed in parental animals was generally consistent with findings reported in other repeat-dose oral toxicity studies in rats. This included vacuolation of the liver, increased adrenal weights and

effects on the testes (testicular tubular degeneration) and epididymides (decreased sperm). Effects on the offspring included a decreased viability index (post-natal days 0–4) that was observed in both sexes of the F1 generation and increased adrenal weights at a dose level that also caused parental systemic toxicity. Reproductive toxicity was observed with a decreased live birth index, decreased fertility index, and altered reproductive parameters (decreased sperm count, increased abnormal sperm, decreased ovarian follicles) at a dose level that also caused parental systemic toxicity. The findings identified in the 2-generation reproductive toxicity study conducted in rats suggested that there was a serious endpoint in the young, in the form of decreased survival, but no increased sensitivity of the young animal when compared to the adult animal as the effects in the young were observed in the presence of parental toxicity.

Developmental toxicity studies were conducted via oral gavage in rats and rabbits. In the main oral developmental toxicity study in the rabbit, there were no treatment-related adverse effects observed in the maternal animals or in fetuses at the highest dose level tested. This was the same dose level that showed a significant decrease in body weight gain in maternal animals in the dose range-finding study in the rabbit. At the next higher dose tested in the dose range-finding study in the rabbit, maternal animals exhibited decreased food consumption and body weight loss, and all females were sacrificed on gestation day (GD) 11 or 12 due to excessive maternal toxicity. These findings in the dose-range finding study in the rabbit suggest that the dose levels used in the main oral developmental toxicity study in the rabbit were considered sufficiently high and there was, therefore, no suggestion in rabbits of increased sensitivity of the developing young. In the developmental toxicity study in rats, there were no adverse effects noted in maternal animals up to the highest dose tested. At this same dose level, developmental effects included an increased incidence of fetal and litter skeletal variations (incomplete supraoccipital cartilage of the skull, bifurcated xiphoid cartilage of the sternum) and malformations (fused cartilaginous ventral plate of the cervical vertebrae, bifurcated intersternal cartilage of the sternum, bifid sternebrae). These findings in rats are considered serious in nature and provide evidence of increased sensitivity of the developing young when compared to the adult animal.

The neurotoxic potential of isocycloseram was investigated in rats following acute gavage dosing and repeat-dose dietary administration in rats. The effects observed in the acute and 90-day neurotoxicity studies were within the pre-test range results, were not statistically significant, showed no-dose response, or were observed at one time point only and were therefore considered incidental in nature. The decreased motor activity that was noted at the high dose in the acute neurotoxicity study was present at a dose level where body weight loss was evident. Therefore, the decreased motor activity was considered to be secondary to the systemic effect of body weight loss and not indicative of selective neurotoxicity. Overall, there was no evidence of selective neurotoxicity following exposure to isocycloseram.

Isocycloseram, a mixture of four isomers, is comprised of 80-100% SYN548088 (5S,4R) isomer and 20-0% of the SYN548089 (5S,4S), SYN548090 (5R,4R), and SYN548091 (5R,4S) isomers. In a 28-day oral (dietary) toxicity study in the rat, four separate test materials, containing different levels of each of the four isomers, were assessed in order to compare the potential toxicity of the four isomers.

Based on the study results, SYN548088 appears to be the toxicologically active isomer and effects noted in this comparison study, including decreased body weight gain and histopathological changes in the adrenals and liver, are generally consistent with those observed in other short-term oral toxicity studies in rats.

Recognizing that SYN548088 is the toxicologically active isomer, it was determined that an approach would be necessary to address potential differences in potency that may have resulted from the varying levels of SYN548088 that were present in the assorted batches of test material used in the submitted toxicity studies. It was concluded that the use of a correction factor was deemed appropriate when establishing toxicology reference values, which would take into consideration the fact that isocycloseram can contain up to 100% of the toxicologically active isomer SYN548088.

A literature search was conducted and no published scientific studies relevant to the human health hazard assessment were identified as of 20 June 2025.

The identification of select isocycloseram 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 on laboratory animals with isocycloseram and one of its metabolites are summarized in Appendix I, Table 5. Results of the toxicology studies conducted on laboratory animals with the associated end-use products are summarized in Appendix I, Table 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.[9]

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 gavage developmental toxicity studies in rats and rabbits, an enhanced 1-generation gavage reproductive toxicity study in rats, and a dietary 2-generation reproductive toxicity study in rats. Dose range-finding studies were also available to support dose level selection in the main developmental toxicity studies. As discussed above, although no adverse effects were observed in the rabbit developmental toxicity study, the doses were considered sufficiently high based on the results of the dose range-finding study. Additionally, the available evidence does not suggest a unique susceptibility of the rabbit to developmental effects when compared to the rat.

With respect to potential prenatal and postnatal toxicity, no evidence of sensitivity of the young was observed in the rabbit. In the main oral developmental toxicity study in the rabbit, there were no treatment-related adverse effects in the maternal animals or fetuses at the highest dose level

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

tested. This was the same dose level that showed decreased body weight gain in maternal animals in the oral developmental toxicity dose range-finding study in the rabbit. In the rat, evidence of sensitivity of the young was noted in the developmental toxicity study as indicated by increased fetal and litter incidences of skeletal variations (incomplete supraoccipital cartilage of the skull, bifurcated xiphoid cartilage of the sternum) and malformations (fused cartilaginous ventral plate of the cervical vertebrae, bifurcated intersternal cartilage of the sternum, bifid sternebrae) in the absence of maternal toxicity.

There were no treatment-related effects in offspring in the enhanced 1-generation gavage reproductive toxicity study in rats. In the dietary 2-generation reproductive toxicity study in rats, a decreased viability index was observed in both sexes of the F1 generation offspring at the same dose level that resulted in vacuolation of the liver and small intestine, and increased weight of the adrenals and liver in parental animals. Additionally, at the same dose level, decreased live birth index and fertility index were noted, along with altered reproductive parameters (increased abnormal sperm, decreased sperm count, decreased number of ovarian follicles) and histopathological changes to reproductive organs (testicular tubular degeneration/atrophy). Concern for these findings was tempered by the presence of parental toxicity at the same dose level.

Overall, the database is adequate for determining the sensitivity of the young. There is a high level of concern for prenatal toxicity and sensitivity of the young based on the seriousness of the endpoint (malformations) observed in the absence of maternal toxicity. Therefore, the full 10-fold *Pest Control Products Act* factor (PCPA factor) was retained for scenarios in which the endpoint of malformations in rats was used to establish the point of departure for assessing risk to women of reproductive age.

For exposure scenarios involving children, there is a low level of concern for sensitivity of the young. Although the offspring effects are considered serious endpoints, they are well-characterized and concern was tempered by the presence of parental toxicity. Therefore, the PCPA factor was reduced to threefold when using the 2-generation rat reproductive toxicity study to establish the point of departure for assessing risk to children.

For exposure scenarios involving other sub-populations, the risk was considered well characterized and the PCPA factor was reduced to one fold.

3.2 Toxicology reference values

As discussed above, the selected points of departure used in the determination of the toxicology reference values for the human health risk assessments were corrected to account for the potential for both the concentration of the toxicologically active isomer SYN548088 within Isocycloseram Technical as well as for the purity of Isocycloseram Technical to be as high as 100%. The corrected value for each selected point of departure was based on the specific isomeric composition and purity of the batch of test material assessed in the relevant studies.

3.2.1 Route and duration of exposure

VANECTO COCKROACH GEL BAIT

Exposure is expected to be via the dermal route only for pest control operators (PCOs), based on the formulation type of the product (paste). Residential postapplication exposure is expected to be via the dermal route for adults, youth and children, and through the oral route (incidental ingestion) for children (1 to <2 years old). For PCOs, exposure is expected to be long-term in duration.

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Exposure is expected to be mainly via the dermal and inhalation routes for all workers in commercial seed treatment facilities, mobile seed treaters, and on-farm workers treating, planting and handling treated seeds. Exposure duration is expected to be short- to intermediate-term for commercial seed treatment workers, on-farm treaters and planters.

Isocycloseram is non-volatile with a vapour pressure of $<6.2 \times 10^{-6}$ Pa at 25°C. This vapour pressure is below the North American Free Trade Agreement (NAFTA) criterion for a non-volatile product at 1×10^{-5} kPa for indoor uses and 1×10^{-4} kPa for outdoor uses at 20–30°C. Therefore, inhalation risk is not of health concern for any occupational scenario.

3.2.2 Occupational and residential toxicology reference values

Short-, intermediate-, and long-term dermal and inhalation occupational exposures

For short-, intermediate-, and long-term dermal and inhalation occupational exposures, the developmental No Observed Adverse Effect Level (NOAEL) of 7.5 mg/kg bw/day from the oral developmental toxicity study in the rat was selected and corrected to a NOAEL of 6.5 mg/kg bw/day (adjusted for purity) for the risk assessment. At the Lowest Observed Adverse Effect Level (LOAEL) of 15 mg/kg bw/day, increased incidences of fetal and litter variations (incomplete supraoccipital cartilage of the skull, bifurcated xiphoid cartilage of the sternum) and malformations (fused cartilaginous ventral plate of the cervical vertebrae, bifurcated intersternal cartilage of the sternum, bifid sternebrae) were observed in the absence of maternal toxicity. Worker populations could include pregnant women and therefore these endpoints were considered appropriate for the occupational risk assessment. The available 28-day dermal toxicity study did not assess the relevant endpoints of concern (that is, effects on fetal development following prenatal exposure), thus necessitating the use of an oral toxicity study for risk assessment purposes.

For these occupational scenarios, the target margin of exposure (MOE) is 1000, which includes the standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability, as well as a PCPA factor of 10-fold for the reasons outlined in the *Pest Control Products Act* hazard characterization Section (Section 3.1.2). The selection of this study and target MOE is considered to be protective of all populations, including the unborn children and nursing infants of exposed female workers.

Incidental oral and dermal residential exposure – children (1 to <11 years old)

For the incidental oral and dermal residential exposure for children, the offspring NOAEL of 4.1 mg/kg bw/day from the oral 2-generation reproductive toxicity study in the rat was selected and corrected to a NOAEL of 3.5 mg/kg bw/day (adjusted for purity) for the risk assessment. At the LOAEL, a decreased viability index for postnatal day (PND) 0–4 in both sexes of the F1 generation was observed in the presence of maternal toxicity. The available 28-day dermal toxicity study did not assess the relevant endpoints of concern (that is, effects on reproduction and offspring development following prenatal exposure), thus necessitating the use of an oral toxicity study for risk assessment purposes.

For these residential scenarios, the target MOE selected for this endpoint is 300, which includes standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability as well as a PCPA factor of 3-fold for the reasons outlined in the *Pest Control Products Act* hazard characterization Section (Section 3.1.2). The selection of this study and target MOE is considered to be protective of children 1 to <11 years old.

Short-, intermediate, and long-term dermal residential exposure – adults (≥16 years old) and youth (11 to <16 years old)

For the short-, intermediate-, and long-term dermal residential exposure for adults and youth, the developmental NOAEL of 7.5 mg/kg bw/day from the oral developmental toxicity study in the rat was selected and corrected to a NOAEL of 6.5 mg/kg bw/day (adjusted for purity) for the risk assessment. At the LOAEL of 15 mg/kg bw/day, increased incidences of fetal and litter variations (incomplete supraoccipital cartilage of the skull, bifurcated xiphoid cartilage of the sternum) and malformations (fused cartilaginous ventral plate of the cervical vertebrae, bifurcated intersternal cartilage of the sternum, bifid sternebrae) were observed in the absence of maternal toxicity. The available 28-day dermal toxicity study did not assess the relevant endpoints of concern (that is, effects on fetal development following prenatal exposure), thus necessitating the use of an oral toxicity study for risk assessment purposes.

The target MOE selected for this endpoint is 1000 which includes standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability as well as a PCPA factor of 10-fold for the reasons outlined in the *Pest Control Products Act* hazard characterization Section (Section 3.1.2). The selection of this study and target MOE is considered to be protective of youth 11 to <16 years old and adults ≥16 years old, including the unborn children and nursing infants of exposed women.

3.2.3 Acute reference dose (ARfD)

Females 13–49 years old

To estimate acute dietary risk to females 13 to 49 years old, the developmental NOAEL of 7.5 mg/kg bw/day from the oral developmental toxicity study in the rat was selected and corrected to a NOAEL of 6.5 mg/kg bw/day (adjusted for purity) for the risk assessment. At the developmental LOAEL of 15 mg/kg bw/day, increased incidences of fetal and litter variations and malformations were observed in the absence of maternal toxicity. These effects are

considered to have potentially resulted from a single exposure, 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 (Section 3.1.2), the PCPA factor of 10-fold was retained. The composite assessment factor (CAF) is thus 1000.

The ARfD is calculated according to the following formula:

$$\text{ARfD (females 13–49 years)} = \frac{\text{NOAEL}}{\text{CAF}} = \frac{6.5 \text{ mg/kg bw/day}}{1000} = 0.007 \text{ mg/kg bw isocycloseram}$$

Infants and children <12 years old

To estimate acute dietary risk to children less than 12 years old, the offspring NOAEL of 4.1 mg/kg bw/day from the oral 2-generation reproductive toxicity study in the rat was selected and corrected to a NOAEL of 3.5 mg/kg bw/day (adjusted for purity) for the risk assessment. At the offspring LOAEL of 12 mg/kg bw/day, a decreased viability index for PND 0–4 in both sexes of the F1 generation was observed in the presence of parental toxicity. This effect could have resulted from a single exposure and 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 (Section 3.1.2), the PCPA factor was reduced to threefold. The CAF is thus 300.

The ARfD is calculated according to the following formula:

$$\text{ARfD (infants and children <12 years)} = \frac{\text{NOAEL}}{\text{CAF}} = \frac{3.5 \text{ mg/kg bw/day}}{300} = 0.012 \text{ mg/kg bw isocycloseram}$$

Youth 12–16 years old and adults ≥ 16 years old (excluding females 13–49 years old)

To estimate acute dietary risk to youth 12 to 16 years old and adults ≥ 16 years old (excluding females 13–49 years old), the NOAEL of 15 mg/kg bw/day for males from the 90-day oral toxicity study in dogs was selected and corrected to a NOAEL of 13 mg/kg bw/day (adjusted for purity) for the risk assessment. At the next highest dose level, bodyweight loss and decreased food consumption were noted 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 (Section 3.1.2), the PCPA factor was reduced to onefold. The CAF is thus 100.

The ARfD is calculated according to the following formula:

$$\text{ARfD (youth 12–16 and adults} \geq \text{16 years)} = \frac{\text{NOAEL}}{\text{CAF}} = \frac{13 \text{ mg/kg bw/day}}{100} = 0.13 \text{ mg/kg bw isocycloseram}$$

3.2.4 Acceptable daily intake (ADI)

To estimate risk following repeated dietary exposure, the developmental NOAEL of 7.5 mg/kg bw/day from the oral developmental toxicity study in the rat was selected and corrected to a NOAEL of 6.5 mg/kg bw/day (adjusted for purity) for the risk assessment. At the LOAEL of 15 mg/kg bw/day, increased incidences of fetal and litter variations and malformations were observed in the absence of maternal toxicity. The points of departure established in the long-term studies in mice and rats were lower than the corrected developmental NOAEL of 6.5 mg/kg bw/day. Despite this, the critical endpoint of malformations was selected for use in the human health risk assessment because it ensured adequate protection for all populations, including nursing infants and the unborn children of exposed workers, when considering the application of the PCPA factor. 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 (Section 3.1.2), the PCPA factor of 10-fold was retained. The CAF is thus 1000.

The ADI is calculated according to the following formula:

$$\text{ADI} = \frac{\text{NOAEL}}{\text{CAF}} = \frac{\text{6.5 mg/kg bw/day}}{1000} = 0.007 \text{ mg/kg bw/day of isocycloseram}$$

The ADI provides a margin of over 2000 to the highest dose tested in the oral developmental toxicity study in the rabbit where no adverse effects were observed. The ADI also provides a margin of 3400 to the dose level at which an equivocal increase in ovarian luteomas tumours was seen in female mice and a margin of 1000 to the dose level at which an equivocal increase in Leydig cell tumours was observed in male rats.

3.2.5 Cancer assessment

As previously discussed, a slight increase in the incidence of ovarian luteomas in females in the mouse dietary oncogenicity study with isocycloseram was considered equivocal based on the weight of evidence. Additionally, the Leydig cell tumours in males in the rat chronic dietary toxicity/oncogenicity study with isocycloseram are of low concern as the slight increase in incidence was considered equivocal based on the weight of evidence. Overall, the toxicology reference values selected for the non-cancer risk assessment are protective of any residual concerns regarding the carcinogenic potential of isocycloseram.

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). Short-, intermediate-, and long-term aggregate exposure to isocycloseram may be comprised of food, drinking water and residential exposure via the incidental oral and dermal routes.

The available dermal toxicity study was not considered appropriate for the establishment of reference values for children 1 to <11 years old as it did not assess the relevant endpoints of concern (that is, effects on reproduction and offspring development following prenatal exposure); therefore, the oral 2-generation reproductive toxicity study in the rat was chosen. The toxicology endpoint selected for aggregation for children 1 to <11 years old was decreased viability in the presence of parental toxicity. The corrected NOAEL of 3.5 mg/kg bw/day was selected with a target MOE of 300 for both the oral and dermal routes of exposure, which includes a 10-fold uncertainty factor for interspecies extrapolation and a 10-fold uncertainty factor for intraspecies variability. The PCPA factor for all routes was reduced to 3-fold as set out in the *Pest Control Products Act* hazard characterization Section (Section 3.1.2).

For the establishment of reference values for youth 11 to <16 years old and adults ≥16 years old, the available dermal toxicity study was not considered appropriate as it did not assess the relevant endpoints of concern (that is, effects on fetal development following prenatal exposure); therefore, the oral developmental toxicity study in the rat was chosen. The toxicology endpoint selected for aggregation for youth 11 to <16 years old and adults ≥ 16 years old was malformations in the absence of maternal toxicity. The corrected NOAEL of 6.5 mg/kg bw/day was selected with a target MOE of 1000 for both the oral and dermal routes of exposure, which includes a 10-fold uncertainty factor for interspecies extrapolation and a 10-fold uncertainty factor for intraspecies variability. For all routes, the PCPA factor of 10-fold was retained as set out in the *Pest Control Products Act* hazard characterization Section (Section 3.1.2).

3.3 Dermal absorption

A triple pack, consisting of a rat in vivo study, rat in vitro study and human in vitro study, was submitted. The in vivo rat study and in vitro human and rat studies were conducted with similar doses and same exposure durations (in other words, time until skin wash). The in vivo study clearly described how the animals were prepared, dose administration, and sample collection and analysis. The in vitro studies provided clear description of skin origin and the preparation and proof of skin integrity, and the choice of receptor fluid. The test product A21377 X was considered representative of the formulations, formulants and doses for the proposed products. The triple pack ratios ranged from 2.6 to 8.4 across the dose groups, indicating that in vitro dermal absorption is a conservative estimate of in vivo dermal absorption.

Two additional human in vitro studies were also submitted and considered acceptable for selecting dermal absorption values for the proposed liquid products. The test products A21708 E and A21550 L were representative of the formulations, formulants and doses for the proposed products. The formulants in these test products spanned the concentrations and ingredients seen in the proposed products and are expected to be predictive of in vivo dermal absorption.

The undiluted product consistently showed the lowest dermal absorption in all three triple pack studies and the two human in vitro studies as expected. For the triple pack studies, there was no clear concentration-relationship between the different dilutions; it was not clear if dermal absorption increased with an increase in concentration/dose levels. For both human in vitro studies using A21708 E and A21550 L, dermal absorption was observed to increase with increasing dilution (in other words, with decreasing concentration). For the triple pack studies, the test substance A21377 X was a suspension concentrate. The in vitro human study with

A21708 E was a dispersible concentrate, while the in vitro human study with A21550 L was a suspension concentrate. The two human in vitro studies were conducted using dose intervals/amounts different from what was used in the triple pack studies. It was not possible to ascertain similarities between the human in vitro study in the triple pack study and the two individual human in vitro studies. In addition, the variation in dermal absorption observed with the triple pack in vitro human study was not consistent with what was observed for the two in vitro human studies. Also, there was some uncertainty in the dermal absorption values determined at the 7.5 g/L dose group of the triple pack given the high recoveries noticed in certain matrices. As such, values from this dose group were not considered.

The dermal absorption value was selected from the lowest dose group in the human in vitro study using A21708 E: 8 % at 0.02 g/L dosing regime, for all exposure scenarios. This study was considered to meet most of the criteria used to assess human in vitro studies. Moreover, the exposure duration was 10 h, it had a higher number of dosing regimes when compared to the other human in vitro study, and the lowest diluted dose (0.02 g/L) was within the range of the lowest exposures estimated for in-field spray dilutions of the proposed products. As stated earlier, there is some uncertainty in the dermal absorption values determined at the 7.5 g/L dose group of the triple pack given the high recoveries noticed in certain matrices. As such, this dose group was not considered appropriate to use in the risk assessment. See Appendix I, Tables 7a, 7b, 7c, 7d, and 7e for a summary of each dermal absorption study.

3.4 Occupational and residential exposure assessment

3.4.1 Acute hazards of end-use products and mitigation measures

VANECTO COCKROACH GEL BAIT

The acute hazard assessment indicated that VANECTO COCKROACH GEL BAIT is of low toxicity by the oral route of exposure. It is minimally irritating to the eyes and skin and does not cause an allergic skin reaction. VANECTO COCKROACH GEL BAIT is considered to be of low acute toxicity by the dermal and inhalation routes of exposure. Based on these acute hazards, no additional personal protective equipment are required beyond a long-sleeved shirt, long pants, chemical-resistant gloves, socks and shoes.

EQUENTO

The acute toxicity of the end-use product EQUENTO, was low by the oral, dermal and inhalation routes of exposure. It was minimally irritating to the eyes, non-irritating to the skin of rabbits and was not a dermal sensitizer in mice based on the results of a local lymph node assay. Based on these acute hazards, no additional personal protective equipment are required.

A23128 ST

The acute toxicity of the end-use product A23128 ST, containing isocycloseram, sedaxane, difenoconazole, metalaxyl-M (and S-isomer) and fludioxonil, was low by the oral and inhalation routes of exposure. A23128 ST is considered to be of low acute toxicity via the dermal route. It was minimally irritating to the eyes and skin and did not cause an allergic skin reaction.

However, a NIOSH-approved N95 (minimum) filtering facepiece respirator (dust mask) that is properly fit tested is required for workers when there is potential for the product to be inhaled as dusts.

3.4.2 Occupational exposure and risk

Mixer/loader/applicator exposure and risk assessment

VANECTO COCKROACH GEL BAIT exposure and risk assessment

Given that VANECTO COCKROACH GEL BAIT is a ready-to-use paste, there is no mixing and loading involved.

Exposure is considered negligible for pest control operators (PCOs) applying VANECTO COCKROACH GEL BAIT based on the USEPA Residential SOPs (2012).

EQUENTO and A23128 ST: Commercial seed treatment (including mobile treaters) exposure and risk assessment

Small grain cereal seeds can be treated with EQUENTO and A23128 ST in commercial seed treatment facilities, including mobile treaters. Individuals have the potential for exposure while treating small grain cereal seeds 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, during cleaning and repair of equipment and driving a forklift. Exposure estimates were generated using the maximum rate for cereals of 7.5 g a.i./100 kg seed and unit exposure values from scenario-specific surrogate passive dosimetry studies (owned by the Agricultural Handlers Exposure Task Force (AHETF)), which are summarized in Appendix I, Table 8. These studies were considered the most appropriate for calculating occupational exposures.

The standard throughput of 92,000 kg seed/day for wheat, for commercial seed treatment (including mobile treaters), was used. Exposure was estimated by coupling the unit exposure values with the amount of product handled per day and the dermal absorption value of 8% and inhalation absorption value of 100%. Exposures were normalized to mg/kg bw/day by using 80 kg adult body weight. Exposure estimates were compared to the selected toxicological reference values to obtain the margins of exposure (MOE). Dermal and inhalation MOEs were combined since the toxicological reference value for both dermal and inhalation routes was derived from the same oral toxicity study. Calculated MOEs were greater than the target MOE of 1000 for all scenarios and are, therefore, not of health concern (Appendix I, Table 9a).

EQUENTO and A23128 ST: On-farm seed treatment and planting exposure and risk assessment

Small grain cereal seeds can be treated on-farm with EQUENTO and A23128 ST. Farmers have the potential for exposure while treating and planting small grain cereal seeds on-farm using open transfer equipment. Exposure estimates were generated using the maximum rate for cereals of 0.075 g a.i./kg seed and an on-farm treatment and planting surrogate passive dosimetry study owned by AHETF. This study was considered the most appropriate for calculating on-farm treatment and planting exposure (Appendix I, Table 8).

The throughput of 14 500 kg seed treated and planted per day for wheat, for on-farm treatment and planting, was used. Exposure was estimated by coupling the unit exposure values with the amount of product handled per day and the dermal absorption value of 8% and inhalation absorption value of 100%. Exposures were normalized to mg/kg bw/day by using 80 kg adult body weight. Exposure estimates were compared to the selected toxicological reference values to obtain the margins of exposure (MOE). Dermal and inhalation MOEs were combined since the toxicological reference value for both dermal and inhalation routes was derived from the same oral toxicity study. Calculated MOEs were greater than the target MOE of 1000 for all scenarios and are, therefore, not of health concern (Appendix I, Table 9b).

3.4.2.2 Postapplication occupational exposure and risk

VANECTO COCKROACH GEL BAIT

Exposure to PCOs re-entering areas treated with VANECTO COCKROACH GEL BAIT is considered negligible given the short exposure durations and limited dermal contact with treated surfaces.

EQUENTO and A23128 ST: Planter exposure and risk assessment

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 EQUENTO and A23128 ST while loading and planting treated seed. Exposure estimates were generated using the maximum rate for cereals of 0.075 g a.i./kg seed and unit exposure values from a planter surrogate passive dosimetry study owned by AHETF. This study was considered the most appropriate for calculating planter exposure (Appendix I, Table 8).

The throughput used for planting commercially treated seeds was 14 500 kg seed planted per day. Exposure was estimated by coupling the unit exposure values with the amount of product handled per day, the dermal absorption value of 8% and inhalation absorption value of 100%. Exposures were normalized to mg/kg bw/day by using 80 kg adult body weight. Exposure estimates were compared to the selected toxicological reference values to obtain the margins of exposure (MOE). Dermal and inhalation MOEs were combined since the toxicological reference value for both dermal and inhalation routes was derived from the same oral toxicity study. The calculated combined MOE exceeded the target MOE of 1000 and is, therefore, not of health concern (Appendix I, Table 9c).

3.4.3 Residential exposure and risk assessment

3.4.3.1 Handler exposure and risk

VANECTO COCKROACH GEL BAIT

Residential handler exposure is not applicable as VANECTO COCKROACH GEL BAIT is not a domestic class product.

EQUENTO and A23128 ST

EQUENTO and A23128 ST are not domestic class products and are not permitted for use in residential settings; therefore, a residential handler exposure and risk assessment is not required.

3.4.3.2 Postapplication residential exposure and risk

VANECTO COCKROACH GEL BAIT

Residential postapplication exposure is considered negligible following outdoor crack and crevice, spot, and void applications by PCOs.

For indoor crack and crevice, spot and void applications, residential dermal and inhalation postapplication exposures to open bait formulations (gels, pastes, foams) are expected to be negligible. Isocycloseram is non-volatile with a vapour pressure of $< 6.2 \times 10^{-6}$ Pa at 25°C; as such, inhalation exposure is expected to be negligible.

Acute incidental oral exposure

The acute incidental oral exposure is not expected to occur as a result of routine behaviour. However, there is the potential for acute incidental oral exposure, similar to an episodic poisoning event. The assessment of the ingestion of a single paste dot would be based on the granule episodic ingestion algorithm from the USEPA Residential SOPs (2012). For the episodic granular ingestion scenario, the assumption is that dry pesticide materials are ingested by children who play in treated areas.

Using the acute toxicology reference value and the assumption that a child (1 to < 2 years) would consume a single bait drop (5 mg isocycloseram; as stated on the label) in a day, the exposure from acute incidental oral ingestion was below the target MOE of 300 (Appendix I, Table 10). Therefore, an additional label statement restricting application by certified or licensed PCOs is required, to ensure that each bait placement will be entirely out of the reach of a child.

EQUENTO and A23128 ST

EQUENTO and A23128 ST are not domestic class products and are not permitted for use in residential settings; therefore, a postapplication residential exposure and risk assessment are not required.

3.4.4 Bystander exposure and risk

VANECTO COCKROACH GEL BAIT

Bystander exposure and risk are not expected to be of health concern.

EQUENTO and A23128 ST

Bystander exposure is expected to be negligible since the product will be used in commercial seed treatment facilities, including mobile treaters (treat-on-the-go air seeders) and on-farm, and the potential for drift during the treatment of seeds is limited.

3.5 Dietary exposure and risk assessment

3.5.1 Exposure from residues in food of plant and animal origin

The residue definition for risk assessment and enforcement in plant and animal commodities is isocycloseram. The data gathering and enforcement analytical methods are valid for the quantitation of isocycloseram residues in crop and livestock matrices. When stored in a freezer at ≤-18°C, the residues of isocycloseram are stable in eggs and bovine matrices (milk, muscle, and liver) for up to 24 months, for up to 3 months in poultry muscle and fat, and in bovine cream, fat and kidney, and up to 1 month in poultry liver. The residues of isocycloseram are stable in representative matrices from five commodity categories (high-water, high-oil, high-protein, high-starch, and high-acid content) for up to 24 months, and up to 21 months in processed commodities when stored at ≤-18°C. The raw agricultural commodities (barley and wheat) were processed, but were not further analyzed due to the lack of quantifiable residues when treated at exaggerated rates.

Adequate feeding studies were carried out to estimate the anticipated residues in livestock matrices resulting from the proposed uses. Crop field trials conducted throughout Canada and the United States using end-use products containing isocycloseram at approved rates in or on wheat and barley are sufficient to support the proposed maximum residue limits. Field rotational crop studies were conducted in/on mustard greens, spinach, radish roots and wheat (forage, grain, hay, and straw). The data are adequate to demonstrate that a 120-day plant-back interval is appropriate for non-labeled crops.

3.5.2 Exposure from drinking water

For the human health risk assessment, estimated environmental concentrations (EECs) in potential drinking water sources are calculated for both groundwater and surface water using the Pesticide Water Calculator (PWC; version 2.0).

For surface water, the PWC calculates the amount of pesticide entering the water body by runoff and drift, and the subsequent degradation of the pesticide in the water system. EECs are calculated by modelling a total land area of 173 ha draining into a 5.3 ha reservoir with a depth of 2.7 m. Groundwater EECs are calculated by simulating leaching through a layered soil profile and reporting the average concentration in the 1 m below the water table.

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

For drinking water, the residue definition was determined as the combined residue of isocycloseram with fifteen of its transformation products (TPs): SYN549431, SYN549107, SYN551203, SYN550455, SYN549546, SYN551415, SYN550321, SYN550603, SYN549433, SYN550602, SYN551190, SYN549557, SYN548569, SYN549110 and SYN550737. Major transformation products (>10% applied radioactivity (AR)) were included in the drinking water residue definition when it was determined that they are likely to form under environmental conditions. EECs for surface water were calculated based on a single standard scenario, which was run for 50 years. EECs in groundwater were calculated for several scenarios representing different regions of Canada; only the highest EECs from across these scenarios are reported. All groundwater scenarios were run for a duration of 100 years due to slow leaching. The major fate inputs used for the surface water and groundwater modelling are presented in Tables 3.5.2.1 and 3.5.2.2, respectively. Level 1 EECs are reported in Table 3.5.2.3.

Table 3.5.2.1 Surface water model input parameters (transformation fractions in parenthesis)

Parameter	Parent[1]	Daughter1[2]	Daughter2[3]
Photolysis at 40° latitude (days)	240.80	Stable (0)	Stable (0)
Hydrolysis at pH 7 at 25°C (days)	347.10	Stable (0)	Stable (0)
Aerobic aquatic half-life at 21°C (days)	157.9	66.4[7] (1.0)	11.3 (0.839)
Anaerobic aquatic half-life at 20.9°C (days)	9.0	Stable (0.747)	624.7 (0.625)
Aerobic soil half-life at 20°C (days)	284.4	Stable (0)	Stable (0)
K_{oc} (L/kg)	1479.3	617.7	10

1 Parent as ICS + SYN551203 + SYN549431 + SYN549107 + SYN550737 + SYN549433 + SYN550602 + SYN550455 + SYN551190

2 Daughter1 as SYN548569 + SYN549546

3 Daughter2 as SYN550603 + SYN551415 + SYN550321 + SYN549557 + SYN549110

Table 3.5.2.2 Groundwater model input parameters

Parameter	Value
Hydrolysis half-life at pH 7 at 25°C (days)	347.10
Aerobic soil half-life at 20°C (days)	284.4
K_{oc} (L/kg)	1479.3

Table 3.5.2.3 Level 1 EECs of combined residue of isocycloseram and 15 of its TPs in potential sources of drinking water

Use pattern	Groundwater (µg a.i./L)		Surface Water (µg a.i./L)		
	Peak[1]	Average[2]	Daily[3]	Yearly[4]	Overall[5]
1 × 44.8 g a.i./ha as seed treatment	0.065	0.055	1.3	0.21	0.18

1 The highest (peak) simulated average concentration in 1 m below the water table.
2 The temporal average concentration in the 1 m below the water table over the post-breakthrough simulation period.
3 90th percentile of the highest 1-day average concentration from each year.
4 90th percentile of yearly average concentrations.
5 Average of all yearly average concentrations.

3.5.3 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 characterization

The basic acute dietary exposure for the supported isocycloseram registered commodities was estimated to be less than 2.5% of the ARfD for females 13 to 49 years of age and <1–9% of the ARfD for all other subpopulations (95th percentile, deterministic). Aggregate exposure from food and drinking water (EEC value = 1.3 µg a.i./L, Level 1, surface water) is not of health concern. Specifically, 3% of the ARfD was obtained for females 13 to 49 years of age, and less than 10% for all other subpopulations.

3.5.3.2 Chronic dietary exposure results and characterization

Aggregate chronic exposure from food and drinking water (EEC value = 0.21 µg a.i./L, Level 1, surface water) is not of health concern. Specifically, a range from 1% to 8% of the ADI was obtained for all population subgroups. The highest exposed population subgroup was children 1 to 2 years of age.

3.6 Aggregate exposure and risk assessment

VANECTO COCKROACH GEL BAIT

The aggregate assessment consisted of combining food and drinking water exposure only, since residential exposure is not expected when following label directions.

EQUENTO and A23128 ST

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

3.7 Cumulative assessment

The *Pest Control Products Act* requires the PMRA to consider the cumulative 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 isocycloseram. Isocycloseram, along with broflanilide, cyproflanilide and fluxametamide, belong to a common pesticidal mode of action (MOA) group (Group 30) as determined by the Insecticide Resistance Action Committee (IRAC) that act as GABA-gated chloride channel allosteric modulators, inhibiting neurotransmission in insects. Treatment-related neurotoxic effects were not observed in the supporting isocycloseram database. This suggests that isocycloseram does not bind to vertebrate GABA receptors in the same capacity as it does to insect GABA receptors and that the pesticidal MOA in insects is not the same as the toxicological MOA in mammals.

Based on approved domestic and international uses for these pesticides, an assessment of a potential common mechanism of toxicity with fluxametamide and broflanilide was undertaken for isocycloseram. Cyproflanilide was not considered in this assessment as there are no registered uses in Canada or the US, and there are no approved import tolerances.

Although the mammalian MOA for isocycloseram has not been elucidated, the available toxicity information demonstrated common toxicological effects between isocycloseram and other pesticides in the group. Specifically, isocycloseram and broflanilide both target the adrenal cortex, and isocycloseram and fluxametamide both target the small intestine (epithelial vacuolation) and affect sperm function. As such, it was determined that these three pesticides would form a common assessment group for the purposes of a cumulative health assessment for repeated exposure scenarios (the common endpoints are not relevant to acute exposures).

For the purposes of this proposed registration of isocycloseram, a qualitative approach to assessing risks from cumulative exposure was undertaken for the pesticides within this common assessment group.

3.7.1 Isocycloseram and fluxametamide

Fluxametamide has a U.S. tolerance for imported tea from Japan, resulting in the potential for exposure from imported foods. The USEPA concluded that risk from chronic exposure to fluxametamide from food only is less than 1% of the ADI for all population subgroups. As such, the contribution of fluxametamide to the cumulative risk with isocycloseram is minimal.

3.7.2 Isocycloseram and broflanilide

Table 3.7.2.1 presents the summary of uses and exposure pathways for isocycloseram and broflanilide.

Table 3.7.2.1 Summary of uses and exposure pathways for isocycloseram and broflanilide

Active ingredient	PMRA published document	Pesticide uses	Potential exposure pathways		
			Food	Drinking water	Residential
Broflanilide	PRD2020-06, RD2020-16	Foliar and soil application to potatoes, corn, sweet potato, CG 5-13, CG4-13, CG8-09, CSG22B and soybean, and seed treatment on small cereal grains	Yes	Yes [EEC[1]]	No
Isocycloseram	Current assessment	Cockroach bait, seed treatment on small grain cereals	Yes	Yes [EEC[1]]	No

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

There is a potential for co-occurrence of exposure for the two pesticides. With the additional restrictions that are required for the cockroach bait product, residential exposure to isocycloseram is negligible and there are no residential uses for broflanilide. Accordingly, the potential contribution to the cumulative exposure of isocycloseram and broflanilide is expected through dietary (food and drinking water) exposure alone.

The most recent dietary risk assessment for broflanilide was conducted in 2023. No other expansion of use has been approved for broflanilide since then. The refined chronic dietary exposure from all supported food uses for the representative population subgroups were less than 2% of the acceptable daily intake (ADI).

When considering the estimated risks from the individual dietary exposure assessments (food + drinking water), exposure was low and represented less than 8% of the ADI in the basic chronic dietary exposure assessment for isocycloseram and less than 2% in the refined chronic dietary exposure assessment for broflanilide. These risk estimates from the individual dietary exposure assessments were calculated using the most conservative points of departure, that are not necessarily based on common effects on the adrenal cortex. As a result, the summing of these individual risk estimates (less than 10% of the risk cup) overestimates the cumulative risk of isocycloseram and broflanilide.

Therefore, based on this qualitative assessment, the cumulative risks from potential co-exposure to GABA-gated chloride channel allosteric modulators through food and drinking water, where relevant, are acceptable.

3.8 Maximum residue limits (MRLs)

Dietary risks from the consumption of food commodities listed in Table 3.8.1 were shown to be acceptable when isocycloseram 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 isocycloseram.

Table 3.8.1 Recommended maximum residue limits

MRL (ppm)	Food commodity
0.04	Fat of cattle, goats, horses, and sheep
0.015	Meat byproducts of cattle, goats, horses, and sheep
0.01	Barley, oats, rye, triticale, wheat; eggs; meat of cattle, goats, hogs, horses, poultry and sheep; fat and meat byproducts of hogs and poultry; milk

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

The nature of the residues in animal and plant matrices, analytical methodologies, field trial data, and acute and chronic dietary risk estimates are summarized in Appendix I, Tables 2b, 11 and 12.

3.9 Health incident reports

As of 21 May 2025, no human or domestic animal incidents involving isocycloseram have been submitted to Health Canada.

4.0 Impact on the environment

4.1 Fate and behaviour in the environment

A summary of all endpoints from environmental fate studies is provided in Appendix I, Tables 13 and 14. In the terrestrial environment, isocycloseram is immobile in soil. Hydrolysis and phototransformation are not expected to be significant routes of dissipation. Isocycloseram is moderately persistent to persistent in aerobic soil, forming two major transformation products (SYN549107 and SYN550738). Isocycloseram is slightly persistent to moderately persistent in anaerobic soil. Isocycloseram has the potential to leach and reach groundwater (Appendix I, Table 15). A label statement informing users of the potential to leach in soils and reach groundwater is required. Residues of isocycloseram are unlikely to carry over into the next growing season. Isocycloseram has limited localized systemicity during early plant development. When applied as a seed treatment application, residues of isocycloseram are not anticipated to be taken up by plants and reach plant tissues such as pollen or nectar.

In aquatic systems, isocycloseram partitions rapidly from the water column to the sediment, where it is slightly persistent under aerobic conditions and non-persistent under anaerobic conditions. Hydrolysis and phototransformation are not expected to be significant routes of dissipation.

Isocycloseram is not expected to bioaccumulate in fish based on bioconcentration factor (BCF) values.

Based on its low vapour pressure, low water solubility and low Henry's law constant, isocycloseram is not expected to volatilize from water, moist soil, or vegetation to air. Although available models (AOPWIN) were not suited for predicting the atmospheric half-life of isocycloseram and its transformation products, in some cases given the large fraction expected to be sorbed to airborne particles, further assessment of the atmospheric half-lives was not considered necessary because isocycloseram and its transformation products did not meet all four of the TSMP Track 1 criteria (Appendix I, Table 29).

4.2 Environmental risk characterization

An environmental risk assessment was conducted as described in the guidance document Health Canada's Approach to Environmental Risk Assessment for Pest Control Products to estimate the potential for adverse effects on non-target species. Environmental exposure and ecotoxicology information were integrated by comparing estimated environmental concentrations (EECs) to effects-based values used to assess risk (effects metrics). EECs were estimated using standard models that consider application rates and chemical and environmental fate properties, including pesticide dissipation between applications. The EECs used in this risk assessment are presented in Appendix I, Table 16.

Acute and chronic ecotoxicological data for non-target terrestrial, freshwater and marine organisms are summarized in Appendix I, Table 17. In the risk assessment, toxicity endpoints were adjusted via an uncertainty factor (UF) to calculate the effects metrics. The effects metrics account for potential differences in species sensitivity as well as varying protection goals (in other words, protection at the community, population or individual level).

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 level of concern (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 runoff. Refinements to the risk assessment continued until the risk was adequately characterized or the available data did not permit further refinements.

4.2.1 Risks to terrestrial organisms

When applied as a seed treatment on small grain cereals (wheat, barley, oats, rye and triticale), terrestrial organisms, such as earthworms, pollinators, other terrestrial arthropods, birds and mammals can be exposed to isocycloseram through direct contact with the treated seed, dust-off at the time of planting, or from ingestion of treated seed, or soil or water containing residues. A risk assessment of isocycloseram and several of its transformation products was undertaken based on available toxicity data. Screening level EECs are presented in Appendix I, Table 16. Toxicity data are summarized in Appendix I, Table 17. The screening level risk assessment for non-target terrestrial organisms (excluding birds and mammals) for isocycloseram and its transformation products is presented in Appendix I, Table 18. The screening level risk assessment for birds and mammals is presented in Appendix I, Table 19. Further risk characterization for birds and mammals is presented in Appendix I, Tables 20, 21 and 22.

The screening level RQs associated with the proposed use of isocycloseram as a seed treatment did not exceed the LOC for the following terrestrial organisms:

- Earthworms and other soil invertebrates
- Beneficial arthropods
- Bees
- Terrestrial vascular plants

The screening level RQs associated with the proposed use of isocycloseram as a seed treatment did exceed the LOC for the following terrestrial organisms and further characterization of the risk was completed for these terrestrial organisms:

- Birds
- Mammals

Earthworms and other soil invertebrates

Earthworms and other soil invertebrates may be exposed to isocycloseram through residues in soil. Effects metrics for earthworms and collembola were compared to the screening level soil EEC. The resulting acute and chronic reproductive RQs did not exceed the LOC (RQ < 0.00001). When used according to label directions, the risks to earthworms and other soil invertebrates from the use of isocycloseram as a seed treatment are acceptable.

Bees

Treated seed could result in dietary exposure to bees via systemic transport of pesticide residues through the plant into pollen and nectar. However, since isocycloseram does not exhibit systemic activity, dietary exposure of bees through residues in pollen and nectar is expected to be negligible.

Because isocycloseram is highly toxic to bees, exposure to dust generated during planting of treated seed was considered in the pollinator risk assessment. Planting methods and equipment associated with proposed types of seeds to be treated are not expected to result in high dust

generation or require use of a dust-reducing fluency agent. However, for types of seeds that tend to be dusty (cereal and legume seeds), label statements are required to inform the user of the toxicity of isocycloseram towards bees and the best management practices to reduce exposure of bees to dust from treated seed during planting.

When used according to label directions and in accordance with risk mitigation measures, the risks to bees from the use of isocycloseram as a seed treatment are acceptable.

Beneficial arthropods

Foliar-dwelling beneficial arthropods are not anticipated to be exposed to isocycloseram through contact with leaf surfaces when applied as a seed treatment. The primary route of exposure for beneficial arthropods from seed treatments is through the diet via systemic transport of pesticide residues from the soil into the plant, or through direct contact with residues in the soil itself. However, since isocycloseram does not exhibit systemic activity, exposure of foliar-dwelling non-target arthropods from seed treatment applications is expected to be negligible. For soil-dwelling beneficial arthropods, the risk assessments conducted for earthworms, collembola and the soil mite, *Hypoaspis aculeifer*, are considered more relevant to seed treatment uses.

Effects metrics for exposure of the predatory mite to isocycloseram and its transformation products were compared to the screening level soil EECs. The resulting RQs did not exceed the LOC (RQ range: < 0.0002–0.07). When used according to label directions, the risks to beneficial arthropods from the use of isocycloseram as a seed treatment are acceptable.

Birds

Birds may be exposed to isocycloseram through the ingestion of treated seed. The screening level risk assessment was conducted using the maximum proposed seed treatment rate of 7.5 g a.i./100 kg seed for wheat, barley, oats, rye and triticale. The screening level LOC was not exceeded for birds of all sizes for acute oral and acute dietary exposure, nor was it exceeded for large birds for chronic exposure. However, the LOC was slightly exceeded for small- and medium-sized birds for chronic exposure (reproductive effects, RQ: 1.3 and 1.02, respectively).

The risk was further characterized by considering the exposure and effects observed in the reproduction studies, the estimated number of seeds required to be consumed daily to reach the chronic effects metric, the estimated area required in which the number of seeds would be available at the soil surface, and the percent diet to reach the chronic effects metric.

The effects metric used in the screening level risk assessment was the chronic NOAEL of 14.6 mg a.i./kg bw/day for the mallard duck over a 21-week exposure period. The observed effects at the LOAEL of 52.5 mg a.i./kg bw/day were a 10% reduction in 14-day offspring survivor weight, a 5% reduction in hatchling survival per number of hatchlings and a 3% reduction in eggshell thickness when compared to controls. The number of uncracked eggs per eggs laid was 99.8 and 100% at the NOAEL and LOAEL of 14.6 and 52.5 mg a.i./kg bw/day, respectively.

The reduction in eggshell thickness, therefore, did not result in an increase in cracked eggs per eggs laid. When considering the chronic LOAEL for the mallard duck, the LOC was not exceeded for small-, medium- or large-sized birds, suggesting that adverse effects to mallard duck may not occur at the proposed seed treatment rate.

It was estimated that the number of seeds small- and medium-sized birds would have to consume daily in order to reach the chronic NOAEL effects metric of 14.6 mg a.i./kg bw/day is 78–195 and 389–973 seeds, respectively, depending on seed weight. Cereal crops are typically sowed by standard drilling equipment (in other words, seeds are placed in shallow rows or furrows) and the field area in which 78–195 seeds would be available at the surface immediately after sowing by standard drilling was estimated to be 1.47–17.6 m^2 for small-sized birds and 7.36–88.0 m^2 for medium-sized birds, depending on the seeding rate and the season of sowing (spring or fall). The percent of diet to reach the chronic effects metric was determined to be 76.7% and 97.6% for small-sized and medium-sized birds, respectively. It is considered unlikely that a sufficiently large portion of a population of small- and medium-sized birds would consume treated seed at a rate and for the duration that would be required to result in population-level chronic effects when seeds are incorporated into the soil by typical standard drilling equipment.

To characterize the risks of isocycloseram to other bird species, additional endpoints with a greater magnitude of effect were considered as part of the weight of evidence. The observed effects at the LOAEL of 83.4 mg a.i./kg bw/day for the bobwhite quail were an approximate 30% reduction in eggs set, viable and live embryos, number of hatchlings and hatchling survival, as well as a 28% increase in cracked eggs. When considering the chronic NOAEL of 25.3 mg a.i./kg bw/day for the bobwhite quail, the LOC was not exceeded for small-, medium- or large-sized birds, suggesting that adverse effects to bobwhite quail are not expected to occur at the proposed seed treatment rate.

Overall conclusions on the risk to birds

Given that there were only slight LOC exceedances for one bird species (mallard duck) at the NOAEL only, that the number of seeds required to reach this effects metric represents a large proportion of diet, and that cereal seeds are expected to be largely unavailable at the soil surface when typical standard drilling equipment is used, the risk to birds is expected to be minimal. However, to ensure that the exposure potential to birds from the consumption of seeds treated with isocycloseram is further reduced, the following risk mitigation statements are required on both the product label as well as containers or packages containing treated seed:

- A hazard labelling statement informing users of the toxicity to birds.
- A statement informing users that any spilled or exposed seeds must be incorporated into the soil or otherwise cleaned-up from the soil surface.

When used according to label directions and in accordance with risk mitigation measures, the risks to birds from the use of isocycloseram as a seed treatment are acceptable.

Mammals

Mammals may be exposed to isocycloseram through the ingestion of treated seed. The screening level risk assessment was conducted using the maximum proposed seed treatment rate of 7.5 g a.i./100 kg seed for wheat, barley, oats, rye and triticale. The screening level LOC was not exceeded for mammals of all sizes for acute oral exposure. However, the LOC was exceeded for chronic exposure across all mammal sizes (reproductive effects, RQ: 1.5–3.1). Similar to the bird risk assessment, the risk to mammals was further characterized.

The effects metric used in the screening level risk assessment was the chronic NOAEL of 3.5 mg a.i./kg bw/day for the Wistar rat for a 2-generation reproduction study. The observed effects at the LOAEL of 10.4 mg a.i./kg bw/day were a 9% reduction in the F1 generation mean live birth index and a 11% reduction in the mean cumulative survival of the F1 generation. When considering the chronic LOAEL for the Wistar rat, the LOC was still slightly exceeded for small mammals only (RQ: 1.05).

It was estimated that the number of seeds required for a small-, medium- and large-sized mammal to consume in order to reach the effects metric would be 14–35, 33–82 and 933–2333 seeds, respectively. When the seed is sowed by standard drilling, it was estimated that the field area with this number of seeds available at the surface immediately after sowing would be 0.265–3.17 m^2 for small mammals, 0.618–7.39 m^2 for medium mammals, and 17.6–211 m^2 for large mammals. The percent of dry diet to reach the effects metric was determined to be 32.2%, 37.4% and 67.9% for small-, medium- and large-sized mammals, respectively.

To further characterize the likelihood of risk to small mammals, additional lines of evidence were considered. There is evidence that some rodents will de-husk certain crop seeds before consuming them, which could reduce exposure. Wood mice have been shown to reduce exposure to seed treatments on cereals by on average 58-84% through de-husking (Brühl et al. 2011). A separate study reported that 100% of observed wood mice de-husked barley and 90% de-husked wheat, while 70% of bank voles de-husked both wheat and barley (Morris and Thompson 2010). In addition, small rodents generally mature rapidly and have high reproductive rates. Populations with adequate resources and high reproductive capacity can recover losses relatively quickly (Calder 1996). Based on the information above, it is considered unlikely that a sufficiently large portion of a population of small-sized mammals would consume treated seed at a rate and for the duration that would be required to result in population-level chronic effects.

Overall conclusions on the risk to mammals

While small mammals may more easily reach the chronic effects threshold when compared to birds, there is evidence that some rodents will de-husk certain crop seeds before consuming them, which is expected to reduce exposure. In addition, small rodents mature rapidly and have high reproductive rates; populations with adequate resources and high reproductive capacity can recover losses relatively quickly. However, to ensure that the exposure potential to mammals from the consumption of seeds treated with isocycloseram is further reduced, the following risk mitigation statements are required on both the product label as well as containers or packages containing treated seed:

- A precautionary label statement indicating toxicity to small wild mammals.
- A statement informing users that any spilled or exposed seeds must be incorporated into the soil or otherwise cleaned-up from the soil surface.

When used according to label directions and in accordance with risk mitigation measures, the risks to mammals from the use of isocycloseram as a seed treatment are acceptable.

Terrestrial vascular plants

When used as a seed treatment, exposure to non-target terrestrial vascular plants is not anticipated.

When used according to label directions, the risks to terrestrial plants from the use of isocycloseram as a seed treatment are acceptable.

4.2.2 Risks to aquatic organisms

When isocycloseram is applied as a seed treatment on small grain cereals (wheat, barley, oats, rye and triticale) aquatic organisms, such as invertebrates, fish, amphibians, plants and algae may be exposed to isocycloseram through runoff entering aquatic habitats. Exposure from spray drift is considered negligible for seed treatment uses, thus risks to aquatic organisms from spray drift of isocycloseram are considered acceptable. A risk assessment of isocycloseram and several of its transformation products was undertaken based on available toxicity data. Toxicity data are summarized in Appendix I, Table 17**Error! Reference source not found.**.

The calculated EECs were compared to the most sensitive effects metric for each group of aquatic organisms. Screening level aquatic EECs were converted from g a.i./100 kg seed to mg a.i./L based on the maximum proposed annual seed treatment application rate of 7.5 g a.i./100 kg seed, a maximum seeding rate for triticale of 209.88 kg/ha, assuming 100% runoff from the seeds into the water body and instantaneous complete mixing. Screening level aquatic EECs are presented in Appendix I, Table 16. The screening level aquatic organism risk assessment for isocycloseram and its transformation products is presented in Appendix I, Tables 23 and 24. When the LOC was exceeded, exposure to aquatic organisms was refined taking exposure from surface runoff into consideration.

The screening level RQs associated with the proposed use of isocycloseram as a seed treatment did not exceed the LOC for the following organisms:

- Freshwater and marine fish
- Freshwater vascular plants
- Freshwater and marine algae
- Amphibians

The screening level RQs associated with the proposed use of isocycloseram as a seed treatment did exceed the LOC for the following aquatic organisms and further characterization of the risk was completed:

- Freshwater and marine invertebrates

Aquatic invertebrates

Screening level aquatic risk assessment from exposure to isocycloseram:

Effects metrics from the most sensitive species were compared to the screening level EEC of 1.97 µg a.i./L for both freshwater and marine invertebrates. The resulting screening level RQs exceeded the LOC for acute and chronic exposure scenarios for both freshwater and marine invertebrates. The risk to aquatic invertebrates from isocycloseram was therefore further characterized taking exposure from runoff into consideration.

Screening level aquatic risk assessment from exposure to transformation products of isocycloseram:

Additional studies conducted with *Daphnia magna* and *Chironomous riparius* exposed to several transformation products of isocycloseram were available for this review. The screening level EECs for the transformation products were conservatively calculated based on a 100% molar conversion from parent compound. Effects metrics for the transformation products were compared to the screening level EECs. The resulting RQs did not exceed the LOC for the water flea, *Daphnia magna*. For the freshwater midge, *Chironomous riparius*, the resulting RQs exceeded the LOC for two of the transformation products, SYN550918 (identified as SYN550738 in the fate studies) and SYN549431 (RQs: 4.0 and 10.8 respectively). The screening level RQs for both of these transformation products are orders of magnitude lower than those of the parent compound. Mitigations put in place to mitigate risks associated with the parent compound will also serve to mitigate any risk associated with the transformation products. Therefore, the residue definition for modelling runoff EECs for the refined risk assessment is limited to parent compound only.

Refined aquatic risk assessment from exposure to isocycloseram:

Runoff:

Refined EECs from runoff are presented in Appendix I, Table 16. The refined risk assessments for aquatic organisms from runoff are presented in Appendix I, Table 25.

The refined assessment from runoff considered modelled runoff EECs of various lengths of exposure compared to the closest matching effects metrics exposures for the most sensitive species of freshwater and marine invertebrates. Acute effects metrics based on 48- to 96-hour exposure scenarios were compared to the 24-hour and 96-hour modelled runoff EECs, respectively, and chronic effects metrics based on 21-day to 60-day exposures were compared to the 21-day and 60-day modelled runoff EECs, respectively.

The refined RQs exceeded the LOC for acute and chronic exposure scenarios for both freshwater (RQs: 9 and 10, respectively) and marine invertebrates (RQs: 4.4 and 5, respectively).

The identified chronic risks for both freshwater and marine invertebrates were further characterized by considering the effects observed at the NOEC and LOEC.

The freshwater midge (*Chironomus dilutes)* NOEC was 0.0013 µg a.i./L (pore water), derived from the 60-day sediment-spiked study. The test concentration representing the LOEC was 0.0045 µg a.i./L (pore water) which was also the highest concentration tested. At the LOEC of 0.0045 µg a.i./L (pore water), 60-day observed effects were a 39% reduction in dry weight, a 16% reduction in development rate, and a 21% reduction of percent adult emergence.

It should be noted that for this review, a chronic freshwater study without sediment, where the test chemical is added to the water column, was not available for the most sensitive organism identified from the acute studies (*Chironomus riparius,* a sediment-dwelling freshwater midge). Such a study was available for the freshwater water flea (*Daphnia Magna*); however, based on acute studies conducted on both the water flea and midge, the midge was shown to be significantly more sensitive than the water flea. In the absence of a chronic water column study conducted with *Chironomus riparius*, the chronic 60-day effects metric from a sediment-spiked study with *Chironomous dilutes* (expressed in µg a.i./L pore water) was compared to the modelled 60-day overlying water EEC instead of the typical modelled pore water EEC. This was done, as a conservative measure, to consider the possible chronic effects to pelagic freshwater invertebrates given that the modelled 60-day overlying water EEC (0.013 µg a.i./L) was slightly higher than the 21-day modelled pore water EEC (0.008 µg a.i./L). Although this may result in increased uncertainty in the chronic risk assessment towards pelagic freshwater invertebrates, this uncertainty is anticipated to be conservative in nature, resulting in an over-estimation of the identified risk.

The marine mysid shrimp (*Americamysis bahia*) NOEC was 0.0042 µg a.i./L (overlying water), derived from a 28-day flow-through study without sediment. The test concentration representing the LOEC was 0.0071 µg a.i./L (overlying water) which was also the highest concentration tested. At the LOEC of 0.0071 µg a.i./L (overlying water), 28-day observed effects were a 39% reduction in number of offspring per female, a reduction of 27% in F_0 post-pairing survival and a reduction of 6.1% in 96-hour F_1 survival.

Overall conclusion on the risk to aquatic invertebrates

The runoff model is conservative in that it assumes 100% of active ingredient is instantaneously introduced to the surrounding soil from the treated seeds at the time of planting. Standard best management practice label statements to reduce runoff entering sensitive aquatic habitats are required on both product labels. When used according to label directions, the risks to aquatic invertebrates from the use of isocycloseram as a seed treatment are acceptable.

Fish

Effects metrics from the most sensitive species were compared to the screening level EEC of 1.97 µg a.i./L. The resulting RQs did not exceed the LOC for freshwater and marine fish (RQ range: 0.02–0.3).

When used according to label directions, the risks to fish from the use of isocycloseram as a seed treatment are acceptable.

Amphibians

Effects metrics from the most sensitive species of freshwater fish were used as a surrogate for amphibian endpoints. When compared to the screening level EEC of 10.5 µg a.i./L, the resulting RQ did not exceed the LOC for amphibians (RQ: 0.9).

When used according to label directions, the risks to amphibians from the use of isocycloseram as a seed treatment are acceptable.

Algae and Aquatic Plants

Effects metrics from the most sensitive species were compared to the screening level EEC of 1.97 µg a.i./L. The resulting RQs did not exceed the LOCs for algae and aquatic vascular plants (RQ range: < 0.004–0.01).

When used according to label directions, the risks to algae and aquatic plants from the use of isocycloseram as a seed treatment are acceptable.

4.2.3 Risks to non-target organisms from structural uses (cockroach baits)

Outdoor applications are proposed for the exterior surfaces of buildings and other structures, at pest entry sites and to other structures acting as a cockroach harborage within 1 m of a building or structure. The proposed use of isocycloseram as a cockroach bait is expected to result in minimal environmental exposure to terrestrial and aquatic organisms.

When used according to label directions, the risks to terrestrial and aquatic organisms from the use of isocycloseram as a structural cockroach bait are acceptable.

4.2.4 Environmental review of co-formulated active ingredients

The proposed end-use product, A23128 ST, is a co-formulation of isocycloseram (15.4 g/L), difenoconazole (36.8 g/L), sedaxane (15.4 g/L), metalaxyl-M (and S-isomer) (9.2 g/L) and fludioxonil (7.6 g/L).

The proposed rates for the co-formulated active ingredients all fall within current registered use patterns. The environmental risk assessments for difenoconazole (PRVD2021-06 and RVD2022-05), sedaxane (PRD2015-03 and RD2015-10), metalaxyl-M (PRVD2007-10 and RVD2008-03) and fludioxonil (PRVD2016-03 and RVD2018-04) may be consulted for additional information on these active ingredients.

4.2.5 Environmental incident reports

As of 21 May 2025, no environmental incident reports involving isocycloseram have been submitted to Health Canada.

5.0 Value

Structural product

VANECTO COCKROACH GEL BAIT will provide control of cockroaches in commercial, industrial and residential areas and will provide users with a new mode of action for the management of cockroaches, which may reduce the risk of resistance development. Value information submitted to support the label claims for VANECTO COCKROACH GEL BAIT consisted of efficacy trials on multiple cockroach species. The submitted value information was sufficient to support a claim of control of cockroaches in commercial, industrial and residential areas.

Seed treatment products

For EQUENTO, wheat (spring and winter) and barley field efficacy trials, winter wheat outdoor pot trials, and scientific rationales supported claims to control wireworms, European chafers and June beetles on wheat, oat, barley, rye and triticale seedlings. In trials, treatment with EQUENTO resulted in consistently positive and often strong effects on plant stand and yield.

For A23128 ST, field barley, durum and spring wheat bridging trials, scientific rationales and the label of the registered product Vibrance Quattro Seed Treatment (Reg. No. 31408) supported claims to control wireworms, European chafers, June beetles on seedlings at moderate insect pest pressures, as well as to control or suppress an array of seed and soil-borne fungal diseases. Control of the aforementioned insects under high pest pressures with a tank mix of A23128 ST and EQUENTO, as directed, was supported by data submitted to support insecticide claims for EQUENTO.

EQUENTO and A23128 ST contain a new Group 30 insecticide that will provide wheat, oat, barley, rye and triticale growers with an additional alternative for control of wireworms, European chafers, and a new active ingredient for control of June beetles. Isocycloseram is lethal to these insect pests; as such, it is expected to reduce pest populations in treated fields. EQUENTO and A23128 ST may facilitate resistance management of European chafers on these crops.

Further details of the supported uses of each of the above products are listed in Appendix I, Tables 26–28.

6.0 Pest Control Product Policy Considerations

6.1 Toxic Substances Management Policy Considerations

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

During the review process, isocycloseram and its transformation products were assessed in accordance with the PMRA Regulatory Directive DIR99-03[10] and evaluated against the Track 1 criteria. Health Canada has reached the conclusion that isocycloseram 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.* The list is used as described in the Science Policy Note SPN2020-01 and is based on existing policies and regulations, including the *Toxic Substance Management Policy* and *Formulants Policy*, and takes into consideration the *Ozone-depleting Substances and Halocarbon Alternatives Regulations* under the *Canadian Environmental Protection Act, 1999*, (substances designated under the *Montreal Protocol*).

Health Canada has reached the conclusion that isocycloseram and its end-use products, EQUENTO, A23128 ST and VANECTO COCKROACH GEL BAIT do not contain any formulants or contaminants identified on Parts 1 or 3 of the *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern*.

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

7.0 Proposed Regulatory Decision

Health Canada's PMRA, under the authority of the *Pest Control Products Act*, is proposing registration for the sale and use of Isocycloseram Technical, VANECTO COCKROACH GEL BAIT, EQUENTO and A23128 ST. VANECTO COCKROACH GEL BAIT, containing

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

isocycloseram, is for the control of cockroaches in commercial, industrial and residential buildings and other listed structures. EQUENTO, containing isocycloseram, is a seed treatment product for the control of insect pests on wheat, oat, barley, rye and triticale. A23128 ST, containing isocycloseram, difenoconazole, sedaxane, metalaxyl-M (and S-isomer) and fludioxonil, is another seed treatment product for the control of insect pests and the control or suppression of seed-borne and soil-borne diseases on wheat, oat, barley, rye and triticale.

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
♀	female
♂	male
>	greater than
≥	greater than or equal to
<	less than
≤	less than or equal to
λ	wavelength
µg	microgram(s)
°C	degrees Celsius
abs.	absolute
a.i.	active ingredient
AD	administered dose
ADI	acceptable daily intake
A/G	albumin/globulin ratio
AHETF	Agricultural Handlers Exposure Task Force
ALP	alkaline phosphatase
AOPWIN	Atmospheric Oxidation Program for Microsoft Windows
AR	applied radioactivity
ARfD	acute reference dose
atm	atmosphere
AUC	area under the curve
BAF	bioaccumulation factor
BBCH	Biologishe Bundesanstalt, Bundessortenamt and Chemical industry
BCF	bioconcentration factor
BDC	bile duct-cannulated
Bq	becquerel
bw	body weight
bwg	body weight gain
C_0	concentration at time = 0
CAF	composite assessment factor
C_{max}	peak concentration
CAS	Chemical Abstracts Service
CEPA	*Canadian Environmental Protection Act*
cm	centimetres
cm^3	cubic centimetre(s)
CR	chemical-resistant
d	day(s)
DFOP	double first-order in parallel
DFZ	difenoconazole
DT_{50}	dissipation time 50% (the dose required to observe a 50% decline in concentration)
dw	dry weight
EC3	concentration required to induce a threshold positive sensitization response (SI=3)

EDE	estimated daily exposure
EEC	estimated environmental concentration
EPI	Estimation Programs Interface
eq	equivalents
ER_{25}	effective rate for 25% of the population
ER_{50}	effective rate for 50% of the population
F1	first filial generation
F2	second filial generation
fc	food consumption
FLD	fludioxonil
g	gram(s)
GABA	gamma-aminobutyric acid
GD	gestation day
GI	gastrointestinal
GUS	groundwater ubiquity score
h	hour(s)
ha	hectare(s)
HAFT	highest average field trial
Hb	hemoglobin
Hct	hematocrit
HPLC	high performance liquid chromatography
HPLC-MS/MS	high performance liquid chromatography with tandem mass spectrometry
ICE	Isolated Chicken Eye
ICS	isocycloseram
ILV	independent laboratory validation
IORE	indeterminate order rate equation model
IRAC	Insecticide Resistance Action Committee
IUPAC	International Union of Pure and Applied Chemistry
i.v.	intravenous
kg	kilogram(s)
K_d	adsorption coefficient
K_{oc}	organic-carbon partition coefficient
K_{ow}	*n*–octanol-water partition coefficient
KOWWIN	K_{ow} for Microsoft Windows
kPa	kilopascal(s)
L	litre(s)
LAFT	lowest average field trial
LC_{50}	lethal concentration causing 50% mortality
LD_{50}	lethal dose causing 50% mortality
LDH	lactate dehydrogenase
LLNA	local lymph node assay
LOAEL	lowest observed adverse effect level
LOC	level of concern
LOD	limit of detection
LOEC	low observed effect concentration
LOQ	limit of quantitation
LR_{50}	lethal rate on 50% of the population
LSC	liquid scintillation counting

m	metre(s)
m^2	square metre(s)
m^3	cubic metre(s)
MAS	maximum average score for 24, 48 and 72 hours
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MEA	method efficiency adjustment
MFN	metalaxyl-M (and S-isomer)
MIS	maximum irritation score
mg	milligram(s)
mL	millilitre(s)
M/L/A	mixer/loader/applicator
MOA	mode of action
MOE	margin of exposure
mol	mole
MRL	maximum residue limit
MS/MS	tandem mass spectrometry
N/A	not applicable
NADPH	Nicotinamide adenine dinucleotide phosphate
NAFTA	North American Free Trade Agreement
ng	nanogram(s)
nm	nanometres
NOAEDD	no observed adverse effect dietary dose
NOAEL	no observed adverse effect level
NOEC	no observed effect concentration
NZW	New Zealand white
OECD	Organisation for Economic Co-operation and Development
P	parental generation
Pa	Pascal(s)
PA	paste
PBI	plant-back interval
PCO	pest control operator
PCPA	*Pest Control Products Act*
PES	post-extraction solids
PHI	preharvest interval
pK_a	dissociation constant
PMRA	Pest Management Regulatory Agency
PND	postnatal day
PPE	personal protective equipment
ppm	parts per million
PWC	pesticide water calculator
QuEChERS	Quick, Easy, Cheap, Effective, Rugged, and Safe
R	correlation coefficient
R^2	coefficient of determination
RBC	red blood cells
rel.	relative
RQ	risk quotient
SDEV	standard deviation

SDX	sedaxane
SFO	single first order
SPN	science policy note
SU	suspension
$T_{1/2}$	half-life of elimination
$T_{1/2\ rep}$	representative half-life
TC	transfer coefficient
TEER	Transepithelial electrical resistance
TG	test guideline
T_{max}	time of peak concentration
TP	transformation product
TRR	total radioactive residue
TSMP	Toxic Substances Management Policy
UCL	upper certified limit
UF	uncertainty factor
U.S.	United States
USEPA	United States Environmental Protection Agency
v/v	volume per volume dilution
w/w	weight for weight
WBC	white blood cells
wt	weight

Appendix I Tables and figures

Table 1a Required personal protective equipment based on the acute toxicity profile of EQUENTO and exposure to isocycloseram

Seed types	Tasks	PPE/Engineering controls
For commercial seed treatment (facilities and mobile treaters)		
Wheat (spring, winter, durum), Barley, Oats, Rye, Triticale	Mixing, loading, treating, calibrating, bagging, sewing seed bags, stacking and driving a forklift	Open or closed transfer. Wear a long-sleeved shirt, long pants, chemical-resistant gloves, socks and shoes.
	Cleaning and repair	Wear chemical-resistant coveralls over a long-sleeved shirt, long pants, chemical-resistant gloves, socks and chemical-resistant footwear.
For on-farm seed treatment and planting of treated seeds		
Wheat (spring, winter, durum), Barley, Oats, Rye, Triticale	Mixing, loading, treating, calibrating, cleaning, repairing, planting and any other activities involving handling treated seeds	Open or closed transfer. Wear long-sleeved shirt, long pants, chemical-resistant gloves, socks and shoes. Use a closed-cab tractor when planting. Gloves are not required within the closed cab.
For planting commercially treated seeds		
Wheat (spring, winter, durum), Barley, Oats, Rye, Triticale	Handling and Planting	Wear coveralls over a long-sleeved shirt, long pants, chemical-resistant gloves, socks, and shoes. Use a closed-cab tractor when planting. Gloves are not required within the closed cab.

Table 1b Required personal protective equipment based on the acute toxicity profile of A23128 ST and exposure to isocycloseram

Seed types	Tasks	PPE/Engineering controls
For commercial seed treatment (facilities including mobile treaters)		
Wheat (spring, winter, durum), Barley, Oats, Rye, Triticale	Mixing, loading, treating, calibrating, bagging, sewing seed bags, stacking and driving a forklift	Open or closed transfer. Wear a long-sleeved shirt, long pants, chemical-resistant gloves, socks and shoes. Wear a respirator[1] when bagging, sewing, stacking bags of treated seed or when transferring seed to a storage bin and when driving a forklift.
	Cleaning and repair	Wear chemical-resistant coveralls over a long-sleeved shirt, long pants, chemical-resistant gloves, socks, chemical-resistant footwear and a respirator.[1]
For on-farm seed treatment and planting of treated seeds		
Wheat (spring, winter, durum), Barley, Oats, Rye, Triticale	Mixing, loading, treating, calibrating, cleaning, repairing, planting and any other activities involving handling treated seeds	Open or closed transfer. Wear a long-sleeved shirt, long pants, chemical-resistant gloves, socks, shoes and a respirator.[1] Use a closed-cab tractor when planting. Gloves and a respirator[1,2] are not required within the closed cab.
For planting commercially treated seeds		
Wheat (spring, winter, durum), Barley, Oats, Rye, Triticale	Handling and Planting	Wear coveralls over a long-sleeved shirt, long pants, chemical-resistant gloves, socks, shoes and a respirator[1]. Use a closed-cab tractor when planting. Gloves and a respirator[1,2] are not required within the closed cab.

[1] A respirator is a NIOSH-approved N95 (minimum) filtering facepiece respirator (dust mask) that is properly fit tested.

[2] The respirator is not required during planting when the closed cab provides both a physical barrier and respiratory protection (such as dust/mist filtering and/or vapour/gas purification system). The closed cab must have a chemical-resistant barrier that totally surrounds the occupant and prevents contact with pesticides outside the cab.

Table 2a Residue analysis in environmental media

Matrix	Method ID	Analyte	Method type	LOQ	Reference (PMRA No.)
Soil (anerobic)	GRM072.12A	Isocycloseram (SYN547407)	HPLC-M/MS	0.001 mg/kg	3245953
		SYN549431		0.001 mg/kg	
		SYN549107		0.001 mg/kg	
		SYN550738		0.001 mg/kg	
Soil (aerobic)	GRM072.16A	SYN551057	HPLC-M/MS	0.0035 mg/kg	3245949
		SYN550321		0.005 mg/kg	
		SYN549110		0.0035 mg/kg	
		SYN551248		0.010 mg/kg	
		SYN548569		0.005 mg/kg	
		SYN549543		0.010 mg/kg	
		SYN550455		0.010 mg/kg	
		SYN550602		0.010 mg/kg	
		SYN550603		0.005 mg/kg	
		SYN549546		0.005 mg/kg	
		SYN551113		0.005 mg/kg	
		SYN549433		0.010 mg/kg	
Water (surface and ground)	GRM072.17A	Isocycloseram	HPLC-M/MS	0.05 µg/L	3245954
		SYN550455		0.05 µg/L	
		SYN549431		0.05 µg/L	
		SYN551485		0.05 µg/L	
		SYN549107		0.05 µg/L	
Pollen	GRM072.05A	Isocycloseram	HPLC-M/MS	1 µg/kg	3245972
Nectar		Isocycloseram		1 µg/kg	

Table 2b Residue analysis in plant and animal matrices

Analytical methods	Matrices	Analyte	Method ID/Type	LOQ (ppm)	Reference (PMRA No.)
Animal matrices					
Enforcement	Bovine milk, cream, muscle, fat, liver, and kidney Poultry eggs, muscle, fat and liver	Isocycloseram	QuEChERS method EN 15662 :2009/ LC-MS/MS	0.01	3245921
ILV of Enforcement	Bovine milk and liver; poultry eggs	Isocycloseram	QuEChERS method EN 15662 :2009/ LC-MS/MS	0.01	3245934
Radiovalidation	Halophenyl-U-^{14}C radiolabel Laying hen: liver, muscle, fat, and egg yolk Lactating goat: liver, kidney, and milk				
Data Gathering	Bovine milk, cream, muscle, fat, liver, and kidney Poultry eggs, muscle, fat, and liver	Isocycloseram	GRM072.02A; GRM072.14A/ LC-MS/MS	0.01	3245920 3245926 3245937 3245943
Plant matrices					
Enforcement	Tomato, soybean, dry broad bean, wheat grain, orange, coffee	Isocycloseram	QuEChERS method EN 15662 :2009/ LC-MS/MS	0.01	3245923
ILV of Enforcement	Tomato, dry broad beans, coffee	Isocycloseram	QuEChERS method EN 15662 :2009/ LC-MS/MS	0.01	3245933
Radiovalidation	Halophenyl-U-^{14}C radiolabel Primary crops: Mustard greens, soybeans (forage, hay), tomatoes, paddy rice (forage, hay, grain) Secondary crops: Immature lettuce, wheat (forage, straw), radish (roots, leaves)				

Analytical methods	Matrices	Analyte	Method ID/Type	LOQ (ppm)	Reference (PMRA No.)
Data Gathering	Cereal (grain, forage, straw); broccoli; tomato; potato; onion; dry beans; fresh beans; orange; apple; sugar beet; peach; lettuce; rice; soybeans; almonds; coffee	Isocycloseram	GRM072.10A; GRM072.10B/ LC-MS/MS	0.01	3245928 3245929
	Soybean seed; coffee beans; wheat straw; almond	Isocycloseram	GRM072.11A; GRM072.11B/ LC-MS/MS	0.01	3245938 3245941 3245942
	Canola oil; orange oil	Isocycloseram	GRM072.15A/ LC-MS/MS	0.01	3245922 3245944

Table 3 Identification of select isomers, metabolites and transformation products of isocycloseram

Code	Chemical name	Description/Source
SYN547407 (Isocycloseram)	Benzamide, 4-[5-(3,5-dichloro-4-fluorophenyl)-4,5-dihydro-5-(trifluoromethyl)-3-isoxazolyl]-N-(2-ethyl-3-oxo-4-isoxazolidinyl)-2-methyl-	Technical grade active ingredient, contains 80–100% of the (5S,4R)-isomer
SYN548088 (Isomer A)	Benzamide, 4-[(5S)-5-(3,5-dichloro-4-fluorophenyl)-4,5-dihydro-5-(trifluoromethyl)-3-isoxazolyl]-N-[(4R)-2-ethyl-3-oxo-4-isoxazolidinyl]-2-methyl-	(5S,4R)-isomer of SYN547407
SYN548089 (Isomer B)	Benzamide, 4-[(5S)-5-(3,5-dichloro-4-fluorophenyl)-4,5-dihydro-5-(trifluoromethyl)-3-isoxazolyl]-N-[(4S)-2-ethyl-3-oxo-4-isoxazolidinyl]-2-methyl-	(5S,4S)-isomer of SYN547407
SYN548090 (Isomer C)	Benzamide, 4-[(5R)-5-(3,5-dichloro-4-fluorophenyl)-4,5-dihydro-5-(trifluoromethyl)-3-isoxazolyl]-N-[(4R)-2-ethyl-3-oxo-4-isoxazolidinyl]-2-methyl-	(5R,4R)-isomer of SYN547407
SYN548091 (Isomer D)	Benzamide, 4-[(5R)-5-(3,5-dichloro-4-fluorophenyl)-4,5-dihydro-5-(trifluoromethyl)-3-isoxazolyl]-N-[(4S)-2-ethyl-3-oxo-4-isoxazolidinyl]-2-methyl-	(5R,4S)-isomer of SYN547407
SYN549433 (CSDK353925)	4-[3-(3,5-dichloro-4-fluoro-phenyl)-4,4,4-trifluoro-3-hydroxy-butanoyl]-N-(2-ethyl-3-oxo-isoxazolidin-4-yl)-2-methyl-benzamide	Rat, soil, water-sediment

Code	Chemical name	Description/Source
SYN549432	4-[5-(3,5-dichloro-4-hydroxy-phenyl)-5-(trifluoromethyl)-4H-isoxazol-3-yl]-N-(2-ethyl-3-oxo-isoxazolidin-4-yl)-2-methyl-benzamide	Rat
SYN549554 (CSDK357066)	2-[[4-[3-(3,5-dichloro-4-fluoro-phenyl)-4,4,4-trifluoro-3-hydroxy-butanoyl]-2-methyl-benzoyl]amino]-3-hydroxy-propanoic acid	Rat, soil, water-sediment
SYN549553	N-[2-amino-1-(hydroxymethyl)-2-oxo-ethyl]-4-[3-(3,5-dichloro-4-fluoro-phenyl)-4,4,4-trifluoro-3-hydroxy-butanoyl]-2-methyl-benzamide	Rat
SYN549543 (CSDK356297)	2-[[4-[5-(3,5-dichloro-4-fluoro-phenyl)-5-(trifluoromethyl)-4H-isoxazol-3-yl]-2-methyl-benzoyl]amino]-3-hydroxy-propanoic acid	Rat, goat, hen, crops, soil, water-sediment, hydrolysis
SYN549436	4-[5-(3,5-dichloro-4-fluoro-phenyl)-5-(trifluoromethyl)-4H-isoxazol-3-yl]-2-methyl-N-(3-oxoisoxazolidin-4-yl)benzamide	Rat, goat, hen, crops
SYN550602 (CSDK426049)	4-[3-(3,5-dichloro-4-fluoro-phenyl)-4,4,4-trifluoro-3-hydroxy-butanoyl]-N-[2-(ethylamino)-1-(hydroxymethyl)-2-oxo-ethyl]-2-methyl-benzamide	Rat, soil, water-sediment
SYN548569 (CSCV769769, CA5697A)	1-(3,5-dichloro-4-fluoro-phenyl)-2,2,2-trifluoro-ethanone	Goat, hen, crops, soil, water-sediment

Table 4 Toxicology reference values for use in health risk assessment for isocycloseram[1]

Exposure scenario	Study	Point of departure and endpoint	CAF[2] or Target MOE
Acute dietary females 13–49 years old	Oral developmental toxicity study in rats	Developmental NOAEL = 7.5 mg/kg bw/day **Corrected = 6.5 mg/kg bw/day** Malformations in the absence of maternal toxicity	1000
ARfD (females 13-49 years old) = 0.007 mg/kg bw			
Acute dietary infants and children <12 years old	Dietary reproductive toxicity study in rats	Offspring NOAEL = 4.1 mg/kg bw/day **Corrected = 3.5 mg/kg bw/day** Decreased viability in the presence of parental toxicity	300

Exposure scenario	Study	Point of departure and endpoint	CAF[2] or Target MOE
ARfD (infants and children <12 years old) = 0.012 mg/kg bw			
Acute dietary youth 12–16 years old and adults 16+ years old	90-day oral toxicity study in dogs	NOAEL = 15 mg/kg bw/day **Corrected = 13 mg/kg bw/day** ↓ bw/bwg (week 1)	100
ARfD (youth 12–16 years old and adults 16+ years old) = 0.13 mg/kg bw			
Repeated (chronic) dietary	Oral developmental toxicity study in rats	Developmental NOAEL = 7.5 mg/kg bw/day **Corrected = 6.5 mg/kg bw/day** Malformations in the absence of maternal toxicity	1000
ADI = 0.007 mg/kg bw/day			
Occupational: Dermal[3] and inhalation[4] (all durations)	Oral developmental toxicity study in rats	Developmental NOAEL = 7.5 mg/kg bw/day **Corrected = 6.5 mg/kg bw/day** Malformations in the absence of maternal toxicity	1000
Residential: Dermal and incidental oral (all durations) (children 1 to <11 years old)	Dietary reproductive toxicity study in rats	Offspring NOAEL = 4.1 mg/kg bw/day **Corrected = 3.5 mg/kg bw/day** Decreased viability in the presence of parental toxicity	300
Residential: Dermal (all durations) (youth 11 to <16 years old, adults 16+ years old)	Oral developmental toxicity study in rats	Developmental NOAEL = 7.5 mg/kg bw/day **Corrected = 6.5 mg/kg bw/day** Malformations in the absence of maternal toxicity	1000
Aggregate residential: Dermal and oral (all durations) (children 1 to <11 years old)	Dermal and oral: Dietary reproductive toxicity study in rats	Common endpoint: Decreased offspring viability in the presence of parental toxicity Dermal and oral: Offspring NOAEL = 4.1 mg/kg bw/day **Corrected = 3.5 mg/kg bw/day**	Dermal and oral: 300

Exposure scenario	Study	Point of departure and endpoint	CAF[2] or Target MOE
Aggregate residential: Dermal and oral (all durations) (youth 11 to <16 years old, adults 16+ years old)	Dermal and oral: Oral developmental toxicity study in rats	Common endpoint: Malformations in the absence of maternal toxicity Dermal and oral: Developmental NOAEL = 7.5 mg/kg bw/day **Corrected = 6.5 mg/kg bw/day**	Dermal and oral: 1000
Cancer	Equivocal increase in Leydig cell tumours in rats (low level of concern to humans). Equivocal increase in ovarian luteomas in mice. Toxicology reference values selected for non-cancer risk assessment are protective of any residual concerns regarding carcinogenic potential.		

[1] The selected points of departure were corrected for the concentration of isomer SYN548088 within Isocycloseram Technical, as well as for the purity of Isocycloseram Technical (up to 100%), to achieve the stated reference values.

[2] 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 and residential assessments.

[3] Since an oral NOAEL was selected, a dermal absorption factor of 8% was used in a route-to-route extrapolation.

[4] Since an oral NOAEL was selected, an inhalation absorption factor of 100% (standard value) was used in route-to-route extrapolation.

Table 5 Toxicity profile of technical isocycloseram

Effects observed in both sexes are presented first followed by sex-specific effects in males, then females, each separated by semi-colons. Organ weight effects reflect both absolute organ weights and relative organ to body weights unless otherwise noted. Effects seen above the LOAEL(s) have not been reported in this table for most studies for reasons of brevity.

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

Study type/ Animal/PMRA No.	Study results
Toxicokinetic studies	
Preliminary absorption, distribution, metabolism, elimination, pharmacokinetics (gavage or i.v., single dose) [Methylphenyl-U-^{14}C]-SYN547407 Wistar rat PMRA No. 3245977	**Study considered acceptable with limitations** [Methylphenyl-U-^{14}C]-SYN547407 was administered as a single low (3 mg/kg bw) or high (300 mg/kg bw) oral gavage dose, or a single low (1 mg/kg bw) i.v. dose to intact rats. Elimination: Feces was the major route of elimination following oral dosing at 3 and 300 mg/kg bw. Excretion was incomplete 168 hours post-dose at the low dose as radioactivity persisted in the carcass and GI tract for both sexes and was near completion by 168 hours post-dose at the high dose with only a minimal amount of radioactivity persisting. Elimination via expired air was negligible. Feces was also the major route of elimination following i.v. administration. Urinary elimination was a minor route of elimination in all doses and administrations. Pharmacokinetics: In the blood, C_{max} at the low oral dose was at 8/4 hours post-dose in ♂/♀. Oral bioavailability was 88/97% in ♂/♀. At the high dose, C_{max} was observed at 30 hours post-dose in both sexes. Oral bioavailability decreased to 22/26% in ♂/♀. The estimates of $T_{1/2}$ and $AUC_{(0\text{-inf})}$ were unreliable at both doses, as the terminal phase could not be adequately defined. Blood concentrations in rats given a single i.v. dose were level through 30 hours then decreased at 48 hours post-dose. In the plasma, C_{max} at the low oral dose was at 6 hours post-dose in both sexes and steadily decreased through 72 hours post-dose. The $T_{1/2}$ was 26/29 hours in ♂/♀. At the high dose, C_{max} in plasma was noted at 24/48 hours post-dose in ♂/♀ and decreased to 72 hours post-dose. The estimates of $T_{1/2}$ and $AUC_{(0\text{-inf})}$ were unreliable. The blood to plasma ratios showed radioactivity that was generally associated more with the plasma at both doses. Metabolism: [^{14}C]-SYN547407 was readily extractable using acetonitrile and acetonitrile/water mixtures and has potential for degradation of SYN547407 in plasma. SYN547407 was extensively metabolized in the rat by oxidative defluorination followed by opening of the isoxazole ring and cycloserine ring, de-ethylation of

Study type/ Animal/PMRA No.	Study results
	the cycloserine ring to SYN549105, and cleavage of oxazolidinone moiety to SYN549106. Limitations: small group sizes, limited characterization of metabolites.
Absorption, Distribution, Excretion (gavage, single dose) [Methylphenyl-U-^{14}C]-SYN547407 [Halophenyl-U-^{14}C]-SYN547407 [Oxoisoxazolidinyl-^{14}C]-SYN547407 Wistar rat PMRA No. 3245974	^{14}C-SYN547407, radiolabeled at three different positions, was administered as a single oral low (1 mg/kg bw) or high (10 mg/kg bw) dose to intact or BDC rats. Absorption: For the BDC rats, the absorption of methylphenyl radiolabel was 68/66% of the AD in ♂/♀ at the low dose and decreased to 53/52% of the AD in ♂/♀ at the high dose. Excretion: Fecal excretion was the major route of elimination in intact animals for all radiolabels at both doses, accounting for 77% to 98% of the AD. Fecal excretion was fairly rapid for all radiolabels, with the majority being eliminated between 24 and 48 hours. Excretion was incomplete by 168 hours post-dosing for all radiolabels, as there was remaining radioactivity detected in the tissue, GI tract, GI tract contents and carcass. In BDC rats, at 72 hours post-dosing with methylphenyl radiolabel at the low dose, the major route of elimination was via the bile with 50/46% of the AD excreted in ♂/♀. At the high dose, excretion via the feces (47/46% in ♂/♀) was slightly higher than via biliary excretion (41/33% in ♂/♀). Excretion was incomplete by 72 hours post-dosing as there was remaining radioactivity detected in the GI tract, GI tract contents and carcass. Distribution: In intact rats with the methylphenyl radiolabel, the kidneys were observed to have the highest tissue concentration. Radioactive concentrations were found in the blood and plasma of intact rats given the methylphenyl, halophenyl and oxoisoxazolidinyl radiolabels at 168 hours post-dosing, and in BDC rats given the methylphenyl radiolabel at 72 hours post-dosing.
Biotransformation (gavage, single or repeat dose) [Methylphenyl-U-^{14}C]-SYN547407 [Halophenyl-U-^{14}C]-SYN547407 [Oxoisoxazolidinyl-^{14}C]-SYN547407 Wistar rat	^{14}C-SYN547407, radiolabeled at three different positions, was administered as a single oral low (1 mg/kg bw) or high (10 mg/kg bw) dose or repeated oral high doses (7 or 10 daily doses of [Methylphenyl-U-^{14}C]-SYN547407 at 10 mg/kg bw/day; ♂ only) to intact or BDC rats. In intact rats given a single dose of the methylphenyl radiolabel, SYN549436 was the largest circulating metabolite component in the plasma at both doses. The majority of the AD was excreted via bile into the feces, with a small fraction excreted in urine for all radiolabels. The major metabolite in feces following both doses of the oxoisoxazolidinyl and methylphenyl radiolabel was SYN549553. The major metabolite in feces following a low dose of

Study type/ Animal/PMRA No.	Study results
PMRA No. 3245975	halophenyl radiolabel was SYN549554 in ♂ and SYN549553 in ♀. With the high dose, SYN550602/SYN549432 and SYN549553 were most prominent in feces of ♂ and ♀, respectively. In ♂ rats given 7 or 14 daily doses, SYN549553 was the major metabolite in feces. In BDC rats, the major metabolite in the feces was SYN549553. In the bile, SYN549543 and the glucuronide conjugates of SYN549432 and SYN549436 were the major metabolites in both sexes at both doses. Unchanged SYN547407 was not detected in any urine sample and was a minor component in the feces with all radiolabels and a minor component with the methylphenyl radiolabel in bile and plasma. Biotransformation led to ring opening of the isoxazole ring, ring opening and cleavage of the oxazolidinone ring, oxidative defluorination and glucuronic acid conjugation.
Pharmacokinetics (gavage and i.v., single dose) [Methylphenyl-U-^{14}C]-SYN547407 Wistar rats PMRA No. 3245976	[Methylphenyl-U-^{14}C]-SYN547407 was administered as a single low (1 mg/kg bw) or high (10 mg/kg bw) oral gavage dose, or a single low (1 mg/kg bw) i.v. dose to intact rats. After a single oral low dose, C_{max} in the blood and plasma was observed at 8/6 hours post-dosing in ♂/♀. In the blood, $T_{1/2}$ was 34/39 hours in ♂/♀. In the plasma, $T_{1/2}$ was 25/26 hours in ♂/♀. Absorption was considered complete, as oral bioavailability was 96/100% in ♂/♀. After a single oral high dose, C_{max} in the blood and plasma was observed at 12/4 hours post-dosing in ♂/♀. In the blood, $T_{1/2}$ was 39 hours in ♂ could not be reliably estimated in ♀. In the plasma, $T_{1/2}$ was 30/ 29 hours in ♂/♀. The oral bioavailability was approximately 88% in both sexes. From the low to high dose, the increase in C_{max} and $AUC_{(0-t)}$ in both sexes were similar in both the blood and plasma. Following a single i.v. dose, C_0 was 0.306/0.308 µg eq/g in ♂/♀. Concentrations in the blood plateaued through 24 hours post-dosing, then decreased steadily through 72 hours. The $AUC_{(0-t)}$ was similar in both sexes. The $T_{1/2}$ was 26 hours in ♀ and in ♂ could not be reliably estimated. Generally, no sex-related differences were noted in the pharmacokinetics at either dose or administration method.
Distribution and Excretion (gavage, single dose) - Whole-body autoradiography [Methylphenyl-U-^{14}C]-SYN547407	[Methylphenyl-U-^{14}C]-SYN547407 was administered as a single low (3 mg/kg bw) or high (50 mg/kg bw) oral gavage dose to intact rats. At the low dose, peak concentrations in tissues were observed at 6–12/6–24 hours post-dosing in ♂/♀. At the high dose, peak concentrations were noted between 30 and 48 hours in both sexes.

Study type/ Animal/PMRA No.	Study results
Wistar rat PMRA No. 3245978	Generally, the highest concentrations of radioactivity were observed in tissues involved with metabolism and excretion, such as the bile duct, liver and GI tract. The $T_{1/2}$ in blood was 51/44 hours for ♂/♀ at the low dose, and 48/59 hours for ♂/♀ at the high dose. Elimination of radioactivity occurred slowly as it was detectable in the blood and tissues at 168 hours post-dosing. The peak amount of radioactivity in the tissues and blood seemed to be dose proportional in both sexes.
Distribution and Excretion (gavage, single or repeat dose) [Methylphenyl-U-^{14}C]-SYN547407 Wistar rats PMRA No. 3245979	[Methylphenyl-U-^{14}C]-SYN547407 was administered as a single oral low (1 mg/kg bw) or high (10 mg/kg bw) dose or repeated oral high doses (14 daily doses at 10 mg/kg bw/day; ♂ only) to intact rats. Distribution: Peak tissue concentrations occurred at 8 and 4 hours following a single oral administration of the low and high doses, respectively. The liver, kidneys and adrenals had the highest concentrations of radioactivity. Tissue distribution was similar between sexes and dose levels. The $t_{1/2}$ of radioactivity in tissues were variable and were similar or greater than the blood or plasma. Overall, blood had a longer $T_{1/2}$ compared to the plasma. Following repeat oral doses, peak tissue concentrations were observed 24 hours after the last dose and were the highest in the kidneys and liver. Following both single and repeat doses, the GI tract, GI contents, carcass, the liver and kidneys had a high amount of radioactivity, which is consistent with biliary or fecal elimination of an oral dose. Excretion: Following repeated oral dosing, the main route of elimination was via the feces, while urinary elimination was a minor route. Elimination was considered incomplete 24 hours following the first and seventh dose with about 29% and 15%, respectively, of the AD excreted over the period. Elimination neared completion 10 days after the fourteenth dose as 2.9% of the AD remained in tissues, GI tract and carcass.
In Vitro Metabolism (non-guideline) [Methylphenyl-U-^{14}C]-SYN547407 [Halophenyl-U-^{14}C]-SYN547407	**Study considered acceptable with limitations** In vitro metabolism of SYN547407 was considered NADPH-dependent and occurred in human and rat liver microsomes following an incubation of 60 minutes. Eleven radio-HPLC peaks were observed. The same major metabolite was observed in the human (approximately 14% of the AD) and rat (approximately 8% of the AD) liver microsomes. The unchanged parent compound, SYN547407, accounted for approximately 80% of the AD in human and 86% of the AD in rat liver microsomes. There was likely no

Study type/ Animal/PMRA No.	Study results
[Oxoisoxazolidinyl-^{14}C]-SYN547407 Human liver microsomes Wistar rat liver microsomes PMRA No. 3245986	cleavage of the molecule as the majority of the metabolites identified with [methylphenyl-U-^{14}C]- and [oxoisoxazolidinyl-4,5-^{14}C] SYN547407 were also detected with [halophenyl-U-^{14}C] SYN547407. Overall, SYN547407 was metabolised in both the human and rat liver microsomes and the metabolic composition was similar in both species. Limitations: non-guideline study; not conducted to satisfy a guideline requirement but provides limited supplemental information; metabolites were not characterized.
Acute toxicity studies – Technical grade active ingredient	
Acute Oral Toxicity (Up/Down) Wistar rat PMRA No. 3245989	LD_{50} > 5000 mg/kg bw (♀) No clinical signs of toxicity. Low acute oral toxicity
Acute Oral Toxicity (Horn's method – not an OECD TG) Sprague-Dawley rat PMRA No. 3302603	LD_{50} = 4569 mg/kg bw (♀) Clinical signs of toxicity included emaciation, perineal soiling, low spontaneous movement, secretions around nose/mouth. Low acute oral toxicity
Acute Dermal Toxicity Wistar rat PMRA No. 3245990	LD_{50} > 5000 mg/kg bw (♂/♀) No clinical signs of toxicity. Low acute dermal toxicity
Acute Inhalation Toxicity (nose-only) Wistar rat PMRA No. 3245991	LC_{50} > 4.62 mg/L (♂/♀) Clinical signs of toxicity included red/brown staining of the head/eyes and nose. Low acute inhalation toxicity
Eye Irritation NZW rabbit PMRA No. 3245993	MAS = 0 MIS = 4.7/110 at 1 hour Non-irritating to the eye
Eye Irritation (In vitro ICE) COBB 500 chicken eyes	Overall ICE class = 3 × Class I Not a severe irritant and not a non-irritant according to OECD TG 438

Study type/ Animal/PMRA No.	Study results
PMRA No. 3245994	
Dermal Irritation NZW rabbit PMRA No. 3245992	MAS = 0 MIS = 0 Non-irritating to the skin
Sensitization (LLNA) CBA/Ca mouse PMRA No. 3245995	Positive EC3 = 41.2% Potential dermal sensitizer
Short-term toxicity studies	
28-Day Oral Toxicity (diet) CD-1 mouse PMRA No. 3245997	**Study considered acceptable with limitations** NOAEL = 17/21 mg/kg bw/day (♂/♀) LOAEL = 56/61 mg/kg bw/day (♂/♀) Effects at LOAEL: ↑ reticulocytes, ↑ WBC, ↑ spleen wt, ↑ hepatocellular hypertrophy (♂/♀); ↓ cholesterol, ↑ adrenal wt, ↑ thyroid wt, epithelial vacuolation of duodenum (♂); ↑ total protein, ↑ liver wt, ↑ severity of extramedullary hematopoiesis in the spleen (♀) Toxicokinetics: Blood concentrations of isocycloseram ↑ generally in a dose-proportional manner. There were no consistent differences in concentration between the sexes. Limitations: reactivity to stimuli, assessment of grip strength and motor activity were not conducted.
90-Day Oral Toxicity (diet) CD-1 mouse PMRA No. 3245999 PMRA No. 3246001	**Study considered acceptable with limitations** NOAEL = 8.0/9.9 mg/kg bw/day (♂/♀) LOAEL = 49/52 mg/kg bw/day (♂/♀) Effects at LOAEL: ↑ WBC, ↑ leukocytes, ↑ total protein, ↑ globulin, ↓ A/G ratio, ↓ cholesterol, ↑ liver wt, ↑ spleen wt, ↑ lymphoid cellularity in spleen (♂/♀); ↑ reticulocyte count, ↓ calcium, pale liver, ↑ erythropoiesis in spleen, vacuolation of the zona glomerulosa of the adrenals (♂); ↓ triglycerides, ↑ neutrophils, ↑ monocytes, vacuolation of the zona fasciculata of the adrenals, ↑ adrenal wt, ↑ thymus wt (♀) Toxicokinetics: Blood concentrations of isocycloseram ↑generally in a dose-proportional manner. Concentrations in ♂ were lower on Days 28 and 85 relative to Day 2; concentrations in ♀ were consistent at the various time points. There were no consistent differences in toxicokinetic parameters between the sexes.

Study type/ Animal/PMRA No.	Study results
	Limitations: no ophthalmoscopic examination, urinalysis, or assessment of clotting potential
28-Day Oral Toxicity (diet) Wistar rat PMRA No. 3245998	**Study considered acceptable with limitations** NOAEL = 4.3/4.5 mg/kg bw/day (♂/♀) LOAEL = 16/50 mg/kg bw/day (♂/♀) Effects at LOAEL: ↑ adrenal wt, hypertrophy of zona fasciculata of adrenal gland (♂/♀); 1 ♀ sacrificed on Day 12 due to clinical signs of toxicity (hunched posture, laboured respiration, bw loss, piloerection), ↓ bw/bwg, bw loss during first week, ↑ WBC, ↑ lymphocytes, ↑ monocytes, ↑ basophils, ↑ large unclassified cells, ↑ urea, ↓ cholesterol, ↓ albumin,↓ total protein, hepatocellular vacuolation, cortical tubular vacuolation in the kidneys (♀). Toxicokinetics: Blood concentrations ↑ with dose, reaching maximum levels on Days 9 and 16. Limitations: reactivity to stimuli, assessment of grip strength and motor activity were not conducted.
90-Day Oral Toxicity (diet) Wistar rat PMRA No. 3246000 PMRA No. 3246002	NOAEL = 3.9/13 mg/kg bw/day (♂/♀) LOAEL = 11/24 mg/kg bw/day (♂/♀) Effects at LOAEL: ↑ adrenal wt, ↑ WBC, testicular tubular degeneration, epididymis cellular debris, ↓ sperm in epididymis (♂) Toxicokinetics: Systemic exposure to isocycloseram (based on C_{max} and AUC) ↑ with dose, were highest for ♂ on Day 85 and for ♀ on Day 28 and were comparable between sexes on Day 2, but greater in ♀ than ♂ after extended dosing.
28-Day Oral Toxicity (capsule) (non-guideline) Beagle dog PMRA No. 3245996	**Study considered acceptable with limitations** **NOAELs not established** Effects at ≥50/35 mg kg bw/day: bw loss (♂/♀); ↓ fc (♂); ↓ overall bwg, ↑ rel. liver wt (♀). Effects at 70 mg/kg bw/day (♀): premature sacrifice of all but 1 animal, ↓ fc, clinical signs of toxicity (regurgitation of food, loose feces, emesis) Effects at 150 mg/kg bw/day [dosing at 150 mg/kg bw/day stopped on Day 4 then resumed at 80 mg/kg bw/day on Day 15 after a 10-day treatment-free period] (♂): premature sacrifice of all animals on Day 18, ↓ bw, clinical signs of toxicity (abnormal head movements, falling over, regurgitation of food, loose feces, emesis) Toxicokinetics: Systemic exposure estimates (C_{max}, AUC) were comparable between sexes and at various time points, and generally ↑ with dose. T_{max} was shorter on Day 28 (0.5–2 hours) compared with Day 1 (12–24 hours).

Study type/ Animal/PMRA No.	Study results
	Limitations: small group size
90-Day Oral Toxicity (capsule) Beagle dog PMRA No. 3246003	NOAEL = 15/5 mg/kg bw/day (♂/♀) LOAEL = 35[25]/15 mg/kg bw/day (♂/♀) Effects at ♀ LOAEL (≥15 mg/kg bw/day): ↓ bw/bwg (toward end of study at 15 mg/kg bw/day), ↓ fc (♀) Effects at ♂ LOAEL (35mg/kg bw/day [dosing at 35 mg/kg bw/day stopped on Day 13 then resumed at 25 mg/kg bw/day on Day 20 or 22 after a 7 or 9 day treatment-free period]): bw loss (as early as week 1) (♂/♀); ↓ bw/bwg (as early as week 1), ↓ fc (♂); ↓ RBC, ↓ Hb, ↓ Hct, ↑ MCH, ↑ MCHC (♀) Toxicokinetics: Systemic exposure (AUC and C_{max}) ↑ proportionally with dose level, with no difference between sexes. Concentrations ↑ up to 2 hours post-dosing, following by a biphasic decline up to 8 hours with a subsequent ↑ in concentration up to 24 hours.
28-Day Dermal Toxicity Wistar rat PMRA No. 3246005 PMRA No. 3246004	NOAEL = 100 mg/kg bw/day (♂/♀) LOAEL = 300 mg/kg bw/day (♂/♀) Effects at LOAEL: ↓ bwg, ↑ adrenal wt, hypertrophy and vacuolation of the adrenals (zona fasciculata) (♂/♀); ↓ fc, ↑ WBC, ↑ ALP, epithelial vacuolation in the duodenum and jejunum (♀) Toxicokinetics: Blood concentrations of isocycloseram appeared to ↑ sub-proportionally in ♂ and proportionally in ♀ relative to the administered dose. Blood concentrations were similar in both sexes at 100 mg/kg bw/day, but higher in ♀ when compared to ♂ at 300 and 1000 mg/kg bw/day.
Repeat-dose Inhalation Toxicity – Waiver Request PMRA No. 3283891	The request to waive the requirement for a repeat-dose inhalation toxicity study in rodents was approved on the basis that the reported vapour pressure of isocycloseram is $<6.2 \times 10^{-6}$ Pa at 25°C indicating low volatility suggesting that workers would not be exposed to the pesticide as a gas, vapour or aerosol. Toxicokinetic data following single low dose oral and i.v. administration was compared with bioavailability to demonstrate that systemic exposure would not be enhanced via inhalation. Additionally, the toxicity and exposure databases for isocycloseram demonstrated a low level of concern for potential route-specific toxicity via inhalation exposure considering there were no changes in lung weights and no histopathological findings noted in the lungs for any study in the database. Further, the acute inhalation toxicity of all end-use formulations were low, and thus further testing in rats would not generate additional useful information. Results of the in vitro airway irritation were considered equivocal due to the lack of positive control tissues to confirm the histological findings.

Study type/ Animal/PMRA No.	Study results
Chronic toxicity/Oncogenicity studies	
80-Week Oral Toxicity (diet) CD-1 mouse PMRA No. 3246017 PMRA No. 3411736	NOAEL = 1.7/1.8 mg/kg bw/day (♂/♀) LOAEL = 6.7/7.1 mg/kg bw/day (♂/♀) Effects at the LOAEL: ↑ mononuclear cell infiltration (epididymis) (♂); ↑ plasmacytosis in lymph nodes (mandibular, mesenteric, bronchial), ↑ mononuclear cell infiltration (larynx, rectum), ↑ plasma cell infiltration (spleen, thymus) (♀) Benign ovarian luteoma (%): 2.6, 0, 3.0, 12.1 (equivocally related to treatment) **Equivocal evidence of tumourigenicity**
2-Year Oral Carcinogenicity (diet) Wistar rat PMRA No. 3246015 PMRA No. 3246016 PMRA No. 3290052	NOAEL = 2.3/3.0 mg/kg bw/day (♂/♀) LOAEL = 7.0/9.2 mg/kg bw/day (♂/♀) Effects at LOAEL: ↓ RBC, ↓ Hct, ↓ Hb, ↑ phosphate (♂/♀); testicular tubular degeneration, epididymis cellular debris, ↓ sperm in epididymis, centrilobular hepatocyte vacuolation, ↑ WBC (♂); ↓ bwg (11% overall), ↑ WBC, ↑ creatinine, ↑ bile acids, ↓ globulin, centrilobular hepatocyte vacuolation (♀) Leydig cell adenoma (%): 2.6, 2.6, 3.0, 7.5 (low level of concern to humans, equivocally related to treatment) **Equivocal evidence of tumourigenicity**
Developmental/Reproductive toxicity studies	
Enhanced 1-Generation Reproductive Toxicity (gavage) Wistar rat PMRA No. 3245985 PMRA No. 3245987 The purpose of this study was to investigate the effects on gonadal function, estrous cycle, mating behaviour, conception, gestation, parturition, lactation and weaning.	Parental Toxicity NOAEL = 7.5 mg/kg bw/day (♂/♀) LOAEL = 15 mg/kg bw/day (♂/♀) Effects at LOAEL: epithelial vacuolation of the duodenum (♂/♀); centrilobular hepatocyte vacuolation (♂); epithelial vacuolation of the jejunum (♀) Offspring Toxicity NOAEL = 15 mg/kg bw/day (♂/♀) LOAEL not determined No treatment-related effects in offspring. Reproductive Toxicity NOAEL = 7.5/15 mg/kg bw/day (♂/♀) LOAEL = 15 mg/kg bw/day/not determined (♂/♀) Effects at LOAEL: testicular tubular degeneration (♂) Toxicokinetics: Mean blood concentrations of isocycloseram ↑ in a dose-proportional manner for both sexes. Concentrations peaked (T_{max}) at 2 hours for the low dose groups, 2-4 hours in the mid dose groups, and 4-8 hours in the high dose groups. Generally, there was a higher C_{max} and AUC in ♀ at the 7.5 and 15.0 mg/kg bw/day dose

Study type/ Animal/PMRA No.	Study results
	levels. The $T_{1/2}$ values ranged from 7.3–14.8 hours for the low and mid dose groups and were not calculable for the high dose groups.
2-Generation Reproductive Toxicity (diet) Wistar rat PMRA No. 3246019 PMRA No. 3246020 PMRA No. 3245987 PMRA No. 3435039	Parental Toxicity NOAEL = 4.0/4.1 mg/kg bw/day (♂/♀) LOAEL = 12 mg/kg bw/day (♂/♀) Effects at LOAEL: epithelial vacuolation of the duodenum/jejunum (P, F1) (♂/♀); ↑ abs. liver wt (F1), ↑ adrenal wt. (P), centrilobular hepatocyte vacuolation (P, F1) (♂) Offspring Toxicity NOAEL = 4.1 mg/kg bw/day LOAEL = 12 mg/kg bw/day 12 mg/kg bw/day: ↓ viability index day 0-4 (F1)(♂/♀); ↑ adrenal wt. (F1, F2) (♂) Reproductive Toxicity NOAEL = 4.0/4.1 mg/kg bw/day (♂/♀) LOAEL = 12 mg/kg bw/day (♂/♀) 12 mg/kg bw/day: ↓ live birth index (F1) (♂/♀); ↓ fertility index (F1), testicular tubular degeneration/atrophy (P, F1), ↓ sperm count (P, F1), ↑ abnormal sperm (P, F1) (♂); ↓ ovarian follicles (F1) (♀) No evidence of sensitivity of the young
Developmental Toxicity (gavage) – Dose range-finding Wistar rat PMRA No. 3246024	**Study considered acceptable with limitations.** **NOAELs not established.** Maternal Toxicity: ≥ 7.5 mg/kg bw/day: bw loss GD 6-7, ↓ overall bwg, ↓ fc 15 mg/kg bw/day: ↓ bw Developmental Toxicity: No treatment-related developmental effects (assessment included viability, weight, sex, external and visceral abnormalities). Toxicokinetics: Mean blood concentrations of isocycloseram were 241, 660, and 1700 ng/mL for the 3.5, 7.5, and 15 mg/kg bw/day dose groups, respectively. Limitations: dose range-finding study with small group sizes and limited fetal examination.
Developmental Toxicity (gavage) Wistar rat PMRA No. 3246022	Maternal Toxicity NOAEL = 15 mg/kg bw/day LOAEL not determined There were no adverse effects noted in the maternal animals. Developmental Toxicity NOAEL = 7.5 mg/kg bw/day

Study type/ Animal/PMRA No.	Study results
PMRA No. 3246021 PMRA No. 3246025 PMRA No. 3246023	LOAEL = 15 mg/kg bw/day Effects at the LOAEL: ↑ fetal and litter incidence of variations (incomplete supraoccipital cartilage of the skull) and malformations (fused cartilaginous ventral plate of the cervical vertebrae, bifurcated intersternal cartilage of the sternum, bifid sternebrae). **Evidence of sensitivity of the young** **Evidence of treatment-related malformations**
Developmental toxicity (gavage) – Dose range-finding NZW rabbit PMRA No. 3246026	**Study considered acceptable with limitations** **NOAELs not established** Maternal Toxicity Effects at 15 mg/kg bw/day: ↓ bwg Effects at 30 mg/kg bw/day: bw loss GD 6 onward, ↓ fc GD 6 to 8 and thereafter, all females sacrificed on GD 11 or 12, abnormally pale liver and/or jejunum upon necropsy Developmental Toxicity No treatment-related developmental effects (assessment included viability, weight, sex, external and visceral abnormalities). Toxicokinetics: Mean blood concentrations of isocycloseram were 400, 1170, and approximately 3000 ng/mL for the 7.5, 15, and 30 mg/kg bw/day dose groups, respectively. Limitations: dose range-finding study with small group sizes and limited fetal examination.
Developmental Toxicity (gavage) NZW rabbit PMRA No. 3246027 PMRA No. 3246028	Maternal Toxicity NOAEL = 15 mg/kg bw/day LOAEL not determined Developmental Toxicity NOAEL = 15 mg/kg bw/day LOAEL not determined No treatment-related developmental effects. No evidence of sensitivity of the young No treatment-related malformations
Genotoxicity Studies	
Bacterial Reverse Mutation Assay Salmonella typhimurium TA1535, TA1537, TA100, TA98; E. coli strains	Negative with or without metabolic activation. Tested to limit concentration.

Study type/ Animal/PMRA No.	Study results
WP2uvrA (pKM101) and WP2 (pKM101) PMRA No. 3246007	
Bacterial Reverse Mutation Assay Salmonella typhimurium TA1535, TA1537, TA100, TA98; E. coli strains WP2uvrA (pKM101) and WP2 (pKM101) PMRA No. 3246008	Negative with or without metabolic activation. Tested to limit concentration.
In vitro Forward Gene Mutation Assay Mouse Lymphoma Thymidine Kinase locus (cell line L5178Y) PMRA No. 3246011	Negative with or without metabolic activation. Tested to cytotoxic and precipitating concentrations.
In vitro Forward Gene Mutation Assay Mouse Lymphoma Thymidine Kinase locus (cell line L5178Y) PMRA No. 3246012	Negative with or without metabolic activation. Tested to cytotoxic and precipitating concentrations.
In vitro Chromosomal Aberration Human Primary Lymphocytes PMRA No. 3246010	Negative with or without metabolic activation. Tested to cytotoxic or precipitating concentrations.

Study type/ Animal/PMRA No.	Study results
In vivo Micronucleus Assay Wistar rat PMRA No. 3246014	Negative
Neurotoxicity Studies	
Acute Oral Neurotoxicity (gavage) – Dose range-finding Wistar rat PMRA No. 3246029 The purpose of this study was to determine time to peak effect and dose levels for the main acute oral neurotoxicity study	**Study considered acceptable with limitations** **NOAELs not established** Effects at ≥ 300 mg/kg bw: ↓ body tone (♂/♀) Effects at ≥ 1000 mg/kg bw: bw loss, ↓ bwg, ↓ fc, ↓ activity, ↓ rearing counts, tremors, ↓ body temperature (♂/♀); piloerection (♀). Effects at ≥ 1500 mg/kg bw: hunched posture, reduced arousal, flattened gait, partial closure of eyelids (♂/♀); piloerection (♂). Time to peak effect: approximately 7 hours Limitations: non-guideline study, small group sizes, no concurrent control group.
Acute Oral Neurotoxicity (gavage) Wistar rat PMRA No. 3246030 PMRA No. 3246031	NOAEL = 50/200 mg/kg bw (♂/♀) LOAEL = 200/1000 mg/kg bw (♂/♀) Effects at LOAEL: ↓ fc, bw loss (♂) No evidence of selective neurotoxicity
90-Day Neurotoxicity (diet) Wistar rat PMRA No. 3246032	NOAEL = 25/33 mg/kg bw/day (♂/♀) LOAEL not determined No treatment-related effects noted at any dose level in either sex. No evidence of neurotoxicity
Developmental Neurotoxicity – Waiver Request PMRA No. 3246033	The request to waive the conditional requirement for a developmental neurotoxicity study was granted on the basis that there was no evidence of selective neurotoxicity and no neurohistopathological findings observed in the acute oral neurotoxicity or the subchronic oral neurotoxicity studies submitted for review. The lack of treatment-related neurotoxic effects in the database suggests that isocycloseram does not bind to mammalian GABA receptors in the same capacity as it does to insect GABA receptors and, therefore, the pesticidal mode of action in insects is not the same as the toxicological mode of action in mammals. Although there was evidence of sensitivity of the young and the

Study type/ Animal/PMRA No.	Study results
	presence of malformations in the rat developmental toxicity study, these findings were related to skeletal effects and did not involve the nervous system, supporting the notion that the mammalian nervous system does not appear to be a target.
Special Studies	
Immunotoxicity – Waiver Request PMRA No. 3245984	The request to waive the immunotoxicity study was granted on the basis that immunotoxicity studies (that test for immune suppression) are not a standard PMRA requirement. Additionally, a detailed analysis of parameters related to immune function using the EPA's weight of evidence approach guidance were considered, including findings in the adrenal glands, spleen, thymus, lymph nodes and hematology assessment. The effects observed in the isocycloseram database involved only minor changes in magnitude; most were increased instead of decreased and showed no correlation with the toxicological effects observed. While the observed effects are not consistent with immunosuppression, they do reflect inappropriate stimulation of the immune system.
Airway Irritation Potential in vitro (non-guideline) Human airway epithelium (MucilAir™ Airway Model) PMRA No. 3283894	**Study considered acceptable with limitations.** Airway damage was evaluated by measuring TEER, LDH release and resazurin metabolism. Histopathological examination of the tissues was also conducted. There were no treatment-related changes in LDH release, TEER levels, or resazurin metabolism. Epithelial cell thinning and the number of necrotic cells appeared to be increased at the highest concentration of isocycloseram. Limitations: Non-guideline study; not conducted to satisfy a guideline requirement but provides supplemental information; there was insufficient tissue remaining in all samples exposed to the positive control substance to allow for examination and comparison to the test material.
28-Day Oral Toxicity (diet) Isomer comparison Wistar rat PMRA No. 3446238 The purpose of this study was to compare the potential toxicity of the test substance SYN547407 (isocycloseram;	SYN547407 [~99% SYN548088] NOAEL = 15/8.2 mg/kg bw/day (♂/♀) LOAEL = 25/22 mg/kg bw/day (♂/♀) based on ↓ bw/bwg/fc, ↑ abs. adrenal wt, adrenal hypertrophy (zona fasciculata), epithelial vacuolation (duodenum) SYN548089 NOAEL= 28/25 mg/kg bw/day (♂/♀) LOAEL = Not determined (♂; no adverse effects) and 45 mg/kg bw/day (♀) based on ↓ bw/bwg/fc SYN548090 NOAEL = 29/51 mg/kg bw/day (♂/♀) LOAEL not determined

Study type/ Animal/PMRA No.	Study results
comprised mostly of the toxicologically active isomer SYN548088), with the isomers SYN548089 and SYN548090, as well SYN548285, a mixture of isomers.	SYN548285 [~76% SYN548088] NOAEL= 27/24 mg/kg/day (♂/♀) LOAEL = Not determined (♂; no adverse effects) and 46 mg/kg bw/day (♀) based on ↓ bw/bwg/fc, ↑ abs. adrenal wt, adrenal hypertrophy (zona fasciculata), epithelial vacuolation (duodenum) Toxicokinetics: For all test materials measured, blood concentrations of isocycloseram generally ↑ in a dose-proportional manner for ♂. A greater than dose-proportional ↑ was observed in ♀. Concentrations were greatest for SYN547407, followed by SYN548089, then SYN548090. In the SYN547407-dosed groups, concentrations peaked at Day 9 (mid- and high-doses) or 16 (low-dose) for ♂ and Day 16 for ♀. For the SYN548089-dosed groups, concentrations peaked at Day 9 (low- and mid-doses) or 16 (high-dose) for ♂ and Day 9 for ♀. In the SYN548090-dosed groups, concentrations were highest in ♂ at Day 2 (low- and high-doses) and fluctuated considerably at the mid-dose, while highest concentrations were noted in ♀ at Day 9 (mid-dose) or Day 16 (low- and high-doses). Concentrations in ♀ > ♂ for all test materials measured.
Metabolite SYN548569 (CA5697A)	
Bacterial Reverse Mutation Assay S. typhimurium strains TA1535, TA1537, TA98, TA100 and E. coli strains WP2 uvrA (pKM101), WP2 (pKM101) PMRA No. 3246006	Negative with or without metabolic activation Tested up to cytotoxic concentrations.
In vitro Micronucleus Test Human Lymphocytes PMRA No. 3246009	Positive with or without metabolic activation to induce micronuclei Tested up to cytotoxic concentrations.
In vivo Micronucleus Assay NMRI Mouse PMRA No. 3246013	Negative Clinical signs of toxicity included closed eyes, piloerection, hunched posture, partially closed eyes, prostration, tip toe gait, ↓ activity.

Table 6 Toxicity profile of end-use products containing isocycloseram

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

Study Type/Animal/PMRA No.	Study Results
VANECTO COCKROACH GEL BAIT (0.98% isocycloseram)	
Acute Oral Toxicity (Up and Down) Sprague-Dawley rat PMRA No. 3246609	LD_{50} > 5000 mg/kg bw (♀) No clinical signs of toxicity. Low acute oral toxicity
Acute Dermal Toxicity PMRA No. 3246610	The requirement for this study has been waived on the basis that this study is no longer a routine data requirement. Additionally, based on the results of the acute oral toxicity study, an acute dermal toxicity study is not required. VANECTO COCKROACH GEL BAIT is considered to be of low acute dermal toxicity.
Acute Inhalation Toxicity PMRA No. 3246611	The requirement for this study has been waived on the basis that VANECTO COCKROACH GEL BAIT is a paste/gel bait, the active ingredient is of low volatility (<6.2×10^{-6} Pa at 20°C), and the proposed product is not expected to become airborne due to its gel-based formulation and, thus, presents minimal risk of inhalation under normal conditions of use. VANECTO COCKROACH GEL BAIT is considered to be of low acute inhalation toxicity.
Eye Irritation NZW rabbit PMRA No. 3246615	MAS = 0 (eyes washed at 1 hour) MIS = 7.3/110 at 1 hour Minimally irritating to the eye
Eye Irritation (In vitro ICE) Ross 308 chicken eyes PMRA No. 3246614	Overall ICE class = 1 × Class I, 2 × II Non-irritant to the eye according to OECD TG 438

Study Type/Animal/PMRA No.	Study Results
Dermal Irritation NZW rabbit PMRA No. 3246613	MAS = 0 MIS = 0 Non-irritating to the skin
Dermal Irritation (In vitro EpiSkin™) Reconstructed human epidermis (EpiSkin™) PMRA No. 3246612	Relative tissue viability = 107.8% Non-irritant to the skin according to OECD TG 439
Sensitization (LLNA) CBA/CaOlaHsd mouse PMRA No. 3246616	Negative
EQUENTO (9.32% isocycloseram)	
Acute Oral Toxicity (Up and Down) Sprague-Dawley rat PMRA No. 3246661	LD_{50} > 5000 mg/kg bw (♀) Clinical signs limited to red feces. Low acute oral toxicity
Acute Dermal Toxicity Wistar rat PMRA No. 3246662	LD_{50} > 5000 mg/kg bw (♂/♀) No clinical signs of toxicity. Low acute dermal toxicity

Study Type/Animal/PMRA No.	Study Results
Acute Inhalation Toxicity (nose-only) Sprague-Dawley rat PMRA No. 3246663	LC_{50} > 5.10 mg/L (♂/♀) Clinical signs included abnormal respiration and sensitivity to touch. Low acute inhalation toxicity
Eye Irritation NZW rabbit PMRA No. 3246666	MAS = 1.3/110 MIS = 13.7/110 (1 hr) Minimally irritating to the eye
Eye Irritation (In vitro ICE) Ross 308 chicken eyes PMRA No. 3246667	Overall ICE class = 2 × Class I, 1 × III The test material was stuck on all corneal surfaces after the post-treatment rinse. Corneal surfaces were cleared at 30 minutes following the post-treatment rinse. Not a severe irritant and not a non-irritant to the eye according to OECD TG 438
Dermal Irritation NZW rabbit PMRA No. 3246665	MAS = 0 MIS = 0 Non-irritating to the eye
Dermal Irritation (In vitro EpiSkin™) Reconstructed human epidermis (EpiSkin™) PMRA No. 3246664	Relative tissue viability = 69.4% Non-irritant to the skin according to OECD TG 439

Study Type/Animal/PMRA No.	Study Results
Sensitization (LLNA) CBA/J mouse PMRA No. 3246668	Negative
A23128 ST (1.4% isocycloseram, 1.5% sedaxane, 3.5% difenoconazole, 0.9% metalaxyl-M and S-isomer, 0.7% fludioxonil)	
Acute Oral Toxicity (Up and Down) Sprague-Dawley rat PMRA No. 3246808	LD_{50} >5000 mg/kg bw (♀) No clinical signs of toxicity. Low acute oral toxicity
Acute Dermal Toxicity PMRA No. 3246809	The requirement for this study has been waived on the basis that this study is no longer a routine data requirement. Additionally, based on the results of the acute oral toxicity study, an acute dermal toxicity study is not required. A23128 ST is considered to be of low acute dermal toxicity.
Acute Inhalation Toxicity (nose-only) Sprague-Dawley rat PMRA No. 3246810	LC_{50} > 5.43 mg/L (♂/♀) Clinical signs included ocular discharge and irregular respiration. Low acute inhalation toxicity
Eye Irritation NZW rabbit PMRA No. 3246814	MAS = 0.7/110 MIS = 2.0/110 (1 hr) Minimally irritating to the eye

Study Type/Animal/PMRA No.	Study Results
Eye Irritation (In vitro ICE) Cobb 500 chicken eyes PMRA No. 3246815	Overall ICE class = 2 × Class II, 1 × IV Slight swelling of the cornea was observed in all eyes treated with the test material at the 4-hour observation. Severe corneal opacity change (3 eyes) and slight fluorescein retention change (3 eyes) were noted. A minimal amount of test material was stuck on all surfaces of the cornea following the post-treatment rinse. Corneal surfaces were not cleared at 240 minutes after the post-treatment rinse. Not a severe irritant and not a non-irritant to the eye according to OECD TG 438
Dermal Irritation NZW rabbit PMRA No. 3246813	MAS = 0.3/8 MIS = 0.6/8 at 24 hours Minimally irritating to the skin
Dermal Corrosion (In vitro EpiDerm™) Reconstructed human epidermis (EPI-200-SCT) PMRA No. 3246811	Relative tissue viability (3 min) = 106.9% Relative tissue viability (1 hr) = 94.6% Non-corrosive to the skin according to OECD TG 431
Dermal Irritation (In vitro EpiDerm™) Reconstructed human epidermis (EPI-200-SIT) PMRA No. 3246812	Relative tissue viability = 19.9% Skin irritant according to OECD TG 439
Sensitization (LLNA) CBA/J mouse PMRA No. 3246816	Negative

Table 7a Summary of in vivo study results

Matrix analyzed	Residues in matrix (% of applied dose)[1]							
	2 mg/cm^2 (200 g/L)				0.075 mg/cm^2 (7.5 g/L)[2]			
	10h	24h	72h	120h	10h	24h	72h	120h
Skin Wash (10h)	99.4 ± 1.94	98.88 ± 2.08	98.24 ± 2.64	98.45 ± 2.97	93.35 ± 7.04	78.66 ± 8.00	70.32 ± 8.93	74.71 ± 4.45
Skin Wash (terminal)		2.34 ± 0.75	1.37 ± 1.23	0.16 ± 0.12		18.95 ± 2.96	12.66 ± 10.11	2.46 ± 2.21
Dressings (10h)	0.01 ± 0.01	0.02 ± 0.01	0.03 ± 0.02	0.07 ± 0.02	0.01 ± 0.01	0.01 ± 0.01	0.02 ± 0.02	0.01 ± 0.00
Dressings (terminal)		0.01 ± 0.01	0.02 ± 0.00	0.04 ± 0.03		0.01 ± 0.00	0.41 ± 0.36	0.45 ± 0.20
O-rings (terminal)	0.28 ± 0.14	0.16 ± 0.13	0.15 ± 0.05	0.10 ± 0.01	4.02 ± 2.57	2.31 ± 3.86	4.41 ± 4.19	1.08 ± 0.54
Tape strips (stratum corneum total)	0.44 ± 0.23	0.2 ± 0.10	0.13 ± 0.13	0.02 ± 0.03	1.84 ± 0.98	0.85 ± 0.66	0.72 ± 0.74	0.27 ± 0.19
Skin at application site	1.37 ± 0.92	0.51 ± 0.51	0.42 ± 0.32	0.05 ± 0.04	5.25 ± 2.89	2.16 ± 1.62	2.98 ± 2.59	1.39 ± 0.97
Hair clippings	0.02 ± 0.01	0.01 ± 0.00	0.01 ± 0.01	0.00 ± 0.00	0.16 ± 0.16	0.16 ± 0.11	0.34 ± 0.40	0.15 ± 0.14
Urine	0.00 ± 0.00	0.00 ± 0.00	0.01 ± 0.01	0.05 ± 0.02	0.00 ± 0.00	0.00 ± 0.00	0.13 ± 0.16	0.54 ± 0.08
Feces	0.01 ± 0.01	0.01 ± 0.01	0.28 ± 0.46	1.51 ± 0.60	0.00 ± 0.00	0.01 ± 0.01	2.81 ± 3.17	12.12 ± 1.11
Cage wash	0.01 ± 0.01	0.02 ± 0.01	0.03 ± 0.04	0.04 ± 0.01	0.00 ± 0.00	0.01 ± 0.00	0.09 ± 0.04	0.30 ± 0.06
GIT + contents	0.00 ± 0.01	0.01 ± 0.01	0.17 ± 0.20	0.17 ± 0.05	0.01 ± 0.01	0.07 ± 0.07	2.13 ± 2.45	1.30 ± 0.21
Carcass	0.05 ± 0.04	0.00 ± 0.00	0.28 ± 0.33	0.38 ± 0.07	0.29 ± 0.23	0.21 ± 0.15	4.22 ± 3.02	4.07 ± 0.20
Total Recovery (sum of above)	101.57 ± 2.41	102.4 ± 2.5	101.13 ± 1.94	101.04 ± 2.78	104.95 ± 1.92	103.4 ± 0.37	101.14 ± 3.26	98.84 ± 3.91
Dermal absorption	1.88 ± 1.15	1.00 ± 0.59	1.33 ± 0.65	2.24 ± 0.73	7.56 ± 4.23	3.47 ± 2.38	13.42 ± 8.71	20.14 ± 1.63

[1] Mean ± standard deviation of 4 animals/group

[2] Note that recovery of administered dose from blood, plasma and untreated skin is accounted for within the carcass sample. Only a partial sample was collected for concentration analysis.

Table 7b Summary of in vivo rat study results

Matrix analyzed	Residues in matrix (% of applied dose)[1,2]							
	0.02 mg/cm^2 (2 g/L)				0.002 mg/cm^2 (0.2 g/L)			
	10h	24h	72h	120h	10h	24h	72h	120h
Skin wash (10h)	95.01 ± 2.98	76.11 ± 5.77	77.33 ± 6.35	74.97 ± 8.40	96.60 ± 5.31	94.71 ± 2.44	92.83 ± 1.85	92.22 ± 2.86
Skin wash (terminal)		12.16 ± 3.41	5.18 ± 3.12	1.71 ± 0.53		2.71 ± 0.91	0.44 ± 0.31	0.33 ± 0.36
Dressings (10h)	0.01 ± 0.01	0.01 ± 0.00	0.03 ± 0.02	0.01 ± 0.00	0.09 ± 0.15	0.00 ± 0.00	0.00 ± 0.00	0.02 ± 0.02
Dressings (terminal)		0.24± 0.39	0.50 ± 0.53	0.58 ± 0.55		0.07 ± 0.06	0.17 ± 0.15	0.36 ± 0.32
O-rings (terminal)	1.04 ± 0.57	5.41 ± 6.11	0.96 ± 0.20	1.04 ± 0.71	2.15 ± 2.93	0.50 ± 0.13	0.53 ± 0.26	1.09 ± 0.89
Tape strips (stratum corneum total)	1.27 ± 0.59	0.59 ± 0.32	0.68 ± 0.36	0.21 ± 0.12	0.55 ± 0.25	0.19 ± 0.07	0.09 ± 0.01	0.15 ± 0.18
Skin at application site	3.65 ± 2.06	2.16 ± 1.34	2.58 ± 0.86	1.30 ± 1.18	3.37 ± 1.38	0.72 ± 0.08	0.31 ± 0.08	0.34 ± 0.03
Hair clippings	0.28 ± 0.15	0.13 ± 0.09	0.33 ± 0.18	0.12 ± 0.06	0.29 ± 0.13	0.32 ± 0.22	0.23 ± 0.18	0.10 ± 0.09
Urine	0.00 ± 0.00	0.01 ± 0.00	0.09 ± 0.08	0.25 ± 0.06	0.01 ± 0.01	0.04 ± 0.01	0.16 ± 0.06	0.22 ± 0.07
Feces	0.00 ± 0.00	0.06 ± 0.02	2.05 ± 1.79	8.27 ± 2.15	0.00 ± 0.00	0.37 ± 0.25	1.87 ± 0.86	2.13 ± 0.72
Cage wash	0.00 ± 0.00	0.00 ± 0.00	0.18 ± 0.19	0.29 ± 0.07	0.01 ± 0.01	0.02 ± 0.02	0.12 ± 0.01	0.11 ± 0.06
GIT + contents	0.02 ± 0.00	0.11 ± 0.07	1.07 ± 1.06	1.15 ± 0.14	0.20 ± 0.06	0.28 ± 0.14	0.39 ± 0.06	0.19 ± 0.10
Carcass	0.37 ± 0.16	0.42 ± 0.19	2.75 ± 1.89	3.79 ± 0.53	0.72 ± 0.42	0.75 ± 0.52	1.02 ± 0.28	0.49 ± 0.36
Total Recovery (sum of above)	101.64 ± 1.36	97.41 ± 1.72	93.68 ± 6.84	93.71 ± 4.40	103.99 ± 1.68	100.69 ± 2.38	98.16 ± 1.60	95.25 ± 6.27
Dermal absorption	5.59 ± 2.29	3.48 ± 1.52	9.73 ± 4.59	15.39 ± 3.73	5.15 ± 0.92	2.70 ± 0.82	4.19 ± 1.20	3.74 ± 0.96

[1] Mean ± standard deviation of 4 animals/group

[2] Note that recovery of administered dose from blood, plasma and untreated skin is accounted for within the carcass sample. Only a partial sample was collected for concentration analysis.

Table 7c Summary of in vitro human and rat study results

Matrix analysed	Residues in matrix (% of applied dose)[1]							
	Human skin				Rat skin			
	2 mg/cm²	0.0075 mg/cm²	0.02 mg/cm²	0.002 mg/cm²	2 mg/cm²	0.0075 mg/cm²	0.02 mg/cm²	0.002 mg/cm²
Skin wash (10h)	49.04 ± 12.64	28.51 ± 4.76	35.40 ± 7.09	39.37 ± 7.92	47.09 ± 11.8	32.72 ± 10.06	39.90 ± 6.74	53.23 ± 4.57
Pipette swab (10h)	48.59 ± 13.80	54.34 ± 6.07	48.59 ± 15.54	42.31 ± 8.81	42.26 ± 11.45	23.15 ± 9.16	31.33 ± 11.25	27.38 ± 4.42
Pipette Tip (10h)	0.03 ± 0.02	0.15 ± 0.12	0.05 ± 0.04	0.26 ± 0.27	0.03 ± 0.03	0.19 ± 0.27	0.14 ± 0.15	0.009 ± 0.005
Skin wash (24h)	0.43 ± 0.38	3.62 ± 1.54	4.61 ± 2.86	6.07 ± 3.51	2.38 ± 1.06	8.55 ± 3.52	14.03 ± 7.58	7.65 ± 2.8
Pipette swab (10h)	0.52 ± 0.28	3.39 ± 1.70	9.12 ± 7.41	4.11 ± 3.49	2.31 ± 0.63	5.52 ± 3.48	5.34 ± 3.93	3.38 ± 1.73
Pipette Tip (24h)	0.0006 ± 0.0006	0.06 ± 0.08	0.005 ± 0.004	0.01 ± 0.01	0.003± 0.01	0.09 ± 0.13	0.03 ± 0.03	0.01 ± 0.01
Donor chamber wash	0.04 ± 0.04	0.56 ± 0.57	0.46 ± 0.34	0.57 ± 0.58	0.06 ± 0.04	0.88 ± 1.70	0.71 ± 0.89	0.40 ± 0.58
Tape Strips (1-20) (*Stratum corneum*)	0.28 ± 0.19	1.66 ± 0.94	1.82 ± 0.51	4.70 ± 3.09	1.66 ± 0.94	6.75 ± 4.27	1.91 ± 1.09	1.52 ± 0.88
Unexposed skin	0.00 ± 0.00	7.01 ± 3.52	0.02 ± 0.02	0.03 ± 0.04	0.00 ± 0.00	0.27 ± 0.34	1.30 ± 2.63	0.24 ± 0.33
Epidermis	0.05 ± 0.06	2.99 ± 1.35	0.27 ± 0.14	0.65 ± 0.51	3.34 ± 1.86	19.15 ± 8.40	4.25 ± 2.32	2.57 ± 1.35
Dermis	0.01 ± 0.01	0.19 ± 0.17	0.19 ± 0.28	0.24 ± 0.25	0.44 ± 0.41	2.46 ± 2.44	1.71 ± 1.82	1.15 ± 0.74
Receptor fluid	0.00 ± 0.00	0.005 ± 0.002	0.02 ± 0.01	0.03 ± 0.02	0.024 ± 0.02	0.32 ± 0.28	0.53 ± 0.19	1.46 ± 0.82
Receptor chamber wash	0.0034 ± 0.00	0.02 ± 0.02	0.07 ± 0.08	0.15 ± 0.35	0.007 ± 0.00	0.03 ± 0.03	0.04 ± 0.02	0.08 ± 0.04

Matrix analysed	Residues in matrix (% of applied dose)[1]							
	Human skin				Rat skin			
	2 mg/cm²	0.0075 mg/cm²	0.02 mg/cm²	0.002 mg/cm²	2 mg/cm²	0.0075 mg/cm²	0.02 mg/cm²	0.002 mg/cm²
Recovery (Sum of above)	99.02 ± 1.12	104.28 ± 1.64	100.62 ± 1.64	98.51 ± 2.49	99.60 ± 1.48	100.10 ± 1.38	101.30 ± 0.98	99.18 ± 1.36
Dermal absorption	0.36 ± 0.24	10.22 ± 3.74	2.39 ± 0.64	5.81 ± 3.50	5.47 ± 2.69	28.98 ± 12.48	9.52 ± 5.16	6.90 ± 1.99

[1] Mean ± standard deviation of 8 animals/group

Table 7d Summary of in vitro human study results – A21708 E

Matrix analysed	Residues in matrix (% of applied dose)[1]			
	Human in vitro			
	1000 µg/cm²	30 µg/cm²	3 µg/cm²	0.2 µg/cm²
Skin wash (10h)	11.73 ± 8.29	35.83 ± 9.54	40.88 ± 6.81	44.69 ± 8.80
Tissue swab (10h)	85.08 ± 12.53	43.22 ± 11.13	43.41 ± 12.78	39.40 ± 10.63
Pipette Tip (10h)	0.03 ± 0.05	0.03 ± 0.01	0.05 ± 0.02	0.09 ± 0.07
Sum of skin wash, tissues swab, pipette tip at 10h	96.84 ± 6.44	79.08 ± 6.62	84.33 ± 8.81	84.18 ± 4.76
Skin wash (24h)	0.67 ± 0.89	4.49 ± 2.39	4.43 ± 2.52	5.94 ± 2.16
Tissue swab (24h)	1.95 ± 4.39	4.97 ± 3.30	4.78 ± 3.13	5.79 ± 2.29
Pipette Tip (24h)	0.003 ± 0.004	0.02 ± 0.02	0.02 ± 0.02	0.02 ± 0.02
Donor chamber wash	0.53 ± 0.48	2.31 ± 1.94	0.83 ± 0.59	0.88 ± 0.56
Tape strips (all stratum corneum)	0.52 ± 0.56	3.46 ± 0.77	3.77 ± 2.04	5.01 ± 1.05
Unexposed skin	0.0008 ± 0.0007	0.003 ± 0.002	0.004 ± 0.003	0.02 ± 0.02
Exposed skin	0.24 ± 0.10	2.15 ± 0.59	1.93 ± 0.63	2.18 ± 0.75
Receptor fluid	0.07 ± 0.08	0.26 ± 0.17	0.27 ± 0.22	0.07 ± 0.08
Receptor chamber wash	0.01 ± 0.01	0.03 ± 0.01	0.04 ± 0.04	0.07 ± 0.02

Matrix analysed	Residues in matrix (% of applied dose)[1]			
	Human in vitro			
	1000 µg/cm²	30 µg/cm²	3 µg/cm²	0.2 µg/cm²
Recovery (Sum of above)	100.85 ± 0.83	97.77 ± 2.67	100.39 ± 2.46	104.39 ± 4.46
Dermal absorption	0.85 ± 0.68	5.90 ± 0.99	6.00 ± 2.42	7.58 ± 0.77

[1] Mean ± standard deviation of 8 replicates/group

Table 7e Summary of in vitro human study results - A21550 L

Matrix analysed	Residues in matrix (% of applied dose)[1]		
	Human in vitro		
	3225 µg/cm²	45.2 µg/cm²	1.87 µg/cm²
Skin wash (10h)	39.33 ± 12.98	36.76 ± 24.72	28.83 ± 7.90
Tissue swab (10h)	58.38 ± 14.44	58.06 ± 29.59	58.84 ± 13.41
Pipette tip (10h)	0.14 ± 0.15	0.05 ± 0.06	0.07 ± 0.14
Sum of skin wash, tissues swab, pipette tip at 6 h	97.86 ± 2.89	94.87 ± 6.36	83.74 ± 6.50
Skin wash (24h)	0.86 ± 0.64	2.50 ± 1.87	3.61 ± 1.74
Tissue swab (24h)	0.89 ± 0.65	2.59 ± 2.52	3.55 ± 1.87
Pipette tip (24h)	0.001 ± 0.001	0.004 ± 0.002	0.01 ± 0.01
Donor chamber wash	0.68 ± 0.18	0.71 ± 0.41	0.41 ± 0.27
Tape Strips (all stratum corneum)	0.47 ± 0.28	2.35 ± 2.36	3.38 ± 2.68
Unexposed skin	0.01 ± 0.01	0.01 ± 0.01	0.06 ± 0.06
Exposed skin	0.15 ± 0.11	0.83 ± 0.39	2.76 ± 1.73
Receptor fluid	0.002 ± 0.001	0.04 ± 0.03	0.11 ± 0.05
Receptor chamber wash	0.003 ± 0.005	0.01± 0.01	0.03 ± 0.02
Recovery (Sum of above)	100.92 ± 1.58	104.25 ± 2.81	97.08 ± 2.84
Dermal absorption	0.63 ± 0.30	3.22 ± 2.90	6.34 ± 3.92

[1] Mean ± standard deviation of 8 replicates/group (for the 45.2 µg/cm² dose level (Dilution 1), only 7 samples were used: Cell 12 was an outlier for exposed skin and dermal delivery, attributed to an inefficient wash at 6 h, and was therefore excluded).

Table 8 Summary of seed treatment exposure studies used for isocycloseram risk assessments on cereals (Wheat (spring, durum, winter), Barley, Oats, Rye, Triticale)

Study	Crops assessed	PPE	Activity	Unit exposure values (µg/kg a.i.)	
				Dermal	Inhalation
Commercial open transfer application					
Krolski, 2006 (AH803)	Wheat	Open M/L, Single layer + socks, leather boots, rubber/latex gloves, and a hat	Mixing, loading, application	265.7	2.47
Brennecke and Muller, 2003a (AH809)	Barley	CR coveralls over single layer, CR gloves	Cleaner	2.13	0.102
Wilson, 2009 (AH817)	Wheat	Single layer (one worker wore CR coveralls), some wore face and respiratory protection	Bagger/Sewer/ Stacker/Forklift driver	17.67	0.89
On-farm treatment and planting					
Krolski, 2006 (AH803)	Wheat	Open M/L, single layer, CR gloves, closed cab planter	Treating, loading, planting	254.35	13.03
Planting commercially treated seed					
Krainz, 2013 (AH823)	Wheat	Coveralls over single layer, CR gloves, closed cab	Loading, planting	1171.83	360.64

PPE = personal protective equipment; single layer = long-sleeved shirt, long pants; M/L = mixing/loading; CR = chemical-resistant

Table 9a Commercial seed treatment exposure and risk assessment for isocycloseram

Crop	Formulation	Activity	Application rate (g a.i./kg seed)	Throughput[a] (kg seed/day)	Unit exposure values (µg/kg a.i.)		Exposure (mg/kg bw/day)[b]		MOE (Target = 1000)[c]		
					Dermal	Inhalation	Dermal	Inhalation	Dermal	Inhalation	Combined[d]
Krolski, 2006 (AH803) - Open M/L, Single layer + socks, leather boots, rubber/latex gloves, and a hat											
Wheat (spring/durum, winter), Barley, Oats, Rye, Triticale	Liquid	Mixing, loading, application	0.075	92000	265.7	2.47	0.001833	0.000213	3545	30511	3176
Brennecke and Muller, 2003a (Barley) – CR coveralls over single layer and CR gloves											
Wheat (spring/durum, winter), Barley, Oats, Rye, Triticale	Liquid	Cleaner	7.5 g a.i./100 kg seed	-	2.13 µg a.i./ g a.i./100 kg seed	0.102 µg a.i./ g a.i./100 kg seed	0.000016	0.000010	406886	679739	254528
Wilson, 2009 (Wheat) – Single layer											
Wheat (spring/durum, winter), Barley, Oats, Rye, Triticale	Liquid	Bagger, sewer, stacker, forklift driver	0.075	92000	17.67	0.89	0.000122	0.000077	53312	84677	32715

[a] Standard throughput for commercial seed treatment.

[b] Exposure (excluding cleaners) = (application rate × kg/1000 g × throughput) × unit exposure values × Absorption (8% for dermal and 100% for inhalation) / 80 kg body weight × 1000 µg/mg

Cleaner Exposure = application rate (g a.i./100 kg seed) × unit exposure values × Absorption (8% for dermal and 100% for inhalation) / 80 kg body weight × 1000 µg/mg

[c] Based on a NOAEL (all durations) of 6.5 mg/kg bw/day and a target MOE of 1000. MOE = NOAEL/exposure.

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

Table 9b On-farm seed treatment exposure and risk assessment for isocycloseram

Crop	Formulation	Activity	Application rate (g a.i./kg seed)	Throughput[a] (kg seed/day)	Unit exposure values (µg/kg a.i.)		Exposure (mg/kg bw/day)[b]		MOE (Target = 1000)[c]		
					Dermal	Inhalation	Dermal	Inhalation	Dermal	Inhalation	Combined[d]
Krolski, 2006 (Wheat) - Open mix/load, closed cab planter, wearing single layer, CR gloves											
Wheat (spring/durum, winter), Barley, Oats, Rye, Triticale	Liquid	All tasks (treating, loading, planting)	0.075	14,500	254.35	13.03	0.00028	0.00018	23499	36697	14326

[a] On-farm standard throughput.
[b] Exposure = (application rate × kg/1000 g × throughput) × unit exposure values × Absorption (8% for dermal and 100% for inhalation) / 80 kg body weight × 1000 µg/mg
[c] Based on a NOAEL (all durations) of 6.5 mg/kg bw/day and a target MOE of 1000. MOE = NOAEL/exposure.
[d] Combined MOE = 1/[(1/dermal MOE)+(1/inhalation MOE)].

Table 9c Planting treated seed exposure and risk assessment for isocycloseram

Crop	Formulation	Activity	Application rate (g a.i./kg seed)	Throughput[a] (kg seed/day)	Unit exposure values (ug/kg a.i.)		Exposure (mg/kg bw/day)[b]		MOE (Target = 1000)[c]		
					Dermal	Inhalation	Dermal	Inhalation	Dermal	Inhalation	Combined[d]
Krainz, 2013 (Wheat) – Closed cab planter, coveralls over single layer, CR gloves											
Wheat (spring/winter, durum), Barley, Oats, Rye, Triticale	Liquid	All tasks (loading, planting)	0.075	14 500	1171.83	360.64	0.001274	0.004902	5101	1326	1052

[a] On-farm planting standard throughput
[b] Exposure = (application rate × kg/1000 g × throughput) × unit exposure values × Absorption (8% for dermal and 100% for inhalation) / 80 kg body weight × 1000 µg/mg
[c] Based on a NOAEL (all durations) of 6.5 mg/kg bw/day and a target MOE of 1000. MOE = NOAEL/exposure.
[d] Combined MOE = 1/[(1/dermal MOE)+(1/inhalation MOE)].

Table 10 Acute incidental oral ingestion for VANECTO COCKROACH GEL BAIT

Exposure scenario	Bait deposit (mg a.i./day)[1]	Acute accidental oral exposure (mg/kg/day) [2]	MOE [3]
Child (1 to < 2 years)	5	0.4545	**8**

[1] Bait Deposit = 0.5 g product × guarantee (1%) × Conversion Factor (1000 mg/g) = 5 mg a.i./day (one drop)
[2] Acute Oral Exposure (mg/kg bw/day) = 5 mg a.i./day ÷ 11 kg bw = 0.4545 mg/kg bw/day
[3] MOE =Acute dietary NOAEL of 3.5 mg/kg bw/day ÷ Exposure (mg/kg bw/day) of 0.4545 mg/kg bw/day; Target MOE = 300

Table 11 Integrated food residue chemistry summary

Nature of the residue in laying hen			**PMRA No. 3246054**
Species and numbers	Eighteen laying hens (Hy-Line Brown) were divided into three treatment groups.		
Radiolabel positions	[Methylphenyl-U-^{14}C]	[Halophenyl-U-^{14}C]	[Oxoisoxazolidinyl-4,5-^{14}C]
Specific activity (MBq/mg)	2.353	2.827	2.253
Average doses (ppm feed; dry matter content (DM))	24.02	21.85	22.09
Treatment regimen	Orally dosed once per day using a pet piller		
Study period	14 consecutive days		
Collection time	Excreta and eggs were collected twice daily.		
Tissues collected	Eggs (egg yolks separated from egg whites), composite fat (skin with fat, peritoneal fat), liver, composite muscle (leg/thigh muscle and breast muscle)		
Interval from last dose to sacrifice	12 hours		
Plateau of residues in eggs	Approximately 12 days		
Extraction procedures			
Matrices	**Extraction solvents**		
Liver, muscle, egg white	Subsamples of liver, muscle and egg white were homogenised with acetonitrile/water (80/20, v/v) or (50:50, v/v) as appropriate.		
Composite Fat	The fat sample was partitioned with hexane (5×, v/w) prior to extraction using acetonitrile/water (80/20, v/v).		
Egg yolk	The egg yolk sample was partitioned with hexane (10×, v/w) prior to sequential extraction using acetonitrile/water (80/20, v/v) and acetonitrile/water (50/50, v/v).		
PES	Remaining debris in the egg white, muscle, liver and egg yolk samples were subjected to microwave extraction using acetonitrile/water (80/20, v/v) and/or IPA:1N HCl (1:1) combinations as needed.		

Storage stability at -20°C						
The initial analyses (i.e., extract profiles) of all the tissue and egg samples were completed within six months of the collection date. Therefore, frozen storage stability data were not required.						
Percent of administered radioactivity recovered in laying hens						
Matrices	**[Methylphenyl-U-^{14}C]-Isocycloseram**		**[Halophenyl-U-^{14}C]-Isocycloseram**		**[Oxoisoxazolidinyl-4,5-^{14}C]-Isocycloseram**	
	% AD	**TRRs (ppm)**	**% AD**	**TRRs (ppm)**	**% AD**	**TRRs (ppm)**
Excreta	71.522	-	68.233	-	72.700	-
Cage Wash	1.843	-	1.492	-	1.520	-
Breast muscle	0.283	0.56	0.269	0.52	0.221	0.43
Leg/thigh muscle	0.602	1.03	0.614	1.07	0.430	0.75
Liver	0.719	5.81	0.790	6.57	0.532	4.58
Skin with fat	1.120	4.04	1.192	4.31	0.696	2.43
Peritoneal fat	0.393	6.03	0.347	6.75	0.242	3.39
Total Tissues	3.117	17.47	3.212	19.22	2.121	11.58
Egg whites	0.338	-	0.337	-	0.377	-
Egg yolks	6.632	-	6.844	-	4.459	-
Total Recovered (%)	83.5		80.1		81.2	
%AD = % of administered dose Note: The carcasses, GI tract, GI contents, bile, blood were collected, but not analyzed.						

Summary of major identified metabolites in hen matrices	
Radiolabel Position	[Methylphenyl-U-^{14}C -], [Halophenyl-U-^{14}C-], [Oxoisoxazolidinyl-4,5-^{14}C]
Metabolites Identified	Major Metabolites
Composite muscle	Isocycloseram; SYN549431
Composite fat	Isocycloseram; SYN549431; SYN551475
Liver	Isocycloseram; SYN549431; SYN549543; SYN549544; SYN551583
Egg yolk	Isocycloseram; SYN549431; SYN549544; SYN551479; SYN551583
Egg white	Isocycloseram; SYN549431; SYN549436; SYN549544

Nature of the residue in lactating goats	**PMRA No. 3246055; 3246056; 324057**
Species and Numbers	Two female goats (Alpine); one for each radiolabel, methylphenyl and halophenyl; one female goat (Caprine, strain La Mancha) for oxoisoxazolidinyl radiolabel

Radiolabel positions	[Methylphenyl-U-^{14}C]	[Halophenyl-U-^{14}C]	[Oxoisoxazolidinyl-4,5-^{14}C]
Specific Activity (MBq/mg)	2.220	2.102	2.202
Average doses (ppm feed DM)	35.5	38.7	41.5
Treatment Regimen	Once per day orally to each animal using a bolus gun		

Study period	7 consecutive days
Collection time	Milk (twice daily); urine and feces (once daily)
Tissues collected	Composite muscle (loin, flank), composite fat (perirenal, omental, subcutaneous), kidneys, liver, gastrointestinal tract and contents, whole blood, and bile at necropsy. Additional tissues collected post-necropsy from the carcass were lungs, heart, spleen, ovaries and uterus, bladder, urine from the bladder, additional fat from renal area and mammary tissue.
Interval from last dose to sacrifice	11–12 hours
Plateau of residues in milk	Plateau on Day-5 (oxoisoxazolidinyl); Highest TRRs were 0.47 ppm (methylphenyl) and 0.65 ppm (halophenyl) on day-6, but a plateau was not reached.
Extraction procedures	
Matrices	**Extraction solvents**
Liver and kidney	Subsamples of liver and kidney were extracted with acetonitrile/water (80/20, v/v) or (50:50, v/v) as appropriate.
Composite muscle	The muscle sample was partitioned with acetonitrile/water (9:1, v/v)/hexane (2:1, v/v) followed by acetonitrile/water (2:1, v/v) extraction.
Composite fat	The fat sample was partitioned with hexane (5×, v/w) prior to extraction using acetonitrile/water (80/20, v/v) or (50:50, v/v) as appropriate.
Milk	Samples of milk were extracted using acetonitrile/hexane (10×, v/w) (4:1, v/v)
PES	Remaining debris in the kidney, liver and milk samples were subjected to microwave extraction.
Storage stability at -20°C.	
The initial HPLC radioprofile analyses for all tissue and milk samples was undertaken within six months of collection. The liver sample was re-extracted after ten months of frozen storage at approximately -20°C. The radiocomponents of the stored extract and the initial extract were compared and showed that the extracts were stable during the period of frozen storage.	

Distribution of radioactivity in lactating goats

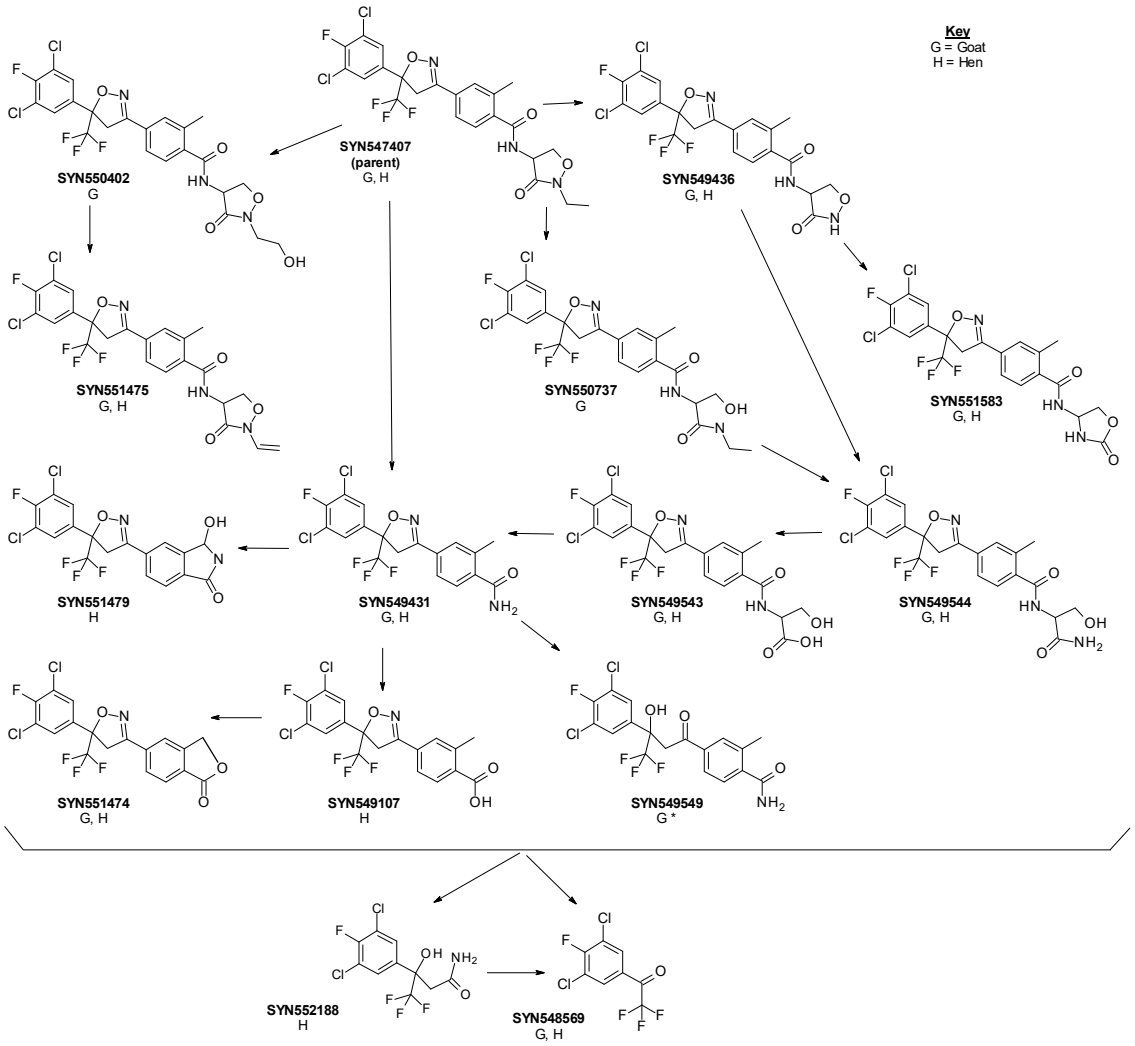
Matrices	**[Methylphenyl-U-^{14}C]-Isocycloseram**		**[Halophenyl-U-^{14}C]-Isocycloseram**		**[Oxoisoxazolidinyl-4,5-^{14}C]-Isocycloseram**	
	% AD	**TRRs (ppm)**	**% AD**	**TRRs (ppm)**	**% AD**	**TRRs (ppm)**
Loin muscle	-	0.77	-	0.81	0.171	0.87
Flank muscle	-	1.01	-	1.25	0.315	1.45
Composite muscle[1]	0.549	0.83	0.711	0.94	0.416	1.15
Perirenal fat	-	4.99	-	6.81	0.299	9.39
Subcutaneous fat	-	2.34	-	4.45	0.125	7.06
Omental fat	-	4.38	-	6.15	0.909	9.43

Composite fat[2]	3.34	3.96	7.74	5.87	0.487	8.75
Liver	1.950	6.04	2.380	8.55	2.231	11.86
Kidneys	0.318	4.26	0.210	3.89	0.249	8.87
Urine	3.013	-	2.792	-	5.969	-
Feces	48.687	-	46.404	-	53.799	-
Cage wash	0.402	-	0.185	-	0.263	-
Milk (Day1-7)	0.987	4.82	1.719	6.43	1.588	-
Bile	0.154	17.67	0.061	17.67	0.507	27.10
GI Tract	4.945	2.45	7.096	3.76	4.121	4.58
GI Contents	11.346	4.07	10.385	4.00	12.245	5.41
Lung and Heart	0.694	1.95	0.553	2.10	-	-
Whole blood	-	0.59	-	0.59	0.005	0.77
Ovaries, uterus, bladder, urine from bladder and renal fat	0.521	3.09	0.695	4.94	-	-
Mammary tissue	0.817	1.35	0.815	2.24	-	-
Total recovered (%)	**77.7**		**81.7**		**81.9**	

%AD = % of administered dose
[1] Flank and loin muscle combined in ratio of 1.5:2 (w:w)
[2] Perirenal, subcutaneous, and omental fat combined in ratio of 1:1.2:2.3 (w:w:w)

Summary of major identified metabolites in goat matrices	
Radiolabel position	[Methylphenyl-U-^{14}C -], [Halophenyl-U-^{14}C-], [Oxoisoxazolidinyl-4,5-^{14}C]
Matrices	Major metabolites (>10% TRR)
Milk, composite muscle, and fat	Isocycloseram
Liver	Isocycloseram, SYN548569, SYN59436, SYN549544
Kidneys	Isocycloseram, SYN59436, SYN549544

Proposed metabolic scheme in livestock



Freezer storage stability in animal matrices		**PMRA No. 3246040, 3246041**
Tested matrices	**Analyte**	**Tested intervals (days) at <-18°C**
Poultry eggs	Isocycloseram	0, 14, 31, 41, 90–92, 188, 320, 376, 551, 734
Poultry muscle		0, 14, 32, 92
Poultry fat		0, 14, 29, 92
Poultry liver		0, 14, 32, 90
Bovine milk		0, 14, 30–31, 90–91, 182, 317, 366, 544, 727
Bovine cream		0, 14, 31, 91
Bovine muscle		0, 14, 31–32, 90–92, 188, 320, 373, 554, 734
Bovine liver		0, 14, 30–31, 91–92, 188, 324, 376, 551, 734
Bovine kidney		0, 14, 30, 91
Bovine fat		0, 14, 32, 90

Residues of isocycloseram are stable for up to 32 days (1 month) in poultry liver; 90–92 days (3 months) in bovine matrices (cream, kidney, and fat); poultry matrices (fat, muscle); and up to 727–734 days (24 months) in eggs, bovine milk, muscle, and liver.	
Livestock feeding – Laying hen	**PMRA No. 3246077**
Species and Numbers	Twelve Tetra Brown laying hens (*Gallus domesticus*) were used for each of the four feeding groups: 1×, 3×, 10×, and 50× (depuration), including eight control hens for a total of 56 hens.
Dose levels	0.041 ppm; 0.122 ppm, 0.397 ppm, and 1.942 ppm
Treatment Regimen	Once by manual insertion of gelatin capsule into esophagus
Study period	28 consecutive days
Egg collection time	2/day (morning and evening)
Interval from last dose to sacrifice	6 hours
Tissues collected	Whole eggs at 1, 4, 7, 10, 13, 16, 19, 22, 25, 28 days. On days 13 and 28, eggs were collected and the egg yolk and white were separated and the whites and yolks from each subgroup were composited. Liver, composite muscle (breast and thigh), and composite fat (abdominal, subcutaneous) were collected on day 29.
Depuration study	3-, 7-, and 14-days post-dosing (Day 32, 36 and 43) from the highest feeding level (1.942 ppm)
Analytical method	
Residues of isocycloseram in muscle, fat, liver, and eggs were analyzed using a modified version of analytical method GRM072.14A.	
Storage stability at <-18°C	
Whole eggs, egg whites, egg yolks, and tissue samples were stored frozen and were extracted within 24-35 days (1 month) after collection, which is within the demonstrated freezer storage interval	

Summary of residues of isocycloseram in laying hen commodities after 28 days of dosing

Analyte	**Residues of isocycloseram (ppm)**							
Feeding level	**0.041**		**0.122**		**0.397**		**1.942**	
(ppm)	**Mean**	**Highest**	**Mean**	**Highest**	**Mean**	**Highest**	**Mean**	**Highest**
Whole eggs	-	-	-	-	-	-	0.029	0.030
Egg white	<0.010	<0.010	<0.010	<0.010	<0.010	<0.010	<0.010	<0.010
Egg yolk	<0.010	<0.010	<0.010	<0.010	0.023	0.025	0.105	0.118
Composite Muscle	<0.010	<0.010	<0.010	<0.010	<0.010	<0.010	0.012	0.014
Composite Fat	<0.010	<0.010	<0.010	<0.010	0.032	0.036	0.153	0.161
Liver	<0.010	<0.010	<0.010	<0.010	0.022	0.025	0.063	0.068

Anticipated residues in poultry matrices			
Matrices	**Residue definition**	**Dietary burden (ppm)**	**Anticipated residues of isocycloseram (ppm)**
Eggs	Isocycloseram	0.07	<0.01
Composite Fat			<0.01
Liver			<0.01
Composite Muscle			<0.01
The only permitted livestock feed items are cereal grains. The Langmuir model cannot be used to estimate anticipated residues in poultry matrices as residues are only quantifiable at 1 or 2 of the 4 feeding levels. The dietary burden for poultry is 0.07 ppm, which is within the lower feeding levels of 0.041 ppm and 0.122 ppm. At these feeding levels, isocycloseram residues were <0.01 ppm in all tested poultry matrices (whole eggs, liver, composite muscle and composite fat).			

Livestock feeding – Dairy cattle	**PMRA No. 3246078**
Species and numbers	Fifteen Holstein dairy cattle (Bos taurus) split into 4 groups for the study: three for the control group, three each for the 1× and 3× groups and six for the 10× group (depuration).
Dose levels	4.42, 13.2 and 44 ppm in feed (DM basis) corresponding to 0.15, 0.46, and 1.49 mg/kg bw/day
Treatment regimen	Once/gelatin capsule using oral balling gun
Study period	28 consecutive days
Milk collection time	Twice per day (morning and evening). Milk samples taken on days 13 and 28 were separated into skim milk and cream.
Interval from last dose to sacrifice	6 hours
Tissues collected	Liver (each lobe), kidney (both), muscle and fat (perirenal, omental and subcutaneous)
Depuration study	3, 7, and 14 days post-dose (Day 31, 35 and 42) from the highest feeding level (44 ppm)
Analytical method	
Residues of isocycloseram in milk and tissues (muscle, fat, kidney, and liver) were analyzed using a modified version of analytical method GRM072.014A.	
Storage stability at <-18°C	
Samples were stored frozen for a maximum of 0.5 month (kidney, liver), 0.9 month (muscle), 1.2 months (fat), and 1.6 months (milk) from collection to analysis. Residues of isocycloseram are stable in freezer storage for 3 months in bovine kidney and fat, and up to 24 months in bovine milk, muscle, and liver.	

Summary of residues of isocycloseram in lactating ruminant commodities after 28 days of dosing

	Residues of isocycloseram (ppm)					
Feeding level (ppm)	**4.42**		**13.2**		**44.0**	
	Mean	**Highest**	**Mean**	**Highest**	**Mean**	**Highest**
Milk	<0.010	<0.010	0.0371	0.0692	0.0827	0.1170

Skim milk	<0.010	<0.010	<0.010	<0.010	<0.010	<0.010
Cream	0.0193	0.0241	0.0624	0.0757	0.2083	0.2720
Muscle	<0.010	<0.010	<0.010	<0.010	0.0211	0.0257
perirenal fat	0.0452	0.0575	0.0767	0.1540	0.1125	0.1630
omental fat	0.0436	0.0501	0.0786	0.1460	0.1897	0.4340
subcutaneous fat	0.0164	0.0190	0.0294	0.0446	0.0625	0.0652
Liver	0.0214	0.0257	0.0676	0.0906	0.1973	0.2300
Kidney	<0.01	<0.010	0.0212	0.0256	0.0684	0.0847

Anticipated residues in animal matrices

Matrices	**Residue definition**	**Dietary burden (ppm)**	**Anticipated residues of isocycloseram (ppm)**
Beef/Dairy cattle			
Whole milk	Isocycloseram	1.82	<0.01
Perirenal fat			0.04
Liver			0.015
Kidney			<0.01
Muscle			<0.01
Swine			
Fat	Isocycloseram	0.010	<0.01
Liver			<0.01
Kidney			<0.01
Muscle			<0.01

The only permitted livestock feeding items are cereal grains. It is preferable not to use the Langmuir Model for milk, muscle, and kidney as there are only 1 or 2 data points out of three feeding levels that have quantifiable residues of the parent compound. At 4.42 ppm (2.4-fold dairy cattle DB), residues of isocycloseram are <LOQ in milk, muscle, and kidney.

Nature of the residue in soybeans			**PMRA No. 3246052**
Radiolabel position	[Methylphenyl-U-^{14}C]	[Halophenyl-U-^{14}C]	[Oxoisoxazolidinyl-4,5-^{14}C]
Specific activity (MBq/mg)	2.157	2.046	2.165
Rate (g a.i./ha)	86.5–90.1/application 265/season	78.0–85.5/application 248/season	85.3–90.8/application 266/season
Test site	Outdoors in sandy loam soil containers		
Treatment	Three post-emergence foliar applications		
Formulation	Emulsifiable concentrate (EC) formulation of isocycloseram (guarantee: 4.785% w/w)		
Preharvest interval	Soybean forage: 37 days after first application; Soybean hay: 69 days after first application; and Soybean stalks and beans: 30 days after third application		
Extraction solvents	Aqueous acetonitrile solvent combinations based on water content in plant fraction.		

PES	Selected post-extraction solids (PES) of soybean forage from halophenyl- and oxoisoxazolidinyl-labelled experiments were further extracted under microwave conditions. The PES of soybean seeds from the oxoisoxazolidinyl-^{14}C experiment were subjected to enzyme (cellulase) and acid/base hydrolysis (1N HCl, NaOH; 6N HCl, NaOH).
Storage Stability	Initial HPLC radio-component profiles of extracts from all soybean commodities were produced within 5 months of harvest. Radioprofiles of extracts stored from 20 to 40 months that were re-extracted were comparable.

Overall TRRs and extractability of residues in soybean matrices

Radiolabel	Crop commodity	Total extractable radioactivity[1]		Non-extractable radioactivity (Final PES)		TRR[2]	TRR[3]
		%TRR	ppm	%TRR	ppm	ppm	ppm
[Methylphenyl-U-^{14}C]	Forage	90.8	0.205	9.2	0.021	0.226	0.209
	Hay	63.9	0.014	36.1	0.008	0.022	0.018
	Beans	59.4	0.010	40.6	0.006	0.016	0.012
[Halophenyl-U-^{14}C]	Forage	95.4 (85.4)	1.145 (1.025)	7.4 (14.6)	0.089 (0.175)	1.200	1.114
	Hay	71.4	0.018	28.5	0.007	0.025	0.028
	Beans	NA	NA	NA	NA	NA	0.006
[Oxoisoxazolidinyl-4,5-^{14}C]	Forage	93.1 (82.6)	0.379 (0.351)	6.4 (13.8)	0.026 (0.056)	0.407	0.366
	Hay	54.6	0.011	45.3	0.009	0.020	0.016
	Beans	99.8 (62.6)	0.086 (0.055)	2.9 (37.4)	0.003 (0.032)	0.087	0.081

NA - not further analyzed due to low TRRs
[1] Combined extracts following solvent extraction, microwave extraction and enzyme and acid/base hydrolysis, as applicable; values in parentheses represent residues released following solvent extraction only.
[2] TRRs determined by summation of radioactivity present in the extracts and debris after initial fractionation.
[3] TRRs obtained by direct combustion/LSC analysis.

Summary of major identified metabolites in plant matrices

Radiolabel position	**[Methylphenyl-U-^{14}C -], [Halophenyl-U-^{14}C-], [Oxoisoxazolidinyl-4,5-^{14}C]**
Metabolites identified	**Major metabolites**
Soybean seed	None
Soybean forage	Isocycloseram; SYN549431
Soybean hay	Isocycloseram; SYN549431; SYN549543

Nature of the residue in tomatoes			**PMRA No. 3246053**
Radiolabel position	[Methylphenyl-U-^{14}C]	[Halophenyl-U-^{14}C]	[Oxoisoxazolidinyl-4,5-^{14}C]
Specific activity (MBq/mg)	2.157	2.046	2.165

Rate (g a.i./ha)	125.9–131.1/application 384/season	124.8–131.2/application 385/season	117.9–134/application 379/season
Test site	Outdoors in sandy loam soil containers		
Treatment	Three post-emergence foliar applications		
Formulation	Emulsifiable concentrate (EC) formulation of isocycloseram (guarantee: 4.785% w/w)		
Preharvest interval	Tomato leaves and fruits: 3 and 21 days after third application		
Extraction solvents	Aqueous acetonitrile solvent combinations based on water content in plant fraction.		
PES	No further analyses were conducted.		
Storage stability	Initial analyses of all the crop samples were completed within three months of the harvest date.		

Overall TRRs and extractability of residues in tomato matrices

Radiolabel crop	**Commodity**	**PHI (days)**	**Total extractable radioactivity[1]**		**Non-extractable radioactivity[2] (Final PES)**		**TRR[3]**	**TRR[4]**
			%TRR	**ppm**	**%TRR**	**ppm**	**ppm**	**ppm**
[Methylphenyl-U-^{14}C]	Tomato leaves	3	94.8	6.593	5.2	0.362	6.954	6.972
	Mature tomato	3	93.3	0.029	6.7	0.002	0.032	0.033
	Tomato leaves	21	92.2	4.801	7.9	0.411	5.207	4.691
	Immature tomato	21	88.1	0.008	11.8	0.001	0.008	0.009
	Mature tomato	21	NA	NA	NA	NA	NA	0.003
[Halophenyl-U-^{14}C]	Tomato leaves	3	96.1	6.548	3.9	0.266	6.814	6.345
	Mature tomato	3	95.2	0.020	4.8	0.001	0.021	0.021
	Tomato leaves	21	95.3	5.911	4.7	0.292	6.203	5.839
	Immature tomato	21	NA	NA	NA	NA	NA	0.008
	Mature tomato	21	NA	NA	NA	NA	NA	0.004
[Oxoisoxazolidinyl-4,5-^{14}C]	Tomato leaves	3	95.9	5.777	4.1	0.247	6.023	5.742
	Mature tomato	3	92.3	0.020	7.7	0.002	0.022	0.021
	Tomato leaves	21	94.6	5.052	5.4	0.288	5.340	4.817

	Immature tomato	21	NA	NA	NA	NA	NA	0.008
	Mature tomato	21	87.0	0.010	13.0	0.001	0.011	0.010

NA - not further analyzed due to low TRRs
[1] The total extractable radioactivity recovered based on the amount of radioactivity present in solvent extracts.
[2] Remaining unextracted residues (PES) following solvent extraction.
[3] The overall TRR values were determined by summation of radioactivity present in the extracts and unextracted residues following solvent extraction.
[4] The overall TRR values were determined by combustion.

Summary of major identified metabolites in plant matrices		
Radiolabel position		**[Methylphenyl-U-^{14}C -], [Halophenyl-U-^{14}C-], [Oxoisoxazolidinyl-4,5-^{14}C]**
Metabolites identified		**Major metabolites**
Tomato leaves	PHI= 3d	Isocycloseram
Tomato	PHI= 3d	Isocycloseram
Tomato leaves	PHI= 21d	Isocycloseram; SYN549431
Immature tomato	PHI= 21d	Isocycloseram
Mature tomato	PHI= 21d	Isocycloseram

Nature of the residue in paddy rice			**PMRA No. 3246051**
Radiolabel position	[Methylphenyl-U-^{14}C]	[Halophenyl-U-^{14}C]	[Oxoisoxazolidinyl-4,5-^{14}C]
Specific activity (MBq/mg)	2.157	2.046	2.165
Rate (g a.i./ha)	98.1–108.4/application 311/season	101.7–108.4/application 318/season	102.7–110.7/application 317/season
Test site	Outdoors in sandy loam soil containers. After each application, water was added to flood the plots to approximately 2.5 to 5 cm.		
Treatment	Three post-emergence foliar applications		
Formulation	Suspension concentrate (SC) formulation of isocycloseram (guarantee: 4.785% w/w)		
Preharvest interval	Rice Forage: 13 days after first application; Rice Hay: 57 days after second application; and Rice Straw, Husks, Grain: 21 days after third application.		
Extraction solvents	Aqueous acetonitrile solvent combinations based on water content in plant fraction.		
PES	Selected post-extraction solids of paddy rice hay and forage underwent microwave extraction.		
Storage stability	Initial HPLC radio-component profiles of the main residue containing fractions of all rice commodities were produced within 3 months of harvest. Extracts were analyzed later than 6 months for isolation and LC-MS analysis. The radioprofiles of the initial extracts from rice hay and rice forage were compared to the radioprofiles of the same extracts following frozen storage at -20°C for approximately 10 and 14 months, respectively. No change in radioprofiles was observed following frozen storage.		

Overall TRRs and extractability of residues in paddy rice matrices							
Radiolabel crop	**Commodity**	**Total extractable radioactivity[1]**		**Non-extractable radioactivity (Final PES)[2]**		**TRR[3]**	**TRR[4]**
		%TRR	**ppm**	**%TRR**	**ppm**	**ppm**	**ppm**
[Methylphenyl-U-^{14}C]	Forage	94.3	1.470	5.6	0.087	1.559	1.476
	Hay	97.5 (88.3)	2.435 (2.205)	4.3	0.107	2.497	2.440
	Straw	92.4	2.297	7.7	0.191	2.487	2.398
	Grain	94.1	0.175	5.9	0.011	0.186	0.180
	Husks	95.1	3.335	5.0	0.175	3.508	3.594
[Halophenyl-U-^{14}C]	Forage	92.7	1.703	7.3	0.134	1.837	1.638
	Hay	93.2	1.937	3.9	0.081	2.079	1.876
	Straw	93.2 (83.8)	1.937 (1.742)	6.2	0.161	2.596	2.347
	Grain	94.2	0.136	5.8	0.008	0.143	0.124
	Husks	94.1	3.523	5.9	0.221	3.745	3.635
[Oxoisoxazolidinyl-4,5-^{14}C]	Forage	93.1 (89.8)	1.590 (1.533)	8.4	0.143	1.707	1.814
	Hay	91.6 (82.2)	1.146 (1.028)	7.2	0.090	1.251	1.253
	Straw	91.7	3.531	8.3	0.320	3.851	4.088
	Grain	85.9	0.151	14.2	0.025	0.176	0.170
	Husks	96.4	3.970	3.6	0.148	4.117	3.785

[1] The total extractable radioactivity recovered following solvent extraction and microwave extraction, where applicable. Values in brackets represent the solvent extracted radioactivity only.
[2] Remaining unextracted residues (PES) following solvent extraction and microwave extraction, where applicable.
[3] The overall TRR values were determined by summation of radioactivity in the total extracts and remaining unextracted residues following solvent extraction and microwave extraction, where applicable.
[4] The overall TRR values were determined by combustion.

Summary of major identified metabolites in plant matrices	
Radiolabel position	**[Methylphenyl-U-^{14}C -], [Halophenyl-U-^{14}C-], [Oxoisoxazolidinyl-4,5-^{14}C]**
Metabolites identified	**Major metabolites**
Rice forage and hay	Isocycloseram; SYN549431
Rice grain, straw, and husks	Isocycloseram

Nature of the residue in mustard greens			**PMRA No. 3246050**
Radiolabel position	[Methylphenyl-U-^{14}C]	[Halophenyl-U-^{14}C]	[Oxoisoxazolidinyl-4,5-^{14}C]
Specific activity (MBq/mg)	2.157	2.046	2.165
Treatment: In-furrow	A single in-furrow application		
Treatment: Foliar	Three post-emergence foliar applications		
In-Furrow Application Rate (g a.i./ha)	167/application/season	171/application/season	176/application/season

Foliar applications rage (g a.i./ha)	59.7–64.1/application 188/season	62.4–64.4/application 191/season	58.8–73.7/application 200/season
Test site	Outdoors in sandy loam soil containers		
Formulation	Emulsifiable concentrate (EC) formulation of isocycloseram (guarantee: 4.785% w/w)		
Preharvest interval	In-furrow: Immature greens: 34 days; Mature greens: 53 days		
	Foliar: Immature greens: 7 days after first application; and Mature greens: 5 days after second application		
Extraction solvents	Aqueous acetonitrile solvent combinations based on water content in plant fraction.		
PES	Following foliar applications to mustard greens, immature greens from the halophenyl-U-^{14}C experiment were subjected to microwave extraction.		
Storage stability	The initial analyses of all the crop samples were completed within six months of the harvest date. A subsample of mature mustard greens (halophenyl and oxoisoxazolidinyl radiolabels) was extracted after the crops were stored at -20ºC for ca. 6 to 20 months following the same extraction procedure and analyzed to establish the storage interval between initial and final analysis of all samples. Comparison of the initial and final radiocomponent profiles obtained showed no significant change in the profiles during storage.		

Overall TRRs and extractability of residues in mustard green matrices

Radiolabel	**Crop commodity**	**Total extractable radioactivity[1]**		**Non-extractable radioactivity[2] (Final PES)**		**TRR[3]**	**TRR[4]**
		%TRR	**ppm**	**%TRR**	**ppm**	**ppm**	**ppm**
In-furrow							
[Methylphenyl-U-^{14}C]	Immature greens	59.4	0.004	40.6	0.002	0.006	0.006
	Mature greens	NA	NA	NA	NA	NA	0.003
[Halophenyl-U-^{14}C]	Immature greens	NA	NA	NA	NA	NA	0.004
	Mature greens	66.1	0.005	33.9	0.003	0.008	0.007
[Oxoisoxazolidinyl-4,5-^{14}C]	Immature greens	63.3	0.003	36.7	0.001	0.004	0.005
	Mature greens	NA	NA	NA	NA	NA	0.003
Foliar applications							
[Methylphenyl-U-^{14}C]	Immature greens	91.9	1.061	8.1	0.093	1.154	1.113

	Mature greens	96.0	1.959	4.1	0.084	2.041	2.153
[Halophenyl-U-^{14}C]	Immature greens	96.2 (90.2)	1.030 (0.966)	3.3 (9.9)	0.035 (0.106)	1.071	1.023
	Mature greens	96.5	1.877	3.5	0.068	1.945	2.124
[Oxoisoxazolidinyl-4,5-^{14}C]	Immature greens	94.2	1.127	5.8	0.069	1.197	1.273
	Mature greens	94.7	2.037	5.4	0.116	2.150	1.981

NA - not further analyzed due to low TRRs

[1] TRRs calculated following solvent extraction and microwave extraction, where applicable. Values in brackets represent the solvent extracted radioactivity only.

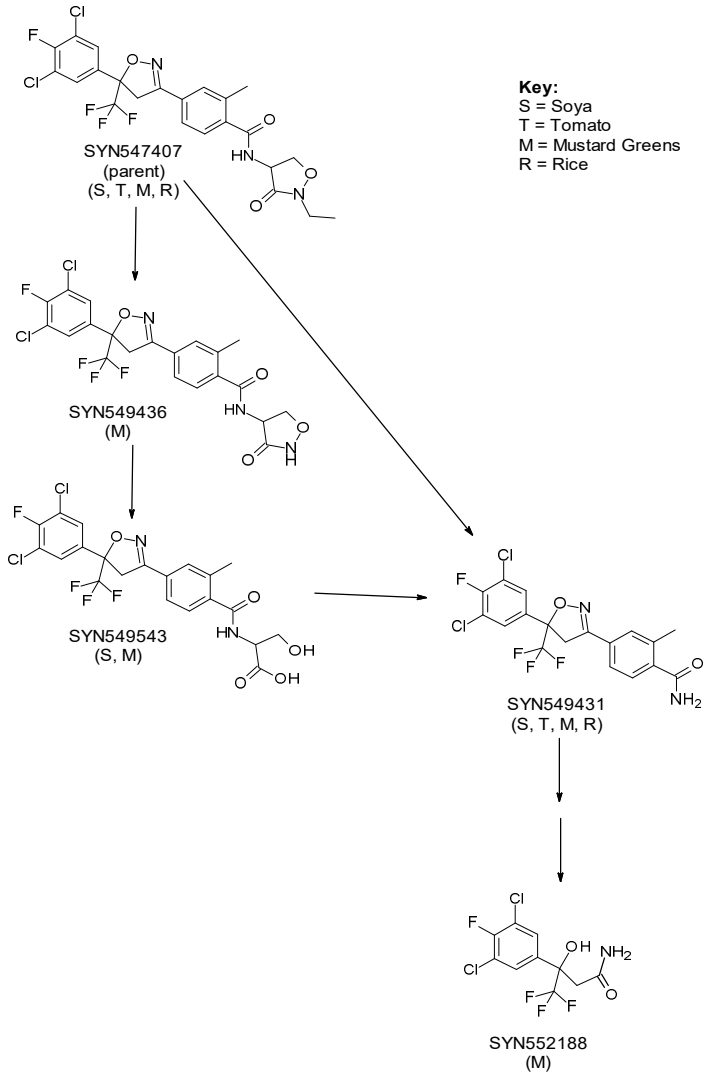
[2] TRRs remaining in the debris following solvent extraction and microwave extraction, where applicable.

[3] The overall TRR values were determined by summation of radioactivity in the total extracts and remaining unextracted residues following solvent extraction and microwave extraction, where applicable.

[4] The overall TRR values were determined by combustion.

Summary of major identified metabolites in plant matrices	
Radiolabel position	**[Methylphenyl-U-^{14}C -], [Halophenyl-U-^{14}C-], [Oxoisoxazolidinyl-4,5-^{14}C]**
Metabolites identified	**Major metabolites**
In-furrow application	
Immature greens	Isocycloseram
Mature greens	Isocycloseram; SYN549431
Foliar applications	
Immature greens, mature greens	Isocycloseram

Proposed metabolic scheme in plants



Freezer storage stability in plant matrices				**PMRA No. 3246042**
Tested matrices	**Analyte**	**Tested intervals (days)**	**Temperature (°C)**	**Categories**
Lettuce	Isocyclosera m	0, 26, 85, 189, 277, 362, 538, 735	≤-18	High water
Dried beans		0, 28, 84, 189, 277, 369, 538, 735		High protein
Wheat grain		0, 28, 83, 189, 275, 356, 539, 735		High starch
Potatoes		0, 27, 82, 189, 275, 356, 538, 736		High starch
Soybeans		0, 28, 84, 189, 277, 362, 538, 733		High oil
Oranges		0, 29, 86, 189, 275, 356, 538, 736		High acid

Wheat straw		0, 30, 86, 189, 280, 356, 539, 734		Other
Coffee beans		0, 31, 86, 190, 275, 356, 539, 735		High oil
Freezer storage stability in processed commodities				**PMRA No. 32460439**
Soybean meal	Isocycloseram	0, 32, 94, 186, 369, 559	≤-18	Not applicable
Soybean oil		0, 28, 91, 184, 422, 559, 638		
Corn meal		0, 32, 94, 186, 368, 559, 641		
Corn oil		0, 28, 91, 184, 422, 559, 641		
Potato flakes		0, 28, 91, 184, 366, 556, 638		
Tomato juice		0, 31, 91, 185, 368, 556, 637		
Tomato paste		0, 31, 91, 185, 369, 556, 637		
Dried tomatoes		0, 30, 91, 295, 367, 556, 638		
Residues of isocycloseram are stable under frozen conditions for up to 733–736 days (24 months) in high-water, high-oil, high-protein, high-starch, and high-acid commodities, and up to 637–641 days (21 months) in processed commodities.				
Crop field trials and residue decline				**PMRA No. 3246069, 3246070, 3246071, 3246086, 326091**

Crop field trials were conducted on wheat and barley in North American regions during the 2017–2018 growing seasons. SYN547407 FS (Guarantees: 100 g a.i./L [barley] and 400 g a.i./L [wheat]) was applied according to the approved rates on the Canadian labels. The number and geographic distribution of trials were generally in accordance with Health Canada's SPN2017-02. Independence of trials was assessed. Adequate storage stability data are available to support the storage intervals of the small grain cereals crop field trials. Samples were analyzed using a validated analytical method.

Crop	**Total application rate (g a.i./100 kg seed)**	**PHI (days)**	**Isocycloseram residue levels (ppm)**					
			n	**LAFT**	**HAFT**	**Median**	**Mean**	**SDEV**
Wheat forage	7.1–8.2	29–255	28	<0.01	<0.01	<0.01	<0.01	-
Wheat hay		36–287	28	<0.01	<0.01	<0.01	<0.01	-
Wheat grain		88–315	28	<0.01	<0.01	<0.01	<0.01	-
Wheat straw		82–276	28	<0.01	<0.01	<0.01	<0.01	-
Barley hay	7.1–8.4	48–238	20	<0.01	<0.01	<0.01	<0.01	-
Barley grain		82–276	20	<0.01	<0.01	<0.01	<0.01	-

Barley straw		82–276	19	<0.01	<0.01	<0.01	<0.01	-

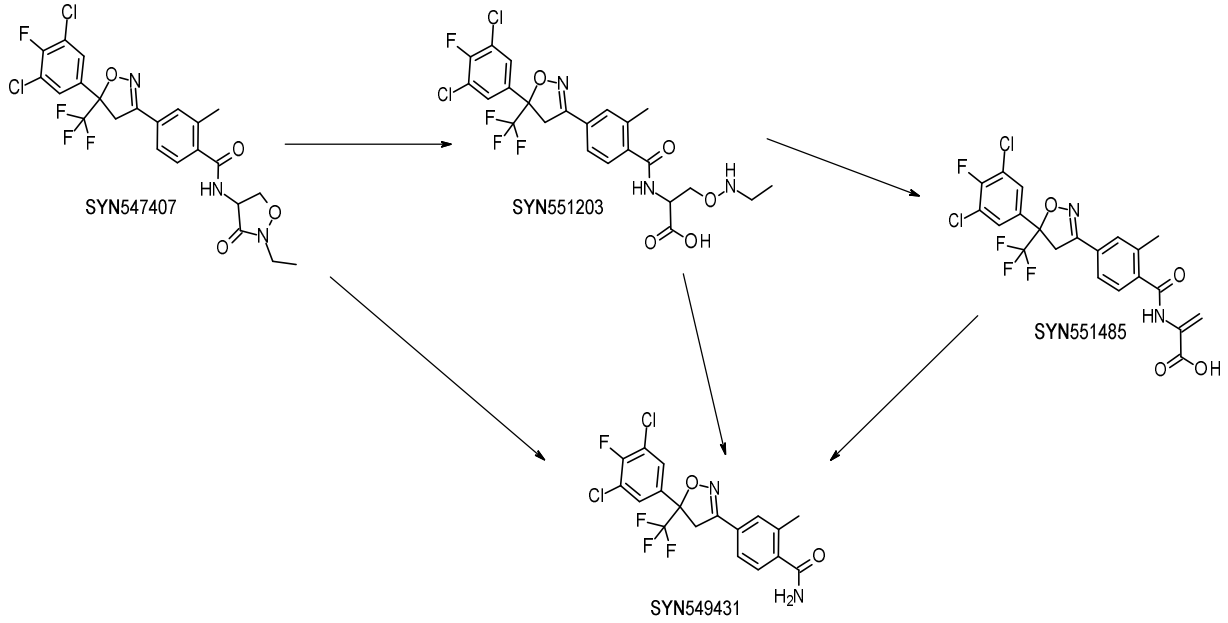
n = number of independent trials.

High-temperature hydrolysis study	**PMRA No. 3246046**

[Halophenyl-U-^{14}C]-Isocycloseram was applied to buffer solutions at pH 4, pH 5 and pH 6, along with acetonitrile to ensure a 1% v/v concentration in each buffer. The units were incubated at the appropriate temperature for the required time before cooling. The concentrations of [^{14}C]-isocycloseram ranged from 0.685 to 1.075 ppm for all pHs. Recovery of applied radioactivity (AR) ranged from 91.3% to 105.3% for all hydrolysis experiments.

Processing	**Pasteurization**	**Baking/Brewing/Boiling**	**Sterilization**
Conditions	**pH 4/90°C/20 min**	**pH 5/100°C/60 min**	**pH 6/120°C/20 min**
Major identified metabolites	Isocycloseram	Isocycloseram	Isocycloseram; SYN551203

Proposed hydrolysis scheme



Processed food and feed – Cereals	**PMRA No. 3246086**

Processing studies were conducted on wheat and barley grown in representative North American growing regions using A22241C FS applied at exaggerated rates. Adequate storage stability data are available to support the storage intervals. Samples were analyzed using a validated analytical method. Isocycloseram residues in wheat and barley grain were <LOQ (<0.01 ppm) following application at exaggerated rates (threefold approved use pattern). Therefore, grains were not further processed.

Confined accumulation in rotational crops – Lettuce (immature, mature), radish (roots, leaves) and wheat (forage, hay, straw, grain)				**PMRA No. 3246092, 3246093**
Radiolabel positions		[Methylphenyl-U-^{14}C]	[Halophenyl-U-^{14}C]	[Oxoisoxazolidinyl-4,5-^{14}C]
Specific activity (MBq/mg)		2.690	2.116	2.568
Application rate (g a.i./ha/season)		335–377	388–407	364–369
Test site/Soil type		Outdoor fenced-off wooden boxes (3 per radiolabel) in NAFTA Region 10/Sandy loam soil		
Treatment		Single application to bare soil and aged for 30, 120 and 273 days.		
Formulation		Suspension Concentrate (SC) formulation of isocycloseram: guarantee: 4.785% w/w		
Extraction solvents		Sequential extractions with different volumes (v/w) of acetonitrile/water (8:2; v/v) depending on matrix.		
PES		Unextracted radioactivity was subjected to microwave extraction (wheat hay and straw halophenyl; 30-120-d PBI, wheat straw methylphenyl; 30-120-d PBI), enzyme hydrolysis (cellulase), as well as mild (1N) and concentrated (6N) acid (HCl) and base hydrolyses (NaOH) for methylphenyl wheat straw (30, 120-d PBI) and halophenyl wheat hay and straw (30, 120-d PBI).		
Storage stability		Initial analysis of the primary fractions for all the samples from the three radiolabels took place within 6 months, with some noted exceptions. Some samples were re-extracted at 18-38 months after harvest and analyzed. No change in the radioprofiles was observed following storage at -20ºC.		

Matrices	**PBI (days)**	**Extractable radioactivity[1]**		**Non-extractable radioactivity[2]**		**TRR[3] summation**
		%TRR	**ppm**	**%TRR**	**ppm**	**ppm**
Immature lettuce	30	67.1–94.2	0.006–0.052	5.8–32.9	0.003	0.010–0.055
	120	92.0	0.013	8.0	0.001	0.014
Mature lettuce	120	91.6	0.014	8.3	0.001	0.015
Radish leaves	30	76.9–93.4	0.010-0.015	6.6-23.1	0.001–0.003	0.013–0.016
	120	92.6	0.017	7.5	0.001	0.018
Radish roots	30	88.6–94.4	0.011–0.070	5.6–11.5	0.001–0.004	0.074
	120	88.0	0.011	11.9	0.001	0.012
	273	86.7–90.1	0.013–0.016	9.9–13.3	0.002	0.015–0.018
Wheat forage	30	67.7–93.0	0.012–0.040	7.0-32.4	0.003–0.005	0.016–0.043
	120	78.6	0.012	21.4	0.003	0.015

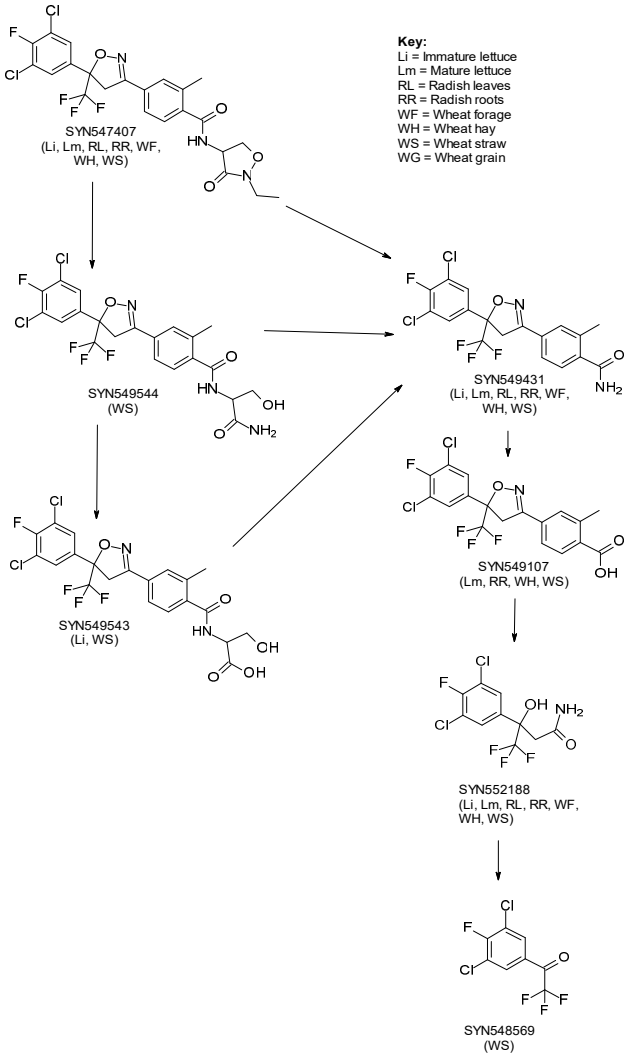
Wheat hay	30	75.3–99.3	0.013–0.154	0.6–24.7	0.001–0.006	0.017–0.155
	120	53.7–97.5	0.009–0.083	2.6–46.2	0.002–0.009	0.015–0.084
Wheat straw	30	71.3–97.7	0.029–0.122	2.3–28.7	0.003–0.019	0.035–0.125
	120	66.1–90.1	0.010–0.081	9.9–33.8	0.005–0.009	0.016–0.089
	273	64.2–81.7	0.010–0.017	18.3–35.8	0.004–0.006	0.016–0.021
Wheat grain	30	61.4	0.013	38.5	0.008	0.020

[1] Extractable radioactivity is the sum of solvent extracts and extracts following hydrolysis of the PES, where applicable.
[2] TRRs remaining following solvent extraction and hydrolysis of the PES.
[3] TRRs are derived from the sum of radioactivity present in the extracts and PES except for commodities where TRRs were <0.01 ppm following combustion, which were not analysed further.

Summary of major identified metabolites in rotated crops			
Radiolabel position	**[Methylphenyl-U-^{14}C -], [Halophenyl-U-^{14}C-], [Oxoisoxazolidinyl-4,5-^{14}C]**		
Metabolites identified	**Major metabolites**		
Plant-back intervals (PBI)	**1st Rotation (30-day PBI)**	**2nd Rotation (120-day PBI)**	**3rd Rotation (273-day PBI)**
Immature lettuce	Isocycloseram; SYN552188; SYN549543	Isocycloseram; SYN549543/ SYN552188/SYN548569[1]	Not extracted
Mature lettuce	Not extracted	Isocycloseram; SYN549543/ SYN552188/SYN548569[1]	Not extracted
Radish roots	Isocycloseram	Isocycloseram	Isocycloseram; SYN549431
Radish leaves	SYN552188; SYN549543	Isocycloseram; SYN552188	Not extracted
Wheat forage	SYN552188	SYN552188	Not extracted
Wheat hay	Isocycloseram; SYN552188	Isocycloseram; SYN552188; SYN549107	Not extracted
Wheat straw	Isocycloseram; SYN552188; SYN549543	Isocycloseram	Isocycloseram; SYN552188; SYN549543
Wheat grain	Not extracted	Not extracted	Not extracted

[1] co-elution and no further separation was attempted.

Proposed metabolic scheme in rotational crops



Residue data in rotational crops	**PMRA No. 3246094**

Thirty-seven trials (radish; spinach and/or mustard greens; wheat) were conducted during the 2017–2018 growing seasons in North American growing regions 5, 6 and 10. Three broadcast spray applications were made to bare soil with A21550L SC (400 g a.i./L) for a maximum seasonal application rate of 366 g a.i./ha. 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)**	**Isocycloseram residue levels (ppm)**					
			n	**LAFT**	**HAFT**	**Median**	**Mean**	**SDEV**
Mustard greens/spinach	357–366	29–31	3	<0.01	<0.01	<0.01	<0.01	NA
Wheat forage	354–363	28–31	3	<0.01	<0.01	<0.01	<0.01	NA
Wheat hay	354–363	28–31	3	<0.01	<0.01	<0.01	<0.01	NA
Wheat grain	354–363	28–31	3	<0.01	<0.01	<0.01	<0.01	NA

Wheat straw	354–363	28–31	3	<0.01	<0.01	<0.01	<0.01	NA
Radish roots	362	28–29	3	<0.01	<0.01	<0.01	<0.01	NA
	361	87–91	3	<0.01	<0.01	<0.01	<0.01	NA
	363	115–121	3	<0.01	<0.01	<0.01	<0.01	NA
Radish leaves	362	28–29	3	<0.01	0.024	<0.01	0.015	0.008
	361	87–91	3	<0.01	0.015	<0.01	0.012	0.003
	363	115–121	3	<0.01	<0.01	<0.01	<0.01	NA
Values based on per-trial averages. For computation, values <LOQ are assumed to be at the LOQ. n = number of independent field trials.								

Table 12 Food residue chemistry overview of metabolism studies and risk assessment

Plant studies	
Residue definition for enforcement and risk assessment **Primary crops (soybean, tomato, mustard green, paddy rice); Rotational crops (lettuce, radish, wheat)**	Isocycloseram
Metabolic profile in diverse crops	Similar in soybean, tomato, mustard green, and paddy rice following foliar application
Animal studies	
Animals	**Ruminant and poultry**
Residue definition for enforcement and risk assessment	Isocycloseram
Metabolic profile in animals **(goat, hen, rat)**	Similar in livestock and laboratory animals
Fat soluble residue	Yes

Dietary risk from food and drinking water			
Basic acute dietary exposure analysis, 95th percentile **ARfD = 0.012 mg/kg bw (all infants, children 1–12 years)** **ARfD = 0.13 mg/kg bw (males 13–49 years, adults 50–99 years)** **ARfD = 0.007 mg/kg bw (females 13–49 years)** **Estimated acute drinking water**	**Population**	**Estimated risk % of acute reference dose (ARfD)**	
		Food alone	**Food and drinking water**
	All infants < 1 year	5.6	6.1
	Children 1–2 years	9.1	9.2
	Children 3–5 years	5.5	5.8

concentration = 0.0013 ppm	Children 6–12 years	3.5	3.8
	Males 13–49 years	0.19	0.21
	Adults 50–99 years	0.11	0.14
	Females 13–49 years	2.4	2.9
Basic chronic dietary exposure analysis **ADI = 0.007 mg/kg bw/day** **Estimated chronic drinking water concentration = 0.00021 ppm**	**Population**	**Estimated risk % of acceptable daily intake (ADI)**	
		Food alone	**Food and drinking water**
	General Population	1.5	1.6
	All Infants < 1 year	2.0	2.2
	Children 1–2 years	7.6	7.7
	Children 3–5 years	4.7	4.7
	Children 6–12 years	2.7	2.8
	Youth 13–19 years	1.4	1.4
	Adults 20–49 years	1.0	1.1
	Adults 50–99 years	0.9	1.0

Table 13 Fate and behaviour in the environment

Property	Test substance	Medium	Value	Kinetic model	Major transformation products	Comments	PMRA No.
Abiotic transformation							
Hydrolysis	Isocycloseram Technical (methylphenyl, halophenyl and oxoisoxazolidinyl radio-labels)	pH 4	DT_{50} and $T_{1/2\text{-}rep}$: Stable	SFO	None	Hydrolysis is pH-dependent. It is an important route of dissipation under alkaline conditions but less so under neutral and acidic conditions.	3246121
		pH 7	DT_{50} and $T_{1/2\text{-}rep}$: 262	SFO			
		pH 9	DT_{50} and $T_{1/2\text{-}rep}$: 1.36	SFO			
Phototransformation in soil	Isocycloseram Technical (methylphenyl, halophenyl and oxoisoxazolidinyl radio-labels)	Dry soil	DT_{50} and $T_{1/2\text{-}rep}$: 85.1	SFO	None	Half-life values adjusted to represent environmental phototransformation half-lives during the summer at 40°N Phototransformation on soil is not expected to be an important route of dissipation.	3246098
		Moist soil	DT_{50} and $T_{1/2\text{-}rep}$: 111.6	SFO			
Phototransformation in water	Isocycloseram Technical (methylphenyl, halophenyl and oxoisoxazolidinyl radio-labels)	pH 4 buffer	DT_{50} and $T_{1/2\text{-}rep}$: 72.7	SFO	SYN549431	Half-life values adjusted to represent environmental phototransformation half-lives during the summer at 40°N	3246122

Property	Test substance	Medium	Value	Kinetic model	Major transformation products	Comments	PMRA No.
						Phototransformation in water is not expected to be an important route of dissipation near the surface in water bodies exposed to sunlight.	
Phototransformation in air	N/A					Based on vapour pressure and Henry's law constant, isocycloseram is not expected to volatilize from water or moist soil.	N/A
Biotransformation							
Biotransformation in aerobic soil	Isocycloseram Technical (methylphenyl, halophenyl and oxoisoxazolidinyl radio-labels)	Soil	DT_{50}: 196.2 (90% upper confidence bound on the mean; n = 5) Range: 56.3–292.9 $T_{1/2,rep}$: 200.1 (90% upper confidence bound on the mean; n = 5)	SFO and DFOP	SYN549107 SYN550738	Classified as moderately persistent to persistent	3246095

Property	Test substance	Medium	Value	Kinetic model	Major transformation products	Comments	PMRA No.
			Range: 56.3–292.9				
	SYN549107 (Transformation product of Isocycloseram)	Soil	DT_{50}: 273 (90% upper confidence bound on the mean; n = 4) Range: 18.9–402.7 $T_{1/2,rep}$: 453 (90% upper confidence bound on the mean; n = 4) Range: 104.5–488	SFO, DFOP and IORE	Not applicable	Classified as slightly persistent to persistent	3246100
	SYN550738 (Transformation product of Isocycloseram)	Soil	DT_{50}: 20.7 (90% upper confidence bound on the mean; n = 5) Range: 12.1–23.1 $T_{1/2,rep}$: 230 (90% upper confidence bound on the mean; n = 5)	SFO, DFOP and IORE	Not applicable	Classified as non-persistent to slightly persistent	3246101

Property	Test substance	Medium	Value	Kinetic model	Major transformation products	Comments	PMRA No.
			Range: 19.1–362				
Biotransformation in anaerobic soil	Isocycloseram Technical (methylphenyl, halophenyl and oxoisoxazolidinyl radio-labels)	Soil	DT_{50}: 79.9 (80^{th} percentile; n = 4) Range: 35.8–129.3 $T_{1/2,rep}$: 79.9 (80^{th} percentile; n = 4) Range: 35.8–129.3	SFO	SYN551203 SYN550455 SYN551248 SYN549546 SYN550321 SYN550603 SYN551113 SYN549433 SYN550602 SYN548569 SYN549110 SYN551057	Classified as slightly persistent to moderately persistent	3246096
Biotransformation in aerobic aquatic systems	Isocycloseram Technical (methylphenyl, halophenyl and oxoisoxazolidinyl radio-labels)	Dyfi Estuary (River) United Kingdom Water pH: 7.89 Sediment pH: 7.7 Calwich Abbey (Pond) United Kingdom Water pH: 7.73	DT_{50}: 26.8 (whole system, 80^{th} percentile; n = 3) Range: 10.0–37.1) $T_{1/2rep}$: 198.9 (whole system, 80^{th} percentile; n = 3) Range: 16.7–313.7)	IORE	SYN549107 SYN550455 SYN549546 SYN550603 SYN549433 SYN550602 SYN551190 SYN550737	Classified as non-persistent to slightly persistent (based on the range of whole system DT_{50} values) Maximum concentrations of isocycloseram were 0.93% and 31.1% AR found in the water column and sediment, respectively, at study termination (104 days)	3246124 and 3246127

Property	Test substance	Medium	Value	Kinetic model	Major transformation products	Comments	PMRA No.
		Sediment pH: 6.4 Golden Lake North Dakota Water pH: 8.21 Sediment pH: 7.9					
Biotransformation in anaerobic aquatic systems	Isocycloseram Technical (methylphenyl, halophenyl and oxoisoxazolidinyl radio-labels)	Calwich Abbey (Pond) United Kingdom Water pH: 8.4 Sediment pH: 6.8 Golden Lake North Dakota Water pH: 8.7 Sediment pH: 7.4	DT_{50}: 5.93 (whole system longest of 2 values) Range: 4.25–5.44 $T_{1/2rep}$: 5.93 (whole system longest of 2 values) Range: 4.25–5.44	SFO	SYN549543 SYN551203 SYN550455 SYN551248 SYN549546 SYN551415 SYN550321 SYN550603 SYN549433 SYN550602 SYN549557 SYN548569 SYN549110 SYN551441 SYN549548	Classified as non-persistent Concentrations of isocycloseram were < LOD and 2.3% AR in the water column and sediment, respectively, at study termination (148 days)	3246125

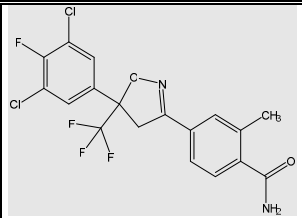
Field studies							
Test site location/planted crops and study duration	**Test substance**	**Application rate**	**DT_{50}, $T_{1/2rep}$ (days)**	**Kinetic model**	**Major transformation products**	**Comments**	**PMRA No.**
Location: Alberta Crop: None (Bareground) Study duration: 447 days	Isocycloseram applied as SYN547407 SC (400)	2 applications of 200 g a.i./ha with 14 days between applications	DT_{50}: 161 $T_{1/2\ rep}$: 343	DFOP	None	Moderately persistent Primarily detected in the top 25 cm soil layer. Maximum depth measured : 70–100 cm (Maximum depth sampled). 21.8% carryover 346 days after last application.	3246102
Location: Alberta Crop: None (Bareground) Study duration: 449 days	Isocycloseram applied as SYN547407 SC (400)	2 applications of 200 g a.i./ha with 14 days between applications	DT_{50}: 73.1 $T_{1/2\ rep}$: 232	IORE	None	Moderately persistent Primarily measured in the top 10 cm soil layer. Maximum depth measured: 45 cm (Maximum depth sampled). 5.8% carryover 349 days after last application.	3246114
Location: New York Crop: None	Isocycloseram applied as SYN547407 SC	3 applications of 132 g a.i./ha with 7 days	DT_{50}: 547 $T_{1/2\ rep}$: 1180	DFOP	None	Persistent Primarily measured in the	3246109

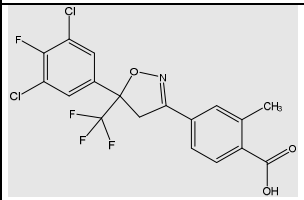
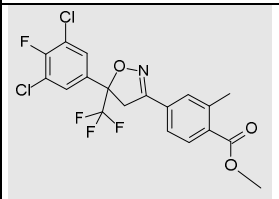
Field studies							
Test site location/planted crops and study duration	**Test substance**	**Application rate**	**DT_{50}, $T_{1/2rep}$ (days)**	**Kinetic model**	**Major transformation products**	**Comments**	**PMRA No.**
(Bareground) Study duration: 538 days	(400)	between applications				top 15.2 cm soil layer. Maximum depth measured: 45.7–61 cm. 17.4% carryover 360 days after last application.	
Location: New York Crop: None (Bareground) Study duration: 507 days	Isocycloseram applied as SYN547407 SC (400)	3 applications of 120 g a.i./ha with 7 days between applications	DT_{50}: 50.8 $T_{1/2\ rep}$: 1075	DFOP	None	Moderately persistent Primarily measured in the top 61 cm soil layer. Maximum depth detected: 61.0–76.2 cm. 21.8% carryover 360 days after last application.	3246104
Location: New York Crop:Turf Study duration: 507 days	Isocycloseram applied as SYN547407 SC (400)	3 applications of 120 g a.i./ha with 7 days between applications	DT_{50}: 532 $T_{1/2\ rep}$: 532	SFO	None	Persistent Primarily measured in the top 15.2 cm soil layer. Maximum depth detected: 30.5–45.7 cm. 25.8% carryover	

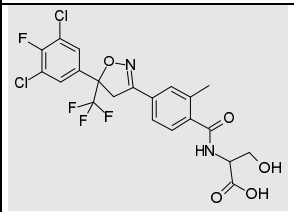
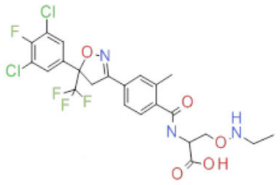
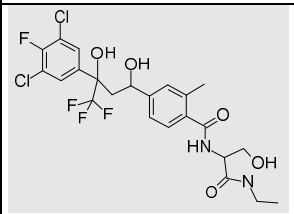
Field studies							
Test site location/planted crops and study duration	**Test substance**	**Application rate**	**DT_{50}, $T_{1/2rep}$ (days)**	**Kinetic model**	**Major transformation products**	**Comments**	**PMRA No.**
						360 days after last application	

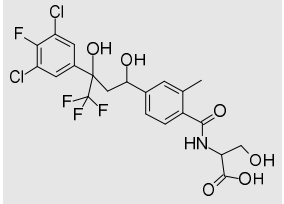
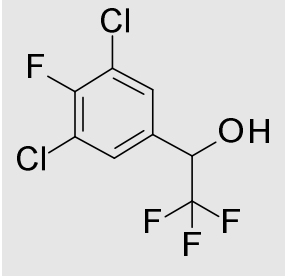
Bioconcentration				
Bioconcentration in fish	Not expected to bioaccumulate. BCF = 877 - 1090 (growth-corrected and normalized to 5% lipid content)			3246159; 3448476
Mobility				
Property	**Test substance**	**K_d/K_{oc} (L/kg)**	**Mobility classification**	**PMRA No.**
Adsorption in soil	Isocycloseram Technical	K_d: 50.0–260.0 K_{oc}: 6279 –1444	Immobile	3246117
	SYN554707 (Transformation product of isocycloseram)	K_d: 106.7–284.3 K_{oc}: 5618–9475	Immobile	3246118
	SYN549107 (Transformation product of isocycloseram)	K_d: 8.8–52.6 K_{oc}: 1139–9400	Low mobility to immobile	3246119
	SYN550738 (Transformation product of isocycloseram)	K_d: 904–3745 K_{oc}: 10 592 826–3662	Immobile	3246120

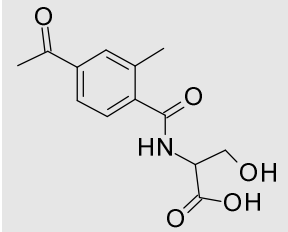
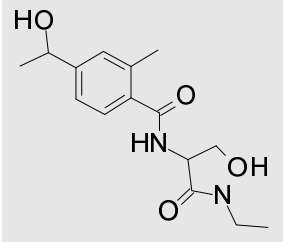
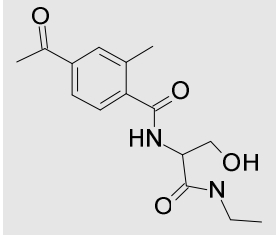
Table 14 Transformation products of isocycloseram in the environment

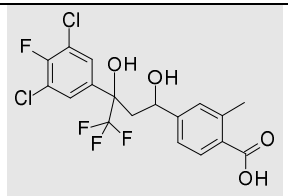
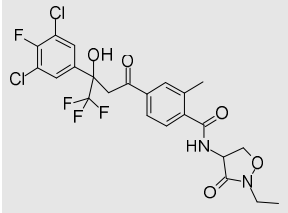
Code and chemical name	Chemical structure	Study		Max %AR (day)	%AR at study end (study length, days)
SYN549431		Hydrolysis at 25°C and pH 7		< LOD	< LOD (29)
		Soil Photo-transformation	Dry Soil	6.5% (12)	6.4 (17)
			Moist Soil	6.1% (17)	≥ 6.1% (17)
		Aqueous Phototransformation in pH 4 buffer		35% (15)	21.1% (20)

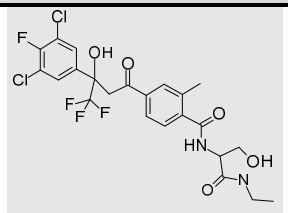
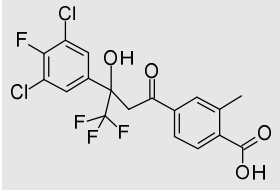
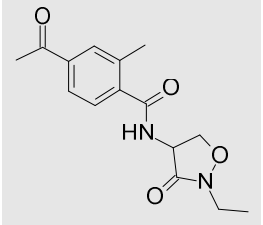
Code and chemical name	Chemical structure	Study	Max %AR (day)	%AR at study end (study length, days)
		Aerobic soil	5.3% (63)	4.6% (120)
		Anaerobic soil	6.2% (150)	6.2% (150)
		Aerobic aquatic with sediment	8.4% (148)	8.4% (148)
		Aerobic aquatic with sediment	< 5% (99)	< 5% (99)
		Anaerobic aquatic with sediment	< 5% (104)	< 5% (104)
		Field studies	4.6% (316)	2.9% (447–449)
		K_{oc}	296 500 (estimated)	
SYN549107 Synonym identifier in ecotox study: SYN547950		Hydrolysis at 25°C and pH 7	< LOD	< LOD (29)
		Soil Phototransformation (Moist soil)	0.7% (17)	0.7% (17)
		Aqueous Phototransformation in Water with pH 4	3.1% (15)	<LOD (20)
		Aerobic soil	27.4% (120)	27.4% (120)
		Anaerobic soil	5.9% (31)	0.1% (150)
		Aerobic aquatic with sediment	11.3% (117)	11.3% (117)
		Aerobic aquatic with sediment	7.3% (99)	7.3% (99)
		Anaerobic aquatic with sediment	< LOD	< LOD (104)
		Field studies	3.4% (441)	2.9% (538)
		K_{oc}	1139–9400 (empirical)	
SYN550738 Synonym identifier in ecotox study: SYN550918		Hydrolysis	Not Measured	Not Measured
		Soil Phototransformation	Not Measured	Not Measured
		Aqueous Phototransformation in water with pH 4 buffer	Not Measured	Not Measured
		Aerobic soil	10.9% (120)	10.9% (120)
		Anaerobic soil	Not Measured	Not Measured
		Aerobic aquatic with sediment	< LOD	< LOD (99)
		Aerobic aquatic with sediment	Not Measured	Not Measured
		Anaerobic aquatic with sediment	< LOD	< LOD (104)

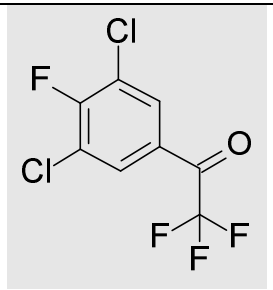
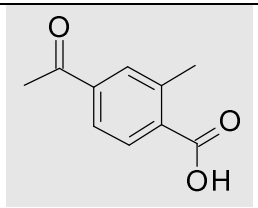
Code and chemical name	Chemical structure	Study	Max %AR (day)	%AR at study end (study length, days)
		Field studies	1.1% (441)	0.9% (538)
		K_{oc}	105928–263662 (empirical)	
SYN549543		Hydrolysis at 25°C and pH 7	pH 7: < LOD	pH 7: < LOD (29)
		Soil Phototransformation	< LOD	< LOD (20)
		Aqueous Phototransformation in Water with pH 4	Not Measured	Not Measured
		Aerobic soil	7.2% (7)	3.2% (120)
		Anaerobic soil	< 8.2% (90)	< 5.1% (150)
		Aerobic aquatic with sediment	6.2 (13)	2.1% (147)
		Aerobic aquatic with sediment	< 5% (99)	< 5% (99)
		Anaerobic aquatic with sediment	11.3% (8)	1.3% (104)
		Field studies	2.6% (58)	0.7% (449)
		K_{oc}	6286 (estimated)	
SYN551203		Hydrolysis at 25°C and pH 7	6.3% (25)	4.1% (29)
		Soil Phototransformation	Not Measured	Not Measured
		Aqueous Phototransformation in water with pH 4 buffer	Not Measured	Not Measured
		Aerobic soil	Not Measured	Not Measured
		Anaerobic soil	22.2% (75)	13.4% (150)
		Aerobic aquatic with sediment	< 5% (99)	< 5% (99)
		Aerobic aquatic with sediment	<5% (148)	<5% (148)
		Anaerobic aquatic with sediment	28.0% (8)	< LOD (104)
		Field studies	Not Measured	Not Measured
		K_{oc}	484700 (estimated)	
SYN550455		Hydrolysis	Not Measured	Not Measured
		Soil Phototransformation	Not Measured	Not Measured
		Aqueous Phototransformation in water with pH 4 buffer	Not Measured	Not Measured
		Aerobic soil	Not Measured	Not Measured

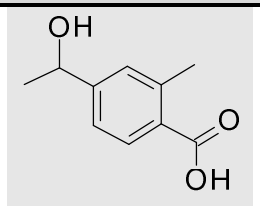
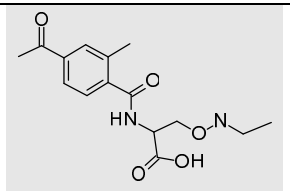
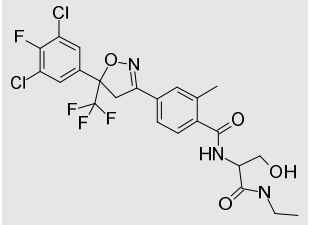
Code and chemical name	Chemical structure	Study	Max %AR (day)	%AR at study end (study length, days)
		Anaerobic soil	19.2% (150)	19.2% (150)
		Aerobic aquatic with sediment	8.5% (14)	2.8% (99)
		Aerobic aquatic with sediment	33.5% (148)	33.5% (148)
		Anaerobic aquatic with sediment	12.6 (104)	12.6 (104)
		Field studies	< LOD	< LOD (538)
		K_{oc}	3876 (estimated)	
SYN551248		Hydrolysis	Not Measured	Not Measured
		Soil Phototransformation	Not Measured	Not Measured
		Aqueous Phototransformation in water with pH 4 buffer	Not Measured	Not Measured
		Aerobic soil	Not Measured	Not Measured
		Anaerobic soil	11.6% (150)	11.6% (150)
		Aerobic aquatic with sediment	< LOD	< LOD (147)
		Aerobic aquatic with sediment	< LOD	< LOD (99)
		Anaerobic aquatic with sediment	< LOD	< LOD (104)
		Field studies	< LOD	< LOD (538)
		K_{oc}	460 (estimated)	
SYN549546		Hydrolysis	Not Measured	Not Measured
		Soil Phototransformation	Not Measured	Not Measured
		Aqueous Phototransformation in water with pH 4 buffer	Not Measured	Not Measured
		Aerobic soil	Not Measured	Not Measured
		Anaerobic soil	48.5% (150)	48.5% (150)
		Aerobic aquatic with sediment	30.5 (100)	24.2 (148)
		Aerobic aquatic with sediment	26.8% (60)	20.1% (99)
		Anaerobic aquatic with sediment	80.9 (63)	78.2 (105)
		Field studies	2.4 (441)	0.4% (449)
		K_{oc}	617 (estimated)	

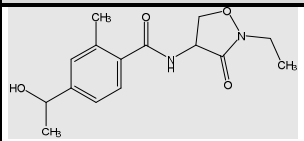
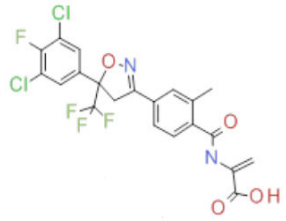
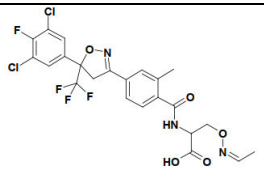
Code and chemical name	Chemical structure	Study	Max %AR (day)	%AR at study end (study length, days)
SYN551415		Hydrolysis	Not Measured	Not Measured
		Soil Phototransformation	Not Measured	Not Measured
		Aqueous Phototransformation in water with pH 4 buffer	Not Measured	Not Measured
		Aerobic soil	Not Measured	Not Measured
		Anaerobic soil	7.8% (60)	<LOD (150)
		Aerobic aquatic with sediment	< LOD (99)	< LOD (99)
		Aerobic aquatic with sediment	< LOD (148)	< LOD (148)
		Anaerobic aquatic with sediment	22.4 (12)	< LOD (105)
		Field studies	Not Measured	Not Measured
		K_{oc}	39 (estimated)	
SYN550321		Hydrolysis	Not Measured	Not Measured
		Soil Phototransformation	Not Measured	Not Measured
		Aqueous Phototransformation in water with pH 4 buffer	Not Measured	Not Measured
		Aerobic soil	Not Measured	Not Measured
		Anaerobic soil	14.1% (122)	11.1% (150)
		Aerobic aquatic with sediment	< LOD	< LOD (148)
		Aerobic aquatic with sediment	< LOD	< LOD (99)
		Anaerobic aquatic with sediment	31.9% (104)	31.9% (104)
		Field studies	< LOD	< LOD (538)
		K_{oc}	10 (estimated)	
SYN550603 Synonym identifier in ecotox study: SYN551513		Hydrolysis	Not Measured	Not Measured
		Soil Phototransformation	Not Measured	Not Measured
		Aqueous Phototransformation in water with pH 4 buffer	Not Measured	Not Measured
		Aerobic soil	Not Measured	Not Measured
		Anaerobic soil	11.1% (122)	6.8% (150)

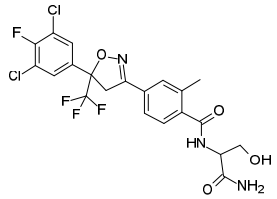
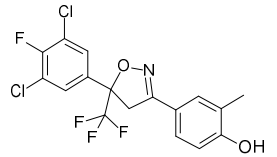
Code and chemical name	Chemical structure	Study	Max %AR (day)	%AR at study end (study length, days)
		Aerobic aquatic with sediment	Not Measured	Not Measured
		Aerobic aquatic with sediment	12.6 (27)	2.1% (146)
		Anaerobic aquatic with sediment	26.6% (63)	24.3% (105)
		Field studies	< LOD	< LOD (538)
		K_{oc}	10 (estimated)	
SYN551113		Hydrolysis	Not Measured	Not Measured
		Soil Phototransformation	Not Measured	Not Measured
		Aqueous Phototransformation in water with pH 4 buffer	Not Measured	Not Measured
		Aerobic soil	Not Measured	Not Measured
		Anaerobic soil	< 22.2% (75)	< 16.8% (150)
		Aerobic aquatic with sediment	Not Measured	Not Measured
		Aerobic aquatic with sediment	9.1% (146)	9.1% (146)
		Anaerobic aquatic with sediment	6.0% (104)	6.0% (104)
		Field studies	< LOD	< LOD (538)
		K_{oc}	996.5 (estimated)	
SYN549433		Hydrolysis	Not Measured	Not Measured
		Soil Phototransformation	Not Measured	Not Measured
		Aqueous Phototransformation in water with pH 4 buffer	Not Measured	Not Measured
		Aerobic soil	Not Measured	Not Measured
		Anaerobic soil	< 18.2% (60)	< 13.4% (150)
		Aerobic aquatic with sediment	18.3% (8)	0.2% (148)
		Aerobic aquatic with sediment	11.4% (14)	1.5% (99)
		Anaerobic aquatic with sediment	16.9% (12)	< LOD (104)
		Field studies	0.6% (0)	< LOD (538)
		K_{oc}	6242 (estimated)	
SYN550602 Synonyms identified		Hydrolysis	Not Measured	Not Measured
		Soil Phototransformation	Not Measured	Not Measured

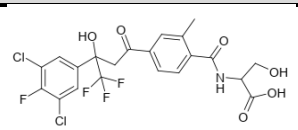
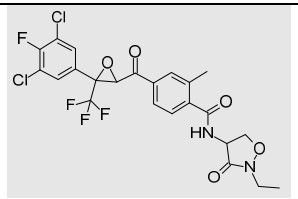
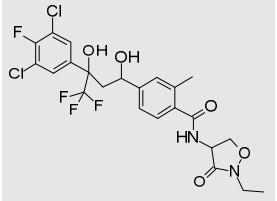
Code and chemical name	Chemical structure	Study	Max %AR (day)	%AR at study end (study length, days)
for ecotox study: SYN551754		Aqueous Phototransformation in water with pH 4 buffer	Not Measured	Not Measured
		Aerobic soil	Not Measured	Not Measured
		Anaerobic soil	14.7 (90)	11.6% (150)
		Aerobic aquatic with sediment	30.3% (27)	17.0 (147)
		Aerobic aquatic with sediment	13.8% (14)	4.3% (99)
		Anaerobic aquatic with sediment	11.0% (27)	< LOD (105)
		Field studies	< LOD	< LOD (538)
		K_{oc}	288 (estimated)	
SYN551190		Hydrolysis	Not Measured	Not Measured
		Soil Phototransformation	Not Measured	Not Measured
		Aqueous Phototransformation in water with pH 4 buffer	Not Measured	Not Measured
		Aerobic soil	Not Measured	Not Measured
		Anaerobic soil	6.2 % (150)	6.2 % (150)
		Aerobic aquatic with sediment	10.8 % (61)	8.7 % (146)
		Aerobic aquatic with sediment	11.0% (99)	11.0% (99)
		Anaerobic aquatic with sediment	< 5%	< 5% (105)
		Field studies	Not Measured	Not Measured
		K_{oc}	1539 (estimated)	
SYN549557		Hydrolysis	Not Measured	Not Measured
		Soil Phototransformation	Not Measured	Not Measured
		Aqueous Phototransformation in water with pH 4 buffer	Not Measured	Not Measured
		Aerobic soil	Not Measured	Not Measured
		Anaerobic soil	5.6 % (150)	5.6 % (150)
		Aerobic aquatic with sediment	< 5% (148)	< 5% (148)
		Aerobic aquatic with sediment	6.2% (14)	< LOD (99)
		Anaerobic aquatic with sediment	44.6% (8)	1.4% (105)

Code and chemical name	Chemical structure	Study	Max %AR (day)	%AR at study end (study length, days)
		Field studies	Not Measured	Not Measured
		K_{oc}	39.1 (estimated)	
SYN548569		Hydrolysis	Not Measured	Not Measured
		Soil Phototransformation	Not Measured	Not Measured
		Aqueous Phototransformation in water with pH 4 buffer	Not Measured	Not Measured
		Aerobic soil	Not Measured	Not Measured
		Anaerobic soil	11.4 % (90)	< LOD (150)
		Aerobic aquatic with sediment	< 5% (148)	< 5% (148)
		Aerobic aquatic with sediment	2.0% (28)	< LOD (99)
		Anaerobic aquatic with sediment	44.9% (12)	0.5% (104)
		Field studies	3.9% (28)	< LOD (538)
		K_{oc}	954.3 (estimated)	
SYN549110		Hydrolysis	Not Measured	Not Measured
		Soil Phototransformation	Not Measured	Not Measured
		Aqueous Phototransformation in water with pH 4 buffer	Not Measured	Not Measured
		Aerobic soil	Not Measured	Not Measured
		Anaerobic soil	18.3% (122)	12.6% (150)
		Aerobic aquatic with sediment	< LOD	< LOD (148)
		Aerobic aquatic with sediment	< LOD	< LOD (99)
		Anaerobic aquatic with sediment	55.7% (41)	33.5% (105)
		Field studies	< LOD	< LOD (538)
		K_{oc}	10 (estimated)	
SYN551057		Hydrolysis	Not Measured	Not Measured
		Soil Phototransformation	Not Measured	Not Measured
		Aqueous Phototransformation in water with pH 4 buffer	Not Measured	Not Measured

Code and chemical name	Chemical structure	Study	Max %AR (day)	%AR at study end (study length, days)
		Aerobic soil	Not Measured	Not Measured
		Anaerobic soil	17.8% (122)	13.6% (150)
		Aerobic aquatic with sediment	< LOD	< LOD (147)
		Aerobic aquatic with sediment	< LOD	< LOD (99)
		Anaerobic aquatic with sediment	16.3% (63)	7.2% (104)
		Field studies	< LOD	< LOD (538)
		K_{oc}	10 (estimated)	
SYN551441		Hydrolysis	Not Measured	Not Measured
		Soil Phototransformation	Not Measured	Not Measured
		Aqueous Phototransformation in water with pH 4 buffer	Not Measured	Not Measured
		Aerobic soil	Not Measured	Not Measured
		Anaerobic soil	Not Measured	Not Measured
		Aerobic aquatic with sediment	< LOD (99)	< LOD (99)
		Aerobic aquatic with sediment	< LOD (148)	< LOD (148)
		Anaerobic aquatic with sediment	11.7% (8)	< LOD (104)
		Field studies	Not Measured	Not Measured
		K_{oc}	16.5 (estimated)	
SYN550737 Synonym: identified as SYN551753 in ecotox studies.		Hydrolysis	Not Measured	Not Measured
		Soil Phototransformation	Not Measured	Not Measured
		Aqueous Phototransformation in water with pH 4 buffer	Not Measured	Not Measured
		Aerobic soil	Not Measured	Not Measured
		Anaerobic soil	< 5.0% (46)	< 5.0% (150)
		Aerobic aquatic with sediment	26.2% (5)	0.4% (147)
		Aerobic aquatic with sediment	11.1% (14)	3.9% (99)
		Anaerobic aquatic with sediment	< 5.0%	< 5.0% (105)
		Field studies	Not Measured	Not Measured
		K_{oc}	100 000 (estimated)	

Code and chemical name	Chemical structure	Study	Max %AR (day)	%AR at study end (study length, days)
SYN549548		Hydrolysis	Not Measured	Not Measured
		Soil Phototransformation	Not Measured	Not Measured
		Aqueous Phototransformation in water with pH 4 buffer	Not Measured	Not Measured
		Aerobic soil	Not Measured	Not Measured
		Anaerobic soil	Not Measured	Not Measured
		Aerobic aquatic with sediment	< LOD (148)	< LOD (148)
		Aerobic aquatic with sediment	< 5% (99)	< 5% (99)
		Anaerobic aquatic with sediment	10.3% (12)	< LOD (105)
		Field studies	Not Measured	Not Measured
		K_{oc}	25.3 (estimated)	
Minor transformation products				
SYN551485		Hydrolysis at 25°C and pH 7	pH 7: < LOD	pH 7: < LOD (29)
		Soil Phototransformation	Not Measured	Not Measured
		Aqueous Phototransformation in Water with pH 4	Not Measured	Not Measured
		Aerobic soil	Not Measured	Not Measured
		Anaerobic soil	Not Measured	Not Measured
		Aerobic aquatic with sediment	Not Measured	Not Measured
		Aerobic aquatic with sediment	Not Measured	Not Measured
		Anaerobic aquatic with sediment	Not Measured	Not Measured
		Field studies	Not Measured	Not Measured
		K_{oc}	68 520 (estimated)	
SYN551478		Hydrolysis at 25°C and pH 7	< LOD	< LOD (29)
		Soil Phototransformation	< LOD	< LOD (17)
		Aqueous Phototransformation in water with pH 4 buffer	Not Measured	Not Measured
		Aerobic soil	Not Measured	Not Measured

Code and chemical name	Chemical structure	Study	Max %AR (day)	%AR at study end (study length, days)
		Anaerobic soil	Not Measured	Not Measured
		Aerobic aquatic with sediment	< LOD	< LOD (99)
		Aerobic aquatic with sediment	< LOD (148)	< LOD (148)
		Anaerobic aquatic with sediment	< LOD (104)	< LOD (104)
		Field studies	Not Measured	Not Measured
		K_{oc}	791100 (estimated)	
SYN549544		Hydrolysis	Not Measured	Not Measured
		Soil Phototransformation	Not Measured	Not Measured
		Aqueous Phototransformation in Water with pH 4	4.4% (10)	3.2% (20)
		Aerobic soil	4.0% (91)	3.5% (120)
		Anaerobic soil	Not Measured	Not Measured
		Aerobic aquatic with sediment	< LOD	< LOD (148)
		Aerobic aquatic with sediment	Not Measured	Not Measured
		Anaerobic aquatic with sediment	< LOD	< LOD (104)
		Field studies	Not Measured	Not Measured
		K_{oc}	No data. (estimation not performed)	
SYN551030		Hydrolysis	Not Measured	Not Measured
		Soil Phototransformation	Not Measured	Not Measured
		Aqueous Phototransformation in Water with pH 4	Not Measured	Not Measured
		Aerobic soil	5.0% (91)	4.0% (120)
		Anaerobic soil	Not Measured	Not Measured
		Aerobic aquatic with sediment	< LOD	< LOD (148)
		Aerobic aquatic with sediment	Not Measured	Not Measured
		Anaerobic aquatic with sediment	< LOD	< LOD (104)
		Field studies	Not Measured	Not Measured
		K_{oc}	No data. (estimation not performed)	

Code and chemical name	Chemical structure	Study	Max %AR (day)	%AR at study end (study length, days)
SYN549554		Hydrolysis	Not Measured	Not Measured
		Soil Phototransformation	Not Measured	Not Measured
		Aqueous Phototransformation in water with pH 4 buffer	Not Measured	Not Measured
		Aerobic soil	Not Measured	Not Measured
		Anaerobic soil	< 5% (150)	< 5% (150)
		Aerobic aquatic with sediment	Not Measured	Not Measured
		Aerobic aquatic with sediment	Not Measured	Not Measured
		Anaerobic aquatic with sediment	9.2% (12)	< LOD (104)
		Field studies	Not Measured	Not Measured
		K_{oc}	No data. (estimation not performed)	
SYN551324		Hydrolysis	Not Measured	Not Measured
		Soil Phototransformation	Not Measured	Not Measured
		Aqueous Phototransformation in water with pH 4 buffer	Not Measured	Not Measured
		Aerobic soil	Not Measured	Not Measured
		Anaerobic soil	≥ 9.4% (150)	≥ 9.4% (150)
		Aerobic aquatic with sediment	Not Measured	Not Measured
		Aerobic aquatic with sediment	Not Measured	Not Measured
		Anaerobic aquatic with sediment	Not Measured	Not Measured
		Field studies	Not Measured	Not Measured
		K_{oc}	20190 (estimated)	
SYN549434		Hydrolysis	Not Measured	Not Measured
		Soil Phototransformation	Not Measured	Not Measured
		Aqueous Phototransformation in water with pH 4 buffer	Not Measured	Not Measured
		Aerobic soil	Not Measured	Not Measured
		Anaerobic soil	< 5.0% (150)	< 5.0% (150)

Code and chemical name	Chemical structure	Study	Max %AR (day)	%AR at study end (study length, days)
		Aerobic aquatic with sediment	< LOD (148)	< LOD% (148)
		Aerobic aquatic with sediment	< 5.0% (99)	< 5.0% (99)
		Anaerobic aquatic with sediment	< 5.0%	< 5.0% (105)
		Field studies	Not Measured	Not Measured
		K_{oc}	No data. (estimation not performed)	

Table 15 Leaching assessment of isocycloseram

Leaching criteria of Cohen ` (1984)[1]		
Criteria	**Value**	**Meets leaching criterion?**
Solubility in water: >30 mg/L	1.2 mg/L	**No**
K_d (mL/g): <5 and usually <1 or 2	K_d range: 50.0–284.3	**No**
K_{oc}: <300	K_{oc} range: 6279–14444 L/kg	**No**
Henry's law constant (atm m^3/mol): $<10^{-2}$	2.80×10^{-8} atm·m^3/mol	**Yes**
pK_a: Negatively charged (either fully or partially) at ambient pH	Value not determined. Low potential for dissociation at ambient pH	**No**
Hydrolysis half-life: >20 weeks (>140 days)	262	**Yes**
Soil phototransformation half-life: >1 week (>7 days)	85.1–111.6	**Yes**
Half-life in soil: >2 to 3 weeks (>14 to 21 days)	196.2	**Yes**
Groundwater ubiquity score (GUS)[2] assessment		
Leachability classification based on calculated GUS indices: >2.8: leacher; >1.8 and <2.8: borderline leacher; <1.8: non-leacher.		
The GUS indices ranged from 0.08 to 0.21. Isocycloseram is expected to be a non-leacher.		
Results from field studies		
Downward movement of isocycloseram was observed under field dissipation studies across multiple sites.		

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

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

Table 16 Estimated environmental concentration (EEC) for isocycloseram in the environment (excluding birds and mammals) from seed treatment applications

Environmental compartment	EEC	Method of calculation	Notes
Terrestrial: screening level risk assessment			
Soil	0.007 mg a.i./kg soil	The maximum annual application rate was calculated based on the maximum single application rate of 7.5 g a.i./100 kg seed for triticale and a maximum seeding rate for triticale of 209.88 kg/ha. This results in a maximum annual application rate of 15.74 g a.i./ha. The EEC in soil was calculated based on the maximum single seed treatment rate, assuming a soil bulk density of 1.5 g/cm^3 and a soil depth of 15 cm. EECs for the major TPs in soil were calculated based on the maximum application rate, assuming that 100% of the parent compound transformed into each TP on a molar basis and that no dissipation occurred between applications. The molar conversion factor was calculated as the molecular weight of the TP divided by the molecular weight of the parent compound.	EECs in mg/kg dw soil were used to evaluate risks to earthworms and soil-dwelling beneficial arthropods.
Foliar surfaces	Negligible	Foliar surface EECs are expected to be negligible from seed treatment.	EECs used to evaluate risks to non-target terrestrial plants (seedling emergence) and non-target foliar dwelling terrestrial invertebrates.

Environmental compartment	EEC		Method of calculation	Notes
				It is noted that multiple use scenarios were considered for beneficials at screening level because of the range of EECs based on drift and deposition/distribution factors.
Water: screening level risk assessment (freshwater and marine)				
Water depth:	**15 cm**	**80 cm**	The maximum annual application rate was calculated based on the maximum single application rate of 7.5 g a.i./100 kg seed for triticale and a maximum seeding rate for triticale of 209.88 kg/ha. This results in a maximum annual application rate of 15.74 g a.i./ha. EECs in surface water were calculated considering a direct overspray of the maximum annual application rate to a 1 ha wetland with depths of 15 and 80 cm. EECs for the major TPs in water were calculated based on the maximum application rate, assuming that 100% of the parent compound transformed into each TP on a molar basis and that no dissipation occurred between applications. The molar conversion factor was calculated as the molecular weight of the TP divided by the molecular weight of the parent compound.	EECs in surface water at 15-cm depth were used to determine risk to amphibians, and the 80-cm depth EECs were used to evaluate risks to all other aquatic organisms.
	10.5 µg a.i./L	1.97 µg a.i./L		

Environmental compartment	EEC			Method of calculation	Notes
Water: refined risk assessment - runoff - seed treatment					
Water depth:	**15 cm**	**80 cm**	**Pore water**	The PWC model calculates the amount of pesticide entering the water body and the subsequent degradation of the pesticide in the water and sediment. In ecological modelling, pesticide enters the water by runoff only, and deposition of pesticide on the water body due to spray drift is not included. The model is run for 50 years. For each year of the simulation, PWC calculates peak (or daily maximum) and time-averaged concentrations. The time-averaged concentrations are calculated by averaging the peak concentrations over different time periods. The highest value of these averages for each calendar year is then calculated. The 90th percentiles of these yearly maxima are reported as the EECs for that period. In addition, the peak and 21-day average EECs in sediment pore water are generated by the model.	EECs relevant for comparison with endpoints in 15 cm was compared to amphibian relevant endpoints. EECs relevant for comparison with endpoints in 80 cm was compared to all other aquatic organism endpoints. EECs relevant for comparison with endpoints in pore water was compared to endpoints for sediment dwelling organisms.
24 hours	0.152 µg a.i./L	0.064 µg a.i./L	N/A		
96 hours	0.051 µg a.i./L	0.04 µg a.i./L	N/A		
21 days	N/A	0.022 µg a.i./L	0.008 µg a.i./L		
60 days	0.013 µg a.i./L	0.013 µg a.i./L	N/A		

Table 17 Toxicity to non-target species

Organism	Test substance	Exposure (observation)	Endpoint value	Effects/Degree of toxicity[1]	PMRA No.
Invertebrates					
Earthworm (*Eisenia fetida*)	Isocycloseram Technical Purity: 96.9% w/w	14 days	14-d LC_{50}: >969 mg a.i./kg dw soil 0% mortality was observed up to the highest concentration tested.	N/A	3246216

Organism	Test substance	Exposure (observation)	Endpoint value	Effects/Degree of toxicity[1]	PMRA No.
	Isocycloseram Technical Purity: 98.4% w/w	56 days, reproduction	28-d LC_{50}: > 10 mg a.i./kg dw soil 56-d $NOEC_{repro}$: 10 mg a.i./kg dw soil	N/A	3246217
Honey bee (*Apis mellifera*)	Isocycloseram Technical Purity: 96.9% w/w – 98.8% w/w	96-hour contact adult	96-h LD_{50}: 0.26 µg a.i./bee	Highly toxic	3246199
		72-hour oral adult	48-h LD_{50}: 0.29 µg a.i./bee 72-h LD_{50}: 0.29 µg a.i./bee	Highly toxic	
		10-day diet adult	10-d $NOAEDD_{mortality}$: 0.0028 µg a.i./bee/day (0.11 mg a.i./kg diet)	N/A	3246197
		72-hour larvae	72-h LD_{50}: 0.08 µg a.i./larva (3.88 mg a.i./kg diet)	Highly toxic	3246207
		22-day larvae	22-d $NOAEDD_{emergence}$: 0.004 µg a.i./larva/day (0.1 mg a.i./kg diet)	N/A	3246206
	SYN549106 (Transformation product of isocycloseram) Synonym identifier in fate studies: SYN549431	96-hour contact adult	96-h LD_{50}: 0.072 µg a.i./bee	Highly toxic	3246200
		96-hour oral adult	96-h LD_{50}: 0.18 µg a.i./bee	Highly toxic	

Organism	Test substance	Exposure (observation)	Endpoint value	Effects/Degree of toxicity[1]	PMRA No.
Bumblebee *(Bombus terrestris L.*	Isocycloseram Technical Purity: 96.9% w/w	48-hour oral adult	LD_{50}: 0.26 µg ai/bee	Highly Toxic	3246198
		48-hour contact adult	LD_{50}: >11.9 µg ai/bee	Practically nontoxic	
Parasitoid wasp (*Aphidius rhopalosiphi*)	SYN547407 DC 100 (Formulated product) Purity: 9.29% w/w	13-day glass plate 48-hours exposure (11 days observation)	48-h LR_{50}: 0.42 g a.i./ha 13-d $ER_{50\ reproduction}$: > 0.3 and < 0.6 g a.i./ha A 13-day $ER_{50\ reproduction}$ could not be determined due to high adult mortality in the test vessels above 0.3 g a.i./ha.	N/A	3246209
	A21708E (Formulated product) Purity: 9.06% w/w	13-day extended lab applied to plant foliage	48-h LR_{50}: 2.46 g a.i./ha 13-d $ER_{50\ reproduction}$: > 2.44 A 13-day $ER_{50\ reproduction}$ could not be determined due to high adult mortality in the test vessels above 2.44 g a.i./ha.	N/A	3633674
Predatory mite (*Typhlodromus pyri*)	SYN547407 DC 100 (Formulated product) Purity: 9.29% w/w	14-day glass plate	7-d LR_{50}: 0.0059 g a.i./ha 14-d $ER_{50\ reproduction}$: 0.0041 g a.i./ha	N/A	3246210
	A21708E (Formulated product) Purity: 9.06% w/w	14-day extended lab (dried residues on foliage)	7-d LR_{50}: 0.0072 g a.i./ha 14-d $ER_{50\ reproduction}$: 0.006 g a.i./ha	N/A	3633672
Predatory mite (*Hypoaspis aculeifer*)	Isocycloseram Technical Purity: 98.4% w/w	14-day artificial soil substrate	14-d LC_{50}: 0.821 mg a.i./kg dw soil 14-d $EC_{50reproduction}$: 0.343 mg a.i./kg dw soil 14-d $NOEC_{reproduction}$: 0.171 mg a.i./kg dw soil	N/A	3246211

Organism	Test substance	Exposure (observation)	Endpoint value	Effects/Degree of toxicity[1]	PMRA No.
	SYN547950 (transformation product of isocycloseram, identified as SYN549107 in fate studies)	14-day artificial soil substrate	14-d LC_{50}: 25 mg a.i./kg dw soil 14-d $EC_{50reproduction}$: 20.8 mg a.i./kg dw soil	N/A	3246212
	SYN549433 (transformation product of isocycloseram)	14-day artificial soil substrate	14-d LC_{50}: > 61.2 mg a.i./kg dw soil 14-d $EC_{50reproduction}$: > 61.2 mg a.i./kg dw soil (0% mortality observed at the highest test concentration of 61.2 mg a.i./kg dw soil) (7.1% reduction in reproduction (mean number of juveniles) at the highest test concentration of 61.2 mg a.i./kg dw soil)	N/A	3246213
	SYN550918 (transformation product of isocycloseram)	14-day artificial soil substrate	14-d LC_{50}: > 61.2 mg a.i./kg dw soil 14-d $EC_{50reproduction}$: > 61.2 mg a.i./kg dw soil (10% mortality observed at the highest test concentration of 61.2 mg a.i./kg dw soil) (39.8% reduction in reproduction (mean number of juveniles) at the highest test concentration of 61.2 mg a.i./kg dw soil)	N/A	3246214
Collembolan (*Folsomia candida*)	Isocycloseram Technical Purity: 98.4% w/w	28-day artificial soil substrate	28-d $EC_{50reproduction}$: 0.217 mg a.i./kg dw soil 28-d $NOEC_{reproduction}$: 0.095 mg a.i./kg dw soil	N/A	3246215

Organism	Test substance	Exposure (observation)	Endpoint value	Effects/Degree of toxicity[1]	PMRA No.
Birds					
Northern bobwhite quail (*Colinus virginianus*)	Isocycloseram Technical Purity: 96.9%	Single dose oral	LD_{50}: > 2000 mg a.i./kg bw No mortality was observed up to the highest dose tested.	Practically nontoxic	3246128
		5-day dietary	5-d LD_{50}: > 953 mg a.i./kg bw/day No mortality was observed at the highest dose tested.	Slightly toxic	3246131
		27-week reproduction	27-week $NOAED_{reproduction}$: 25.3 mg a.i./kg bw/day 27-week $LOAED_{reproduction}$: 83.4 mg a.i./kg bw/day Reproductive endpoints affected at the LOAED: ↑ 27.9 % in cracked eggs ↓ 30.4 % in eggs set ↓ 28.9 % viable embryos ↓ 29.5 % live embryos ↓ 28.9 % number of hatchlings ↓ 30.6 % 14-day hatchling survival ↓ 26.7% eggs laid per hen	N/A	3246133
Mallard duck (*Anas platyrhynchos*)	Isocycloseram Technical Purity: 96.9%	Single dose oral	LD_{50}: > 2000 mg a.i./kg bw No mortality was observed up to the highest dose tested.	Practically nontoxic	3246130
		5-day dietary	5-day LD_{50}: 466.4 mg a.i./kg bw/day	Moderately toxic	3246132

Organism	Test substance	Exposure (observation)	Endpoint value	Effects/Degree of toxicity[1]	PMRA No.
		27-week reproduction	27-week $NOAED_{reproduction}$: 14.6 mg a.i./kg bw/day 27-week $LOAED_{reproduction}$: 52.5 mg a.i./kg bw/day Reproductive endpoints affected at the LOAED: ↓ 5% in hatchling survival per number of hatchlings ↓ 3% in eggshell thickness ↓ 10% in 14-day offspring survivor weight	N/A	3246134
Canary (*Serinus canaria*)	Isocycloseram Technical Purity: 96.9%)	Single dose oral	LD_{50} > 1500 mg a.i./kg bw No mortality was observed up to the highest dose tested.	Slightly toxic	3246129
Mammals					
Wistar rat (*Rattus norvegicus*)	Isocycloseram Technical Purity: 96.9%)	Single dose oral (gavage)	LD_{50}: > 5000 mg a.i./kg bw No mortality was observed up to the highest dose tested.	Practically nontoxic	3245989
		2-generation reproduction (diet)	NOAEL = 3.5 mg a.i./kg bw/day[2] LOAEL = 10.4 mg a.i./kg bw/day[2] (Highest daily dose tested) Observed effects: F1 offspring: ↓ 9% of mean live birth index F1 offspring: ↓ 11% mean cumulative survival	N/A	3246019

Organism	Test substance	Exposure (observation)	Endpoint value	Effects/Degree of toxicity[1]	PMRA No.
Vascular plants					
Four monocot species: onion, oat, ryegrass and maize. Six dicot species: lettuce, oilseed rape, soybean, sugar beet, cucumber and tomato	SYN547407 SC (Formulated product)	Seedling emergence Single pre-emergence application	ER_{25}: 818 g a.i./ha (most sensitive of all species tested) A maximum reduction of 25% mean foliar dry weight for sugar beet across all test species at the highest concentration tested.	N/A	3246143
Four monocot species: onion, oat, ryegrass and maize. Six dicot species: lettuce, oilseed rape, soybean, sugar beet, cucumber and tomato	SYN547407 SC (Formulated product)	Vegetative vigour Single post-emergence application at BBCH growth stages: 12–14.	ER_{25}: > 818 g a.i./ha (for all species tested) A maximum of 13% reduction in mean foliar dry weight was observed across all test species at the highest concentration tested.	N/A	3246144

[1] USEPA classification (1985), where applicable.
[2] Corrected for isomer toxicity
N/A = not available

Test species	Test substance	Exposure	Endpoint value	Degree of toxicity[1]/comments	PMRA No.
Freshwater invertebrates					
Water flea (*Daphnia magna*)	Isocycloseram Technical (Purity: 96.9%)	48-hour acute (static renewal)	48-h EC_{50}: 460.0 µg a.i./L	Highly toxic	3246160
		21-day chronic	21-d $NOEC_{growth}$: 0.030 µg	N/A	3246187

Test species	Test substance	Exposure	Endpoint value	Degree of toxicity[1]/comments	PMRA No.
		(static renewal)	a.i./L		
		21-day chronic (static renewal)	21-d NOEC: Not determined (< 0.063 µg a.i./L)	N/A	3246188
	SYN547950 (Transformation product of Isocycloseram, identified as SYN549107 in fate studies)	48-hour acute (static renewal)	48-h LC_{50}: > 955.0 µg a.i./L	Not determined	3246161
	SYN549433 (Transformation product of Isocycloseram)	48-hour acute (static renewal)	48-h LC_{50}: > 80 µg a.i./L	Not determined	3246162
	SYN550455 (Transformation product of Isocycloseram)	48-hour acute (static renewal)	48-h LC_{50}: > 982 µg a.i./L	Not determined	3246163
	SYN550918 (Transformation product of Isocycloseram, identified as SYN550738 in fate studies)	48-hour acute (static renewal)	48-h LC_{50}: 166 µg a.i./L	Highly toxic	3246164
	SYN551513 (Transformation product of Isocycloseram, identified as SYN550603 in fate studies)	48-hour acute (static)	48-h LC_{50}: > 975 µg a.i./L	Not determined	3246165

Test species	Test substance	Exposure	Endpoint value	Degree of toxicity[1]/comments	PMRA No.
	SYN551754 (Transformation product of Isocycloseram)	48-hour acute (static)	48-h LC_{50}: > 928 µg a.i./L	Not determined	3246166
Freshwater midge (*Chironomous riparius*)	Isocycloseram Technical (Technical grade active ingredient Purity: 96.9%)	48-hour acute without sediment (static)	48-h LC_{50}: 0.014 µg a.i./L	Very highly toxic	3246170
		28-day chronic spiked sediment (static)	28-day NOEC: Not determined	N/A	3246192
	SYN547950 (transformation product of Isocycloseram, identified as SYN549107 in fate studies)	48-hour acute without sediment (static)	48-h LC_{50}: 51 µg a.i./L	Very highly toxic	3246171
	SYN549431 (transformation product of Isocycloseram)	48-hour acute without sediment (static)	48-h LC_{50}: 0.29 µg a.i./L	Very highly toxic	3246172
	SYN549433 (transformation product of Isocycloseram)	48-hour acute without sediment (static)	48-h LC_{50}: 161 µg a.i./L	Highly toxic	3246173
	SYN549546 (transformation product of Isocycloseram)	48-hour acute without sediment (static)	48-h LC_{50}: 829 µg a.i./L	Highly toxic	3246174
	SYN550455 (transformation product of	48-hour acute without sediment (static)	48-h LC_{50}: 2053 µg a.i./L	Moderately toxic	3246175

Test species	Test substance	Exposure	Endpoint value	Degree of toxicity[1]/comments	PMRA No.
	Isocycloseram)				
	SYN550918 (Transformation product of Isocycloseram, identified as SYN550738 in fate studies)	48-hour acute without sediment (static)	48-h LC_{50}: 0.81 µg a.i./L	Very highly toxic	3246176
	SYN551113 (Transformation product of Isocycloseram)	48-hour acute without sediment (static)	48-h LC_{50}: > 977 µg a.i./L	Not determined	3246177
	SYN551513 (Transformation product of Isocycloseram, identified as SYN550603 in fate studies)	48-hour acute without sediment (static)	48-h LC_{50}: 816 µg a.i./L	Highly toxic	3246178
	SYN551753 (Transformation product of Isocycloseram, identified as SYN550737 in fate studies)	48-hour acute without sediment (static)	48-h LC_{50}: 9.0 µg a.i./L	Very highly toxic	3246179
	SYN551754 (transformation product of Isocycloseram)	48-hour acute without sediment (static)	48-h LC_{50}: 644.0 µg a.i./L	Highly toxic	3246180

Test species	Test substance	Exposure	Endpoint value	Degree of toxicity[1]/comments	PMRA No.
Freshwater midge (*Chironomus dilutus*)	Isocycloseram Technical (Purity: 96.9%)	60-day chronic spiked sediment (Intermittent-renewal)	60-d $NOEC_{emergence}$: 0.0013 µg a.i./L (60-d time-weighted measured pore water) 60-d LOEC: 0.0045 µg a.i./L (60-d time-weighted measured pore water) ↓ 39% dry weight ↓ 16% development rate ↓ 21% emergence	N/A	3246193
Rotifer (*Brachionus calyciflorus*)	Isocycloseram Technical (Purity: 96.9%)	24-hour acute (static)	24-h LC_{50}: > 785 µg a.i./L	Highly toxic	3246181
Water louse (*Caecidotea communis*)	Isocycloseram Technical (Purity: 96.9%)	96-hour acute (static-renewal)	96-h LC_{50}: 0.145 µg a.i./L	Very highly toxic	3246182
Grass shrimp (*Palaemonetes paludosus*)	Isocycloseram Technical (Purity: 96.9%)	96-hour acute (static-renewal)	96-h LC_{50}: 0.24 µg a.i./L	Very highly toxic	3246183
Beavertail fairy shrimp (*Thamnocephalus platyurus*)	Isocycloseram Technical (Purity: 96.9%)	96-hour acute (static renewal)	96-h LC_{50}: 0.24 µg a.i./L	Very Highly Toxic	3246185
Northern crayfish (*Faxonius virilis*)	Isocycloseram Technical (Purity: 96.9%)	96-hour acute (static-renewal)	96-h LC_{50}: 1.6 µg a.i./L	Very highly toxic	3246184

Test species	Test substance	Exposure	Endpoint value	Degree of toxicity[1]/comments	PMRA No.
Caddisfly (*Pycnopsyche gentilis*)	Isocycloseram Technical (Purity: 96.9%)	48-hour acute (static)	48-h LC_{50}: 0.47 µg a.i./L	Very highly toxic	3246168
Mayfly (*Hexagenia limbata*)	Isocycloseram Technical (Purity: 96.9%)	48-hour Acute (static)	48-h LC_{50}: 0.32 µg a.i./L	Very highly toxic	3246169
Amphipod (*Hyalella azteca*)	Isocycloseram Technical (Purity: 96.9%)	96-hour Acute (static-renewal)	96-h LC_{50}: 0.04 µg a.i./L	Very highly toxic	3246186
	Isocycloseram Technical (Purity: 96.9%)	42-day chronic 28-d exposure period, 14-d post exposure observation period Spiked sediment (Intermittent-renewal)	28-d $NOEC_{growth}$: 0.0048 µg a.i./L (28-d mean measured pore water)	N/A	3246195
Freshwater fish					
Rainbow trout (*Oncorhynchus mykiss*)	Isocycloseram Technical (Purity: 96.9%)	96-hour acute (flow-through)	96-h LC_{50}: 120 µg a.i./L	Highly toxic	3246155
Carp (*Cyprinus carpio*)	Isocycloseram Technical (Purity: 96.9%)	96-hour acute (flow-through)	96-h LC_{50}: 359 µg a.i./L	Highly toxic	3246156
Fathead minnow (*Pimephales promelas*)	Isocycloseram Technical (Purity: 96.9%)	96-hour acute (flow-through)	96-h LC_{50}: 320 µg a.i./L	Moderately toxic	3246157
		33-day early life-stage (flow-through)	33-d $NOEC_{growth}$: 107 µg a.i./L	N/A	3246158

Test species	Test substance	Exposure	Endpoint value	Degree of toxicity[1]/comments	PMRA No.
Amphibians					
Rainbow trout (*Oncorhynchus mykiss*) Used as surrogate	Isocycloseram Technical (Purity: 96.9%)	96-hour acute (flow-through)	96-h LC_{50}: 120 µg a.i./L	N/A	3246155
Freshwater vascular plants					
Duckweed (*Lemna gibba*)	Isocycloseram Technical (Purity: 96.9%)	7-day (static-renewal)	7-d EC_{50}: > 1100 µg a.i./L A mean reduction of 31% for yield was observed at the highest concentration tested	N/A	3246196
Freshwater algae					
Green algae (*Pseudokirchneriella subcapitata*)	Isocycloseram Technical (Purity: 96.9%)	96-hour acute (static)	96-h EC_{50}: > 1400 µg a.i./L (initial measured) 5% reduction in yield was observed at the highest concentration tested	N/A	3246189
Cyanobacteria (*Anabaena flos-aquae*)	Isocycloseram Technical (Purity: 96.9%)	96-hour acute (static)	96-h EC_{50}: > 1400 µg a.i./L (initial measured) No adverse effects were observed up to the highest concentration tested	N/A	3246190
Diatom (*Navicula pelliculosa*)	Isocycloseram Technical (Purity: 96.9%)	96-hour acute (static)	96-h $EC_{50\ Yield}$: 640 µg a.i./L (initial measured)	N/A	3246191
Marine invertebrates					
Mysid shrimp (*Americamysis bahia*)	Isocycloseram Technical (Purity: 96.9%)	96-hour acute (static renewal)	96-h LC_{50}: 0.018 µg a.i./L	Very Highly Toxic	3246137
		28-day chronic (intermittent renewal)	28-d $NOEC_{repro}$: 0.0042 µg a.i./L $LOAEC_{repro}$: 0.0071 µg a.i./L	N/A	3246138

Test species	Test substance	Exposure	Endpoint value	Degree of toxicity[1]/comments	PMRA No.
Eastern oyster (*Crassostrea virginica*)	Isocycloseram (Technical grade active ingredient Purity: 96.9%)	96-hour acute (flow-through)	96-h EC_{50}: 73 µg a.i./L	Very Highly Toxic	3246139
Estuarine amphipod (*Leptocheirus plumulosus*)	Isocycloseram (Technical grade active ingredient Purity: 96.9%)	28-day intermittent-renewal (spiked sediment)	28-d $NOEC_{emergence}$: 0.0037µg a.i./L (28-d mean measured pore water)	N/A	3246194
Marine fish					
Sheepshead minnow (*Cyprinodon variegatus*)	Isocycloseram (Technical grade active ingredient Purity: 96.9%)	96-hour acute (flow-through)	96-h LC_{50}: 280 µg a.i./L	Highly toxic	3246140
		34 day early life-stage (flow-through)	34-d $NOEC_{weight}$: 7.8 µg a.i./L	N/A	3246142
Marine algae					
Saltwater diatom *(Skeletonema costatum*)	Isocycloseram (Technical grade active ingredient Purity: 96.9%)	96-hour acute (static)	96-h EC_{50}: 395 µg a.i./L	N/A	3246141

[1] USEPA classification, where applicable
N/A = not available

Table 18 Screening level risk assessment for non-target terrestrial organisms (excluding birds and mammals) from isocycloseram used as a seed treatment on triticale

Organism	Test substance	Exposure type	EEC (mg a.i./kg soil dw)	Endpoint value (mg a.i./kg soil dw)	UF	Effects metric	RQ	LOC of 1 exceeded?
Invertebrates								
Soil dwelling organisms								
Earthworm		14-d acute	0.007	> 969	2	> 484	< 0.00001	No

Organism	Test substance	Exposure type	EEC (mg a.i./kg soil dw)	Endpoint value (mg a.i./kg soil dw)	UF	Effects metric	RQ	LOC of 1 exceeded?
(*Eisenia fetida*)	Isocycloseram (Purity 96.9%)	56-d chronic $NOEC_{reproduction}$		10	1	10	0.001	No
Collembolan (*Folsomia candida*)	Isocycloseram (Purity 98.4%)	28-day $EC_{50reproduction}$	0.007	0.217	1	0.217	0.03	No
		28-day $NOEC_{reproduction}$	0.007	0.095	1	0.095	0.07	No
Predatory mite (*Hypoaspis aculeifer*)	Isocycloseram Technical Purity: 98.4% w/w	14-day artificial soil LC_{50}	0.007	0.821	1	0.821	0.02	No
		14-day artificial soil $EC_{50\ reproduction}$		0.343	1	0.343	0.02	No
		14-day artificial soil $NOEC_{reproduction}$		0.171	1	0.171	0.04	No
Predatory mite (*Hypoaspis aculeifer*)	SYN547950	14-day artificial soil LC_{50}	0.0056	25	1	25	0.0004	No
	SYN549433		0.0071	> 61.2	1	61.2	< 0.0002	No
	SYN550918		0.0057	> 61.2	1	61.2	< 0.0002	No

Table 19 Screening level risk assessment for birds and mammals from consumption of small grain cereals (wheat, barley, oats, rye, triticale) treated with isocycloseram at a rate of 7.5 g a.i./100 kg seed

Organism	Test substance	Exposure	Endpoint value (mg ai/kg bw/day)	UF	Effects metric	EDE (mg ai/kg bw/day)	RQ	LOC of 1 exceeded ?
Small-sized bird (0.02 kg)								
Acute dietary	Isocycloseram Technical Purity: 96.9%	5-day dietary	466	10	46.6	19	0.4	No
Reproduction		27-week diet	14.6	1	14.6	19	**1.3**	**Yes**

Organism	Test substance	Exposure	Endpoint value (mg ai/kg bw/day)	UF	Effects metric	EDE (mg ai/kg bw/day)	RQ	LOC of 1 exceeded ?
Medium-sized bird (0.10 kg)								
Acute dietary	Isocyclosera m Technical Purity: 96.9%	5-day dietary	466	10	46.6	15	0.3	No
Reproduction		27-week diet	14.6	1	14.6	15	**1.02**	**Yes**
Large-sized bird (1.00 kg)								
Acute dietary	Isocyclosera m Technical Purity: 96.9%	5-day dietary	466	10	46.6	4	0.09	No
Reproduction		27-week diet	14.6	1	14.6	4	0.3	No
Small-sized mammals (0.015 kg)								
Acute	Isocyclosera m Technical Purity: 96.9%	Single dose oral	5000	10	500.0	11	0.02	No
Reproduction		2-generation diet	3.5	1	3.5	11	**3.1**	**Yes**
Medium-sized mammals (0.035 kg)								
Acute	Isocyclosera m Technical Purity: 96.9%	Single dose oral	5000	10	500.0	9	0.02	No
Reproduction		2-generation diet	3.5	1	3.5	9	**2.7**	**Yes**
Large-sized mammals (1.00 kg)								
Acute	Isocyclosera m Technical Purity: 96.9%	Single dose oral	5000	10	500.0	5	0.01	No
Reproduction		2-generation diet	3.5	1	3.5	5	**1.5**	**Yes**

Table 20 Further risk characterization for birds and mammals from consumption of small grain cereals (wheat, barley, oats, rye and triticale) treated with isocycloseram at a rate of 7.5 g a.i./100 kg seed when considering the NOAELs

Organism	Effects Metric(mg ai/kg bw/day/UF)	EDE[2] (mg ai/kg bw/day)	RQ	Number of seeds needed to reach endpoint		Fraction of dry diet to reach the effects metric (%)	Area required (m^2)			
							No Drilling		Standard drilling	
				min	max		min	max	min	max
Small-sized bird (0.02 kg)										
Reproduction	14.6	19.0	1.3	78	195	76.7	0.135	0.581	1.47	17.6
Medium-sized bird (0.1 kg)										
Reproduction	14.6	15.0	1.02	389	973	97.6	0.677	2.91	7.36	88.0
Small-sized mammals (0.015 kg)										
Reproduction	3.5	10.9	3.1	14	35	32.2	0.024	0.104	0.265	3.17
Medium-sized mammals (0.035 kg)										
Reproduction	3.5	9.36	2.7	33	82	37.4	0.057	0.244	0.618	7.39
Large-sized mammals (1.00 kg)										
Reproduction	3.5	5.154	1.5	933	2333	67.9	1.62	6.97	17.6	211

Table 21 Further risk characterization for birds and mammals from consumption of small grain cereals (wheat, barley, oats, rye, triticale) treated with isocycloseram at a rate of 7.5 g a.i./100 kg seed when considering the LOAEL of 52.5 mg a.i./kg bw/day for the mallard duck and LOAEL of 10.4 for the Wistar rat

	Test substance	Exposure	Endpoint value (mg ai/kg bw/day)	UF	Effects metric	EDE (mg ai/kg bw/day)	RQ	LOC of 1 exceeded ?
Small-sized bird (0.02 kg)								
Acute dietary	Isocycloseram Technical Purity: 96.9%	5-day dietary	466	10	46.6	19	0.4	No
Reproduction		27-week diet	52.5	1	52.5	19	0.4	No
Medium-sized bird (0.10 kg)								
Acute dietary	Isocycloseram	5-day dietary	466	10	46.6	15	0.3	No

	Test substance	Exposure	Endpoint value (mg ai/kg bw/day)	UF	Effects metric	EDE (mg ai/kg bw/day)	RQ	LOC of 1 exceeded ?
Reproduction	m Technical Purity: 96.9%	27-week diet	52.5	1	52.5	15	0.3	No
Large-sized bird (1.00 kg)								
Acute dietary	Isocycloseram Technical Purity: 96.9%	5-day dietary	466	10	46.6	4	0.09	No
Reproduction		27-week diet	52.5	1	52.5	4	0.08	No
Small-sized mammals (0.015 kg)								
Acute	Isocycloseram Technical Purity: 96.9%	Single dose oral	5000	10	500	11	0.02	No
Reproduction		2-generation diet	10.4	1	10.4	11	**1.05**	**Yes**
Medium-sized mammals (0.035 kg)								
Acute	Isocycloseram Technical Purity: 96.9%	Single dose oral	5000	10	500	9	0.02	No
Reproduction		2-generation diet	10.4	1	10.4	9	0.9	No
Large-sized mammals (1.00 kg)								
Acute	Isocycloseram Technical Purity: 96.9%	Single dose oral	5000	10	500	5	0.01	No
Reproduction		2-generation diet	10.4	1	10.4	5	0.5	No

Table 22 Further risk characterization for birds from consumption of small grain cereals (wheat, barley, oats, rye, triticale) treated with isocycloseram at a rate of 7.5 g a.i./100 kg seed when considering the chronic NOAEL of 25.3 mg a.i./kg bw/day for the bobwhite quail

	Test substance	Exposure	Endpoint value (mg ai/kg bw/day)	UF	Effects metric	EDE (mg ai/kg bw/day)	RQ	LOC of 1 exceeded ?
Small-sized bird (0.02 kg)								
Reproduction	Isocycloseram Technical Purity: 96.9%	27-week diet	52.5	1	52.5	19	0.4	No

	Test substance	Exposure	Endpoint value (mg ai/kg bw/day)	UF	Effects metric	EDE (mg ai/kg bw/day)	RQ	LOC of 1 exceeded ?
Medium-sized bird (0.10 kg)								
Reproduction	Isocycloseram Technical Purity: 96.9%	27-week diet	52.5	1	52.5	15	0.3	No
Large-sized bird (1.00 kg)								
Reproduction	Isocycloseram Technical Purity: 96.9%	27-week diet	52.5	1	52.5	4	0.08	No

Table 23 Screening level risk assessment for aquatic organisms from seed treatment application of isocycloseram

Organism	Exposure	Test substance	EEC (µg a.i./L)	Endpoint value (µg a.i./L)	UF	Effects metric (µg a.i./L)	RQ	LOC of 1 exceeded ?
Freshwater species								
Invertebrates								
Freshwater midge (*Chironomus riparius*)	48-h Acute	Isocycloseram (Technical grade active ingredient Purity: 96.9%)	1.97	0.014	2	0.007	**281**	**Yes**
Freshwater midge (*Chironomus dilutes*)	60-d Chronic	Isocycloseram (Technical grade active ingredient Purity: 96.9%)	1.97	0.0013	1	0.0013	**1515**	**Yes**
Fish								
Rainbow trout (*Oncorhynchus mykiss)*	96-h Acute	Isocycloseram (Technical grade active ingredient Purity: 96.9%)	1.97	120	10	12	0.2	No

Organism	Exposure	Test substance	EEC (µg a.i./L)	Endpoint value (µg a.i./L)	UF	Effects metric (µg a.i./L)	RQ	LOC of 1 exceeded ?
Fathead minnow (*Pimephales promelas*)	96-h Acute	Isocycloseram (Technical grade active ingredient Purity: 96.9%)	1.97	320	10	32	0.06	No
	33-d Chronic	Isocycloseram (Technical grade active ingredient Purity: 96.9%)	1.97	107	1	107	0.02	No
Vascular plants and algae								
Alga (*Navicula pelliculosa*)	96-d Acute	Isocycloseram (Technical grade active ingredient Purity: 96.9%)	1.97	640	2	320	0.006	No
Vascular plant Duckweed (*Lemna gibba*)	7-d Dissolved	Isocycloseram (Technical grade active ingredient Purity: 96.9%)	1.97	> 1100	2	> 550	< 0.004	No
Amphibians								
Rainbow trout (*Oncorhynchus mykiss)*	96-h Acute	Isocycloseram (Technical grade active ingredient Purity: 96.9%)	10.5	120	10	12	0.9	No
Marine species								
Invertebrates								
Crustacean Mysid shrimp (*Americamysis bahia*)	96-h Acute	Isocycloseram Technical (Purity: 96.9%)	1.97	0.018	2	0.009	**219**	**Yes**
	28-d Chronic	Isocycloseram Technical (Purity: 96.9%)	1.97	0.0042	1	0.0042	**469**	**Yes**

Organism	Exposure	Test substance	EEC (µg a.i./L)	Endpoint value (µg a.i./L)	UF	Effects metric (µg a.i./L)	RQ	LOC of 1 exceeded ?
Mollusk Eastern oyster (*Crassostrea virginica*)	96-h Acute	Isocycloseram (Technical grade active ingredient Purity: 96.9%)	1.97	73	2	36.5	0.05	No
Marine Amphipod (*Leptocheirus plumulosus*)	28-day chronic spiked sediment	Isocycloseram (Technical grade active ingredient Purity: 96.9%)	1.97	0.0037	1	0.0037	**532**	**Yes**
Fish								
Fish Sheepshead minnow (*Cyprinodon variegatus*)	96-h Acute	Isocycloseram (Technical grade active ingredient Purity: 96.9%)	1.97	280	10	28	0.07	No
	34-d Chronic	Isocycloseram (Technical grade active ingredient Purity: 96.9%)	1.97	7.8	1	7.8	0.3	No
Algae								
Alga (*Skeletonema costatum*)	96-h Acute	Isocycloseram (Technical grade active ingredient Purity: 96.9%)	1.97	395	2	198	0.01	No

Table 24 Screening level risk assessment for aquatic organisms from exposure to transformation products of isocycloseram

Organism	Exposure	Test substance	EEC (µg a.i./L)	Endpoint value (µg a.i./L)	UF	Effects metric (µg a.i./L)	RQ	LOC of 1 exceeded ?
Freshwater species								
Invertebrates								
Water flea (*Daphnia magna*)	48-hour acute (static renewal)	SYN547950 (Transformation product of Isocycloseram, identified as SYN549107 in fate studies)	1.56	48-h LC_{50}: > 955.0 µg a.i./L	2	477.5	< 0.003	No
	48-hour acute (static renewal)	SYN549433 (Transformation product of Isocycloseram)	1.98	48-h LC_{50}: > 80 µg a.i./L	2	40	< 0.05	No
	48-hour acute (static renewal)	SYN550455 (Transformation product of Isocycloseram)	2.00	48-h LC_{50}: > 982 µg a.i./L	2	491	< 0.004	No
	48-hour acute (static renewal)	SYN550918 (Transformation product of Isocycloseram, identified as SYN550738 in fate studies)	1.62	48-h LC_{50}: 166 µg a.i./L	2	83	0.02	No
	48-hour acute (static)	SYN551513 (Transformation product of Isocycloseram, identified as SYN550603 in fate studies)	1.05	48-h LC_{50}: > 975 µg a.i./L	2	487.5	< 0.002	No
	48-hour acute (static)	SYN551754 (Transformation product of Isocycloseram)	1.99	48-h LC_{50}: > 928 µg a.i./L	2	464	< 0.004	No
Freshwater midge (*Chironomu*		SYN547950 (transformation product of Isocycloseram, identified	1.57	48-h LC_{50}: 51 µg a.i./L	2	25.5	0.06	No

Organism	Exposure	Test substance	EEC (µg a.i./L)	Endpoint value (µg a.i./L)	UF	Effects metric (µg a.i./L)	RQ	LOC of 1 exceeded ?
s riparius)	48-hour acute without sediment (static)	as SYN549107 in fate studies)						
		SYN549431 (transformation product of Isocycloseram)	1.56	48-h LC_{50}: 0.29 µg a.i./L	2	0.145	**10.8**	**Yes**
		SYN549433 (transformation product of Isocycloseram)	1.98	48-h LC_{50}: 161 µg a.i./L	2	80.5	0.02	No
		SYN549546 (transformation product of Isocycloseram)	0.94	48-h LC_{50}: 829 µg a.i./L	2	414.5	0.002	No
		SYN550455 (transformation product of Isocycloseram)	1.99	48-h LC_{50}: 2053 µg a.i./L	2	1026.5	0.002	No
		SYN550918 (Transformation product of Isocycloseram, identified as SYN550738 in fate studies)	1.62	48-h LC_{50}: 0.81 µg a.i./L	2	0.405	**4.0**	**Yes**
		SYN551113 (Transformation product of Isocycloseram)	1.59	48-h LC_{50}: > 977 µg a.i./L	2	488.5	< 0.003	No
		SYN551513 (Transformation product of Isocycloseram, identified as SYN550603 in fate studies)	1.05	48-h LC_{50}: 816 µg a.i./L	2	408	0.003	No
		SYN551753 (Transformation product of Isocycloseram, identified as SYN550737 in fate	1.98	48-h LC_{50}: 9.0 µg a.i./L	2	4.5	0.4	No

Organism	Exposure	Test substance	EEC (µg a.i./L)	Endpoint value (µg a.i./L)	UF	Effects metric (µg a.i./L)	RQ	LOC of 1 exceeded ?
		studies)						
		SYN551754 (transformation product of Isocycloseram)	1.99	48-h LC_{50}: 644.0 µg a.i./L	2	322	0.006	No

Table 25 Refined risk assessment for aquatic organisms from seed treatment on wheat, barley, oats and triticale

Organism	Exposure	Test substance	EEC (µg a.i./L)	Endpoint value (µg a.i./L)	UF	Effects metric (µg a.i./L)	RQ	LOC of 1 exceeded ?
Freshwater species								
Invertebrates								
Freshwater midge (*Chironomus riparius*)	48-h Acute	Isocycloseram Technical (Purity: 96.9%)	0.064 µg a.i./L (24-h overlying water)	0.014	2	0.007	**9**	**Yes**
Freshwater midge (*Chironomus dilutes*)	60-d Chronic	Isocycloseram Technical (Purity: 96.9%)	0.013 µg a.i./L (60-day overlying water)	0.0013	1	0.0013	**10**	**Yes**
			0.008 µg a.i./L (21-day pore water)	0.0013	1	0.0013	**6.2**	**Yes**
Marine species								
Invertebrates								
Crustacean Mysid shrimp (*Americamysis bahia*)	96-h Acute	Isocycloseram Technical (Purity: 96.9%)	0.040 µg a.i./L (96-h overlying water)	0.018	2	0.009	**4.4**	**Yes**
	28-d Chronic	Isocycloseram Technical (Purity: 96.9%)	0.022 µg a.i./L (21-day overlying water)	0.0042	1	0.0042	**5**	**Yes**
Marine Amphipod	28-d chronic spiked	Isocycloseram	0.008 µg a.i./L (21-day pore water)	0.0037	1	0.0037	**2.2**	**Yes**

Organism	Exposure	Test substance	EEC (µg a.i./L)	Endpoint value (µg a.i./L)	UF	Effects metric (µg a.i./L)	RQ	LOC of 1 exceeded ?
(*Leptocheirus plumulosus*)	sediment	Technical (Purity: 96.9%)						

Table 26 Supported uses for VANECTO COCKROACH GEL BAIT

Sites	Pest	Application rate
Commercial, industrial and residential areas	Light to moderate infestations of cockroaches	1-3 spots of VANECTO COCKROACH GEL BAIT (0.5-1.5 g product) per m^2
	Heavy infestations of cockroaches	3-4 spots of VANECTO COCKROACH GEL BAIT (1.5-2.0 g product) per m^2

Table 27 Supported Uses for EQUENTO

Crop(s)	Pest(s)	Application Rate(s)	
		Product (mL/100 kg seed)	Active ingredient (g ICS/100 kg seed)
Wheat (spring/winter/durum), barley, rye, oats, triticale	Wireworms	25–75	2.5–7.5
	European chafers, June Beetles	50–75	5.0–7.5

Table 28 Supported Uses for A23128 ST

Crop(s)	Insect pest(s)	Disease(s)	Application rate(s)	
			Product (mL/100 kg seed)	Active ingredient (g a.i./100 kg seed)*
Wheat (spring/winter/durum)	Wireworms, European chafers, June Beetles (moderate pest pressures)	Diseases controlled: Seed rot caused by *Fusarium, Pythium, Rhizoctonia, Penicillium* and *Aspergillus* spp.,	325 mL A23138 ST	5 g ICS, 12 g DFZ, 5 g SDX, 3 g MFN, 2.5 g FLD

Crop(s)	Insect pest(s)	Disease(s)	Application rate(s)	
			Product (mL/100 kg seed)	Active ingredient (g a.i./100 kg seed)*
	Wireworms, European chafers, June Beetles (high pest pressures)	Seedling blight, root rot, and damping-off caused by seed- and soil-borne *Fusarium* spp. or *Rhizoctonia* spp., Seedling blight, root rot, and damping-off caused by soil-borne *Pythium* spp., Seed-borne alternaria (*Alternaria alternata*), Covered smut (*Ustilago hordei*), False loose smut (*Ustilago nigra*), True loose smut (*Ustilago nuda*) Diseases suppressed: Common root rot (*Cochliobolus sativus*), Fusarium crown and foot rot (*Fusarium* spp.), Seed-borne *Cochliobolus sativus,* Take-all (*Gaeumannomyces graminis*)	Tank mix: 325 mL A23138 ST + 25 mL EQUENTO	7.5 g ICS, 12 g DFZ, 5 g SDX, 3 g MFN, 2.5 g FLD
Barley	Wireworms, European chafers, June Beetles (moderate pest pressures)	Diseases controlled: Seed rot caused by *Fusarium, Pythium, Rhizoctonia, Penicillium* and *Aspergillus* spp., Seedling blight, root rot, and damping-off caused by seed- and soil-borne *Fusarium* spp. or *Rhizoctonia* spp.,	325 mL A23138 ST	5 g ICS, 12 g DFZ, 5 g SDX, 3 g MFN, 2.5 g FLD
	Wireworms, European chafers, June Beetles (high pest pressures)		Tank mix: 325 mL A23138 ST + 25 mL EQUENTO	7.5 g ICS, 12 g DFZ, 5 g SDX, 3 g MFN, 2.5 g FLD

Crop(s)	Insect pest(s)	Disease(s)	Application rate(s)	
			Product (mL/100 kg seed)	Active ingredient (g a.i./100 kg seed)*
		Seedling blight, root rot, and damping-off caused by soil-borne *Pythium* spp., Seed-borne alternaria (*Alternaria alternata*), Covered smut (*Ustilago hordei*), False loose smut (*Ustilago nigra*), True loose smut (*Ustilago nuda*) Diseases suppressed: Common root rot (*Cochliobolus sativus*), Fusarium crown and foot rot (*Fusarium* spp.), Seed-borne *Cochliobolus sativus,* Take-all (*Gaeumannomyces graminis*)		
Rye	Wireworms, European chafers, June Beetles (moderate pest pressures)	Diseases controlled: Seed rot caused by *Fusarium, Pythium, Rhizoctonia, Penicillium* and *Aspergillus* spp., Seedling blight, root rot, and damping-off caused by seed- and soil-borne *Fusarium* spp. or *Rhizoctonia* spp., Seedling blight, root rot, and damping-off caused by soil-borne *Pythium* spp., Seed-borne alternaria (*Alternaria alternata*),	325 mL A23138 ST	5 g ICS, 12 g DFZ, 5 g SDX, 3 g MFN, 2.5 g FLD
	Wireworms, European chafers, June Beetles (high pest pressures)		Tank mix: 325 mL A23138 ST + 25 mL EQUENTO	7.5 g ICS, 12 g DFZ, 5 g SDX, 3 g MFN, 2.5 g FLD

Crop(s)	Insect pest(s)	Disease(s)	Application rate(s)	
			Product (mL/100 kg seed)	Active ingredient (g a.i./100 kg seed)*
		Common bunt (*Tilletia tritici*), Dwarf bunt (*Tilletia controversa*) Diseases suppressed: Common root rot (*Cochliobolus sativus*), Fusarium crown and foot rot (*Fusarium* spp.), Seed-borne *Cochliobolus sativus,* Take-all (*Gaeumannomyces graminis*)		
Oats	Wireworms, European chafers, June Beetles (moderate pest pressures)	Diseases controlled: Seed rot caused by *Fusarium, Pythium, Rhizoctonia, Penicillium* and *Aspergillus* spp,. Seedling blight, root rot, and damping-off caused by seed- and soil-borne *Fusarium* spp. or *Rhizoctonia* spp., Seedling blight, root rot, and damping-off caused by soil-borne *Pythium* spp., Seed-borne alternaria (*Alternaria alternata*), Covered smut (*Ustilago hordei*), Loose smut (*Ustilago avenae*) Diseases suppressed: Common root rot (*Cochliobolus sativus*),	325 mL A23138 ST	5 g ICS, 12 g DFZ, 5 g SDX, 3 g MFN, 2.5 g FLD
	Wireworms, European chafers, June Beetles (high pest pressures)		Tank mix: 325 mL A23138 ST + 25 mL EQUENTO	7.5 g ICS, 12 g DFZ, 5 g SDX, 3 g MFN, 2.5 g FLD

Crop(s)	Insect pest(s)	Disease(s)	Application rate(s)	
			Product (mL/100 kg seed)	Active ingredient (g a.i./100 kg seed)*
		Seed-borne *Cochliobolus sativus*		
Triticale	Wireworms, European chafers, June Beetles (moderate pest pressures)	Diseases controlled: Seed rot caused by *Fusarium, Pythium, Rhizoctonia, Penicillium* and *Aspergillus* spp., Seedling blight, root rot, and damping-off caused by seed- and soil-borne *Fusarium* spp. or *Rhizoctonia* spp., Seedling blight, root rot, and damping-off caused by soil-borne *Pythium* spp., Seed-borne alternaria (*Alternaria alternata*), Loose smut (*Ustilago tritici*) Diseases suppressed: Common root rot (*Cochliobolus sativus*), Fusarium crown and foot rot (*Fusarium* spp.), Seed-borne *Cochliobolus sativus,* Take-all (*Gaeumannomyces graminis*)	325 mL A23138 ST	5 g ICS, 12 g DFZ, 5 g SDX, 3 g MFN, 2.5 g FLD
	Wireworms, European chafers, June Beetles (high pest pressures)		Tank mix: 325 mL A23138 ST + 25 mL EQUENTO	7.5 g ICS, 12 g DFZ, 5 g SDX, 3 g MFN, 2.5 g FLD

*ICS = isocycloseram; DFZ = difenoconazole; SDX = sedaxane; MFN = metalaxyl-M (and S-isomer); FLD = fludioxonil

Table 29 Toxic Substances Management Policy considerations - comparison to TSMP Track 1 Criteria

TSMP Track 1 Criteria	TSMP Track 1 Criterion value		Active ingredient endpoints - Isocycloseram	Transformation product endpoints - SYN550738	Transformation product endpoints - SYN549107	All other 20 major transformation products
CEPA toxic or CEPA toxic equivalent[1]	Yes		Yes	Yes	Yes	Yes
Predominantly anthropogenic[2]	Yes		Yes	Yes	Yes	Yes
Persistence[3]:	Soil	Half-life ≥ 182 days	Yes, DT_{50} in aerobic soils = 56.3 – 293 days (range based on 5 values)	No, DT_{50} in aerobic soils = 12.1 – 23.1 days (range based on 5 values)	Yes, DT_{50} in aerobic soils = 18.9–402.7 days (range based on 4 values)	Not available
	Water	Half-life ≥ 182 days	No, DT_{50} in aerobic water/sediment systems = 10.0 – 37.1 days (range based on 3 values)	Not available	Not available	Not available
	Sediment	Half-life ≥ 365 days				
	Air	Half-life ≥ 2 days, or evidence of atmospheric transport to remote regions such as the Arctic	Not determined. Available models are not suited for predicting the atmospheric half-life given the large fraction expected to be sorbed to airborne particles.	Not determined. Available models are not suited for predicting the atmospheric half-life given the large fraction expected to be sorbed to airborne particles.	Not determined. Available models are not suited for predicting the atmospheric half-life given the large fraction expected to be sorbed to airborne particles.	Not determined.

TSMP Track 1 Criteria	TSMP Track 1 Criterion value	Active ingredient endpoints - Isocycloseram	Transformation product endpoints - SYN550738	Transformation product endpoints - SYN549107	All other 20 major transformation products
Bioaccumulation[4]	Log $K_{ow} \geq 5$	No, Log K_{ow} = 4.89	Yes, Log K_{ow} = 6.78	Yes, Log K_{ow} = 6.29	No, Log $K_{ow} < 5.00$ (modelled in EPISUITE)
	BCF ≥ 5000 L/kg	No, steady state BCF = 877–1082 L/kg (growth-corrected and normalized to 5% lipid content)	No, BCF = 2510 L/kg (modelled in EAS-E Suite)	No, BCF = 1140 L/kg (modelled in EAS-E Suite)	No, BCF < 5000 L/kg (modelled in EPISUITE)
	BAF ≥ 5000 L/kg	Not Available	Not Available	Not Available	Not Available
Is the chemical a TSMP Track 1 substance (all four criteria must be met)?		No, does not meet all of the TSMP Track 1 criteria	No, does not meet all of the TSMP Track 1 criteria	No, does not meet all of the TSMP Track 1 criteria	No, does not meet all of the TSMP Track 1 criteria

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

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

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

4 Bioaccumulation describes the process by which a substance accumulates in a living organism - either from the surrounding medium or through food containing the substance. A substance's potential to bioaccumulate can be expressed by the bioaccumulation factor (BAF), the bioconcentration factor (BCF), or the octanol-water partition coefficient (Log K_{OW}). The BAF and the BCF measure the concentration of a substance in a living organism relative to its concentration in the surrounding medium. The BAF accounts for substance intake from both food and the surrounding medium, while the BCF accounts for intake from the surrounding medium only. The Log K_{OW} estimates a substance's tendency to partition from water to organic media, such as lipids present in living organisms. In the absence of BAF or BCF data, the log K_{OW} may be used. Modelled Log K_{OW} values were derived from KOWWIN v.1.68 (EPI SUITE v.4.11). Modelled BCF values were derived from BCFBAF v3.01 (EPISUITE) using both the regression-based estimate and the Arnot-Gobas BCF (including biotransformation) for lower trophic (96 g; 5.98% lipid content) fish or from Exposure and Safety Estimation (EAS-E) Suite.

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

Isocycloseram is an active ingredient that is concurrently being registered in Canada for use on small grain cereals and the United States for use on several fruits, vegetables and large field crops such as small grain cereals. The MRLs proposed for isocycloseram in Canada on small grain cereals are the same as corresponding tolerances to be promulgated in the United States, in accordance with Table 1. In the case of animal commodities, differences in MRLs/tolerances may be due to different livestock feed items and practices.

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

Table 1 compares the MRLs proposed for isocycloseram in Canada with corresponding American tolerances and Codex MRLs.[7] A listing of established Codex MRLs is available on the Codex Alimentarius Pesticide Index webpage, by pesticide or commodity.

Table 1 Differences Between MRLs in Canada and in Other Jurisdictions

Food commodity	Canadian MRL (ppm)	American Tolerance (ppm)	Codex MRL (ppm)
Barley, oats, rye, triticale, wheat	0.01	0.01	Not established
Milk fat	Not established	3	Not established
Fat of cattle, goats, horses and sheep	0.04	0.05	0.4 (mammalian fats; except milk fats)
Meat by-products of cattle, goats, horses and sheep	0.015	0.02	0.3 (edible offal; mammalian)
Fat of hogs and poultry; meat of cattle, goats, hogs, horses, poultry and sheep; meat by-products of hogs and poultry; eggs; milk	0.01	0.01	0.02 (meat; from mammals other than marine mammals) 0.05 (milks)

[7] 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
3245912	2021, Isocycloseram Technical (SYN547407) - Physical and Chemical Properties, DACO: 12.7,2.13.2,2.14.1,2.14.10,2.14.11,2.14.12,2.14.13,2.14.14, 2.14.2,2.14.3,2.14.4,2.14.5,2.14.6,2.14.7,2.14.8,2.14.9,8.2.3.2,Document M,IIA 2.1.1,IIA 2.1.2,IIA 2.17.1,IIA 2.17.2,IIA 2.2,IIA 2.3.1,IIA 2.4.1,IIA 2.4.2,IIA 2.5.1,IIA 2.5.1.1,IIA 2.5.1.5,IIA 2.6,IIA 2.7,IIA 2.8.1,IIA 2.8.2,IIA 2.9.5 CBI
3245913	2021, Isocycloseram (SYN547407) Document M-II, Section 2 - Analytical Methods, DACO: 12.7,2.13.1,2.13.4,2.15,2.16,5.10,7.2.1,7.2.2,7.2.3,7.2.4,7.2.5, 8.2.2.1,8.2.2.2,8.2.2.3,8.2.2.4,8.6,Document M,IIA 4.1.1,IIA 4.1.2,IIA 4.1.3,IIA 4.1.4,IIA 4.2.1,IIA 4.2.2,IIA 4.2.3,IIA 4.2.4,IIA 4.2.5,IIA 4.2.6,IIA 4.2.7,IIA 4.3,IIA 4.4,IIA 4.5,IIA 4.6,IIA 4.7,IIA 4.8,IIA 4.9
3283888	2021, Isocycloseram Technical (SYN547407) - Manufacturing Process Description and Supporting Data, DACO: 2.1,2.11,2.11.1,2.11.2,2.11.3,2.11.4, 2.12,2.12.1,2.13,2.13.1,2.13.2,2.13.3,2.13.4,2.2,2.3,2.3.1,2.4,2.5,2.6,2.7,2.8,2.9 CBI
3319775	2022, Confidential Business Information - PMRA Deficiency Response for Isocycloseram Technical (Canada), DACO: 2.13.2 CBI
3245949	2020, SYN547407 - Analytical Method GRM072.16A for the Determination of Anaerobic Metabolites SYN548569, SYN549110, SYN549433, SYN549543. SYN549546, SYN550321, SYN550455, SYN550602, SYN550603, SYN551057, SYN551113 and SYN551248 in Soil, DACO: 8.2.2.1,8.2.2.2,IIA 4.4,IIA 4.6
3245950	2021, SYN547407 - Independent Laboratory Validation of Residue Method (GRM072.16A) for the Determination of Anaerobic Metabolites SYN548569, SYN549110, SYN549433, SYN549543, SYN549546, SYN550321, SYN550455, SYN550602, SYN550603, SYN551057, SYN551113, and SYN551248 in Soil by LC-MS/MS, DACO: 8.2.2.1,8.2.2.2,IIA 4.4,IIA 4.6
3245951	2021, SYN547407 - Independent Laboratory Validation of Residue Method (GRM072.12A) for the Determination of SYN547407 and its Metabolites SYN549107, SYN549431, and SYN550738 in Soil by LC-MS/MS, DACO: 8.2.2.1,8.2.2.2,IIA 4.4,IIA 4.6
3245952	2019, SYN547407 - Validation of Analytical Method GRM072.12A for the Determination of SYN547407 and its Metabolites SYN549107, SYN549431 and SYN550738 in Soil, DACO: 8.2.2.1,8.2.2.2,IIA 4.4,IIA 4.6

3245953 2020, SYN547407 - Analytical Method GRM072.12A for the Determination of SYN547407 and its Metabolites SYN549107, SYN549431 and SYN550738 in Soil, DACO: 8.2.2.1,8.2.2.2,IIA 4.4,IIA 4.6

3245954 2021, SYN547407 - Residue Method GRM072.17A for the Determination of SYN547407 and Metabolites SYN549107, SYN549431, SYN550455 and SYN551485 in Water Includes Validation Data, DACO: 8.2.2.3,IIA 4.5

3245955 2021, SYN547407 - Independent Laboratory Validation of Residue Method GRM072.17A for the Determination of SYN547407 and Metabolites SYN549107, SYN549431, SYN550455 and SYN551485 in Water, DACO: 8.2.2.3,IIA 4.5

3245972 2021, SYN547407 - Analytical Method GRM072.05A for the Determination of SYN547407 in Pollen and Nectar, DACO: 2.16,8.6,IIA 4.9

3245973 2018, SYN547407 - Validation of the Analytical Method for the Determination of the Test Substance in Pollen and Nectar, DACO: 2.16,8.6,IIA 4.9

3563636 2024, Isocycloseram Statement on the Analysis of 05183-TB-160-B, DACO: 2.13.4 CBI

3563637 2015, SYN547407 - Analysis of a Tox Reserve, DACO: 2.13.4 CBI

3572188 2019, Isocycloseram - Analysis of a Tox Reserve, DACO: 2.13.4 CBI

3246576 2021, A22128E - 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

3246582 2021, A22128E - 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

3246632 2021, A22241C - 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

3246638 2021, A22241C - 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 CBI

3246796 2021, A23128B - 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

3246800 2021, A23128B - 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

2.0 Human and Animal Health

PMRA Document Number	Reference
3245974	2017, SYN547407 - The Absorption and Excretion of [Methylphenyl-14C], [Halophenyl-14C] and [Oxoisoxazolidinyl-14C]-SYN547407 Following Single Oral Administration in the Rat, DACO: 4.5.9,IIA 5.1.1
3245975	2018, SYN547407 - Biotransformation of [14C]-SYN547407 in the Rat, DACO: 4.5.9,IIA 5.1.1
3245976	2017, SYN547407 - Pharmacokinetics of [Methylphenyl-14C]-SYN547407 Following Single Oral and Intravenous Administration in the Rat, DACO: 4.5.9,IIA 5.1.1
3245977	2015, SYN547407 - A Preliminary Study of Pharmacokinetics, Absorption, Metabolism and Excretion in the Rat Following Single Oral and Intravenous Administration of [14C] SYN547407, DACO: 4.5.9,IIA 5.1.1
3245978	2016, SYN547407 - Quantitative Whole-body Autoradiography in the Rat Following Single Oral Administration [Methylphenyl-14C]-SYN547407, DACO: 4.5.9,IIA 5.1.1
3245979	2017, SYN547407 - Tissue Depletion and Elimination of [Methylphenyl 14C]-SYN547407 Following Single and Multiple Oral Administration in the Rat, DACO: 4.5.9,IIA 5.1.1
3245984	2021, Isocycloseram - Waiver Request for a 28-Day Immunotoxicity Study in Rodents, DACO: 4.2.9,4.3.8,4.4.5,4.5.15,4.5.8,4.8,IIA 5.10
3245985	2018, SYN547407 - Enhanced Oral (Gavage) One-Generation Reproduction Toxicity Study in the Rat, DACO: 4.2.9,4.3.8,4.4.5,4.5.1,4.5.8,4.8,IIA 5.10
3245986	2019, SYN547407 - In Vitro Comparative Metabolism of [Methylphenyl-U-14C]SYN547407, [Halophenyl-U-14C]SYN547407 and [Oxoisoxazolidinyl-4,5-14C]SYN547407 in Human and Rat Liver Microsomes, DACO: 4.8,IIA 5.10

3245987 2021, SYN547407 - Summary of the Effects Observed in the Male Reproductive Organs, DACO: 4.8

3245989 2016, SYN547407 - Acute Oral Toxicity Study in Rat (Up and Down Procedure), DACO: 4.2.1,IIA 5.2.1

3245990 2016, SYN547407 - Acute Dermal Toxicity Study in Rats, DACO: 4.2.2,IIA 5.2.2

3245991 2017, SYN547407 - Acute Inhalation Toxicity Study (Nose-Only) in the Rat, DACO: 4.2.3,IIA 5.2.3

3245992 2015, SYN547407 - Primary Skin Irritation Study in Rabbits, DACO: 4.2.5,IIA 5.2.4

3245993 2015, SYN547407 - Acute Eye Irritation Study in Rabbits, DACO: 4.2.4,IIA 5.2.5

3245994 2014, SYN547407 - In Vitro Eye Irritation Test in Isolated Chicken Eyes, DACO: 4.2.4,IIA 5.2.5

3245995 2017, SYN547407 - Local Lymph Node Assay in the Mouse, DACO: 4.2.6,IIA 5.2.6

3245996 2019, SYN547407 - 28 Day Oral (Capsule) Toxicity Study in the Dog, DACO: 4.3.3,IIA 5.3.1

3245997 2015, SYN547407 - 28 Day Oral (Dietary) Toxicity Study in Mice, DACO: 4.3.3,IIA 5.3.1

3245998 2017, SYN547407 - 28 Day Oral (Dietary) Toxicity Study in Rats, DACO: 4.3.3,IIA 5.3.1

3245999 2019, SYN547407 - A 13 Week Oral (Dietary) Toxicity Study in the Mouse, DACO: 4.3.1,IIA 5.3.2

3246000 2019, SYN547407 - A 13 Week Oral (Dietary) Toxicity Study in the Rat, DACO: 4.3.1,IIA 5.3.2

3246001 2021, Supplemental Data to Support - SYN547407 - A 13 Week Oral (Dietary) Toxicity Study in the Mouse, DACO: 4.3.1,IIA 5.3.2

3246002 2021, Supplemental Data to Support - SYN547407 - A 13 Week Oral (Dietary) Toxicity Study in the Rat, DACO: 4.3.1,IIA 5.3.2

3246003 2019, SYN547407 - A 13 Week Oral (Capsule) Toxicity Study in the Dog, DACO: 4.3.2,IIA 5.3.3

3246004 2021, Supplemental Data to Support SYN547407 - Toxicity Study by Dermal Administration to Han Wistar Rats for 4 Weeks, DACO: 4.3.5,IIA 5.3.7

3246005 2019, SYN547407 - Toxicity Study by Dermal Administration to Han Wistar Rats for 4 Weeks, DACO: 4.3.5,IIA 5.3.7

3246006 2020, CA5697A - Salmonella Typhimurium and Escherichia Coli Reverse Mutation Assay, DACO: 4.5.4,IIA 5.4.1

3246007 2016, SYN547407 - Salmonella Typhimurium and Escherichia Coli Reverse Mutation Assay, DACO: 4.5.4,IIA 5.4.1

3246008 2019, SYN547407 tech. - Salmonella Typhimurium and Escherichia Coli Reverse Mutation Assay, DACO: 4.5.4,IIA 5.4.1

3246009 2021, CA5697A - Micronucleus Test in Human Lymphocytes In Vitro, DACO: 4.5.6,IIA 5.4.2

3246010 2016, SYN547407 - Chromosome Aberration Test in Human Lymphocytes In Vitro, DACO: 4.5.6,IIA 5.4.2

3246011 2020, SYN547407 - Cell Mutation Assay at the Thymidine Kinase Locus (TK+/-) in Mouse Lymphoma L5178Y Cells, DACO: 4.5.5,IIA 5.4.3

3246012 2019, SYN547407 tech. - Cell Mutation Assay at the Thymidine Kinase Locus (TK+/-) in Mouse Lymphoma L5178Y Cells, DACO: 4.5.5,IIA 5.4.3

3246013 2021, CA5697A - Micronucleus Assay in Bone Marrow Cells of the Mouse, DACO: 4.5.7,IIA 5.4.4

3246014 2016, SYN547407 - Oral (Gavage) Rat Micronucleus Test, DACO: 4.5.7,IIA 5.4.4

3246015 2019, SYN547407- 104 Week Rat Oral (Dietary) Carcinogenicity Study with a Combined 52 Week Toxicity Study, DACO: 4.4.4,IIA 5.5.1,IIA 5.5.2

3246016 2021, Supplemental Data to Support - SYN547407- 104 Week Rat Oral (Dietary) Carcinogenicity Study with a Combined 52 Week Toxicity Study, DACO: 4.4.4,IIA 5.5.1,IIA 5.5.2

3246017 2019, SYN547407- 80 Week Mouse Oral (Dietary) Carcinogenicity Study, DACO: 4.4.3,IIA 5.5.3

3246018 2021, Supplemental Data to Support - SYN547407- 80 Week Mouse Oral (Dietary) Carcinogenicity Study, DACO: 4.4.3,IIA 5.5.3

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3246122 2019, SYN547407 - Photolysis of 14C-SYN547407 in pH 4 Buffer Solution, DACO: 8.2.3.3.2,IIA 2.9.2,IIA 7.6

3246124 2019, SYN547407 - Aerobic Aquatic-Sediment Metabolism of 14C-SYN547407, DACO: 8.2.3.6,IIA 7.8.3

3246125 2019, SYN547407 - Anaerobic Aquatic-Sediment Metabolism of 14C-SYN547407, DACO: 8.2.3.6,IIA 7.8.3

3246126 2021, SYN547407 - Anaerobic Aquatic-Sediment Metabolism of 14C-SYN547407, DACO: 8.2.3.6,IIA 7.8.3

3246127 2021, SYN547407 - Metabolism of 14C-SYN547407 in One Aerobic Aquatic-Sediment System, DACO: 8.2.3.6,IIA 7.8.3

3246128 2016, SYN547407 - An Acute Oral Toxicity Study with the Northern Bobwhite Using a Sequential Testing Procedure, DACO: 9.6.2.1,9.6.2.2,9.6.2.3,IIA 8.1.1

3246129 2018, SYN547407 - An Acute Oral Toxicity Study with the Canary Using a Sequential Testing Procedure, DACO: 9.6.2.1,9.6.2.2,9.6.2.3,IIA 8.1.1

3246130 2016, SYN547407 - An Acute Oral Toxicity Study with the Mallard Using a Sequential Testing Procedure, DACO: 9.6.2.1,9.6.2.2,9.6.2.3,IIA 8.1.1

3246131 2017, SYN547407 - A Dietary LC50 Study with the Northern Bobwhite, DACO: 9.6.2.4,9.6.2.5,IIA 8.1.2

3246132 2017, SYN547407 - A Dietary LC50 Study with the Mallard, DACO: 9.6.2.6,IIA 8.1.3

3246133 2018, SYN547407 - A Reproduction Study with the Northern Bobwhite, DACO: 9.6.3.1,9.6.3.2,9.6.3.3,IIA 8.1.4

3246134 2018, SYN547407 - A Reproduction Study with the Mallard, DACO: 9.6.3.1,9.6.3.2,9.6.3.3,IIA 8.1.4

3246137 2019, SYN547407 - Acute Toxicity to Mysids (Americamysis bahia) Under Static-Renewal Conditions, DACO: 9.4.2,9.4.3,9.4.4,IIA 8.11.1

3246138 2019, SYN547407 - Life-Cycle Toxicity Test with Mysids (Americamysis bahia), DACO: 9.4.2,9.4.3,9.4.4,IIA 8.11.1

3246139 2018, SYN547407 - Acute Toxicity Test with Eastern Oyster (Crassostrea virginica) Under Flow Through Conditions, DACO: 9.4.2,9.4.3,9.4.4,IIA 8.11.1

3246140 2020, SYN547407 - Acute Toxicity to Sheepshead Minnow (Cyprinodon variegatus) Under Flow Through Conditions, DACO: 9.4.2,9.4.3,9.4.4,IIA 8.11.1

3246141 2018, SYN547407 - 96-Hour Toxicity Test with the Marine Diatom, Skeletonema costatum, DACO: 9.5.2.4.1,IIA 8.11.2

3246142 2018, SYN547407 - Early Life-Stage Toxicity Test with Sheepshead Minnow (Cyprinodon variegatus), DACO: 9.5.2.4.1,IIA 8.11.2

3246143 2019, SYN547407 SC (A21550L) - Evaluation of the Phytotoxicity to Non Target Terrestrial Plant Seedling Emergence and Seedling Growth Test, DACO: 9.8.4,IIA 8.12

3246144 2019, SYN547407 SC (A21550L) - Evaluation of the Phytotoxicity to Non Target Terrestrial Plant Vegetative Vigour Test, DACO: 9.8.4,IIA 8.12

3246155 2018, SYN547407 - Acute Toxicity to Rainbow Trout (Oncorhynchus mykiss) Under Flow-Through Conditions, DACO: 9.5.2.1,9.5.2.3,IIA 8.2.1.1

3246156 2021, SYN547407 - Acute Toxicity to Carp (Cyprinus carpio) Under Flow Through Conditions, DACO: 9.5.2.2,9.5.2.3,IIA 8.2.1.2

3246157 2018, SYN547407 - Acute Toxicity to Fathead Minnow (Pimephales promelas) Under Flow Through Conditions, DACO: 9.5.2.2,9.5.2.3,IIA 8.2.1.2

3246158 2018, SYN547407 - Early Life-Stage Toxicity Test with Fathead Minnow (Pimephales promelas), DACO: 9.5.3.1,IIA 8.2.4

3246159 2020, [14C]SYN547407 - Bioaccumulation in Bluegill Sunfish (Lepomis macrochirus): Aqueous Exposure, DACO: 9.4.8,9.5.6,IIA 8.2.6.1,IIA 8.2.7

3246160 2018, SYN547407 - Acute Toxicity to Water Fleas (Daphnia magna) Under Static Conditions, DACO: 9.3.2,IIA 8.3.1.1

3246161 2021, SYN547950 - Effects on Daphnia magna in a 48-Hour Immobilization Test, DACO: 9.3.2,IIA 8.3.1.1

3246162 2021, SYN549433 - Effects on Daphnia magna in a 48-Hour Immobilization Test, DACO: 9.3.2,IIA 8.3.1.1

3246163 2021, SYN550455 - Effect on Daphnia magna in a 48-Hour Immobilization Test, DACO: 9.3.2,IIA 8.3.1.1

3246164 2021, SYN550918 - Effects on Daphnia magna in a 48-Hour Immobilization Test, DACO: 9.3.2,IIA 8.3.1.1

3246165 2021, SYN551513 - Effects on Daphnia magna in a 48-Hour Immobilization Test, DACO: 9.3.2,IIA 8.3.1.1

3246166 2021, SYN551754 - Effects on Daphnia magna in a 48-Hour Immobilization Test, DACO: 9.3.2,IIA 8.3.1.1

3246168 2020, SYN547407 - Acute Toxicity to Caddisflies (Pycnopsyche gentilis) Under Static Conditions, DACO: 9.3.4,IIA 8.3.1.2

3246169 2021, SYN547407 - Acute Toxicity to Mayflies (Hexagenia limbata) Under Static Conditions, DACO: 9.3.4,IIA 8.3.1.2

3246170 2019, SYN547407 - Acute Toxicity to Midge (Chironomus riparius) Under Static Conditions, DACO: 9.3.4,IIA 8.3.1.2

3246171 2021, SYN547950 - Effect on First-Instar Larvae of Chironomus riparius in a 48-Hour Immobilization Test, DACO: 9.3.4,IIA 8.3.1.2

3246172 2021, SYN549431 - Effects on First-Instar Larvae of Chironomus riparius in a 48-Hour Immobilization Test, DACO: 9.3.4,IIA 8.3.1.2

3246173 2021, SYN549433 - Effects on First-Instar Larvae of Chironomus riparius in a 48-Hour Immobilization Test, DACO: 9.3.4,IIA 8.3.1.2

3246174 2021, SYN549546 - Effects on First-Instar Larvae of Chironomus riparius in a 48-Hour Immobilization Test, DACO: 9.3.4,IIA 8.3.1.2

3246175 2021, SYN550455 - Effects on First-Instar Larvae of Chironomus riparius in a 48-Hour Immobilization Test, DACO: 9.3.4,IIA 8.3.1.2

3246176 2021, SYN550918 - Effects on First-Instar Larvae of Chironomus riparius in a 48-Hour Immobilization Test, DACO: 9.3.4,IIA 8.3.1.2

3246177 2021, SYN551113 - Effects on First-Instar Larvae of Chironomus riparius in a 48-Hour Immobilization Test, DACO: 9.3.4,IIA 8.3.1.2

3246178 2021, SYN551513 - Effects on First-Instar Larvae of Chironomus riparius in a 48-Hour Immobilization Test, DACO: 9.3.4,IIA 8.3.1.2

3246179 2021, SYN551753 - Effects on the First-Instar Larvae of Chironomus riparius in a 48-Hour Immobilization Test, DACO: 9.3.4,IIA 8.3.1.2

3246180 2021, SYN551754 - Effects on First-Instar Larvae of Chironomus riparius in a 48-Hour Immobilization Test, DACO: 9.3.4,IIA 8.3.1.2

3246181 2021, SYN547407 - Acute Toxicity to Freshwater Rotifers (Brachionus calyciflorus) Under Static Conditions, DACO: 9.3.4,IIA 8.3.1.3

3246182 2021, SYN547407 - Acute Toxicity to the Water Louse (Caecidotea communis) Under Static-Renewal Conditions, DACO: 9.3.4,IIA 8.3.1.3

3246183 2021, SYN547407 - Acute Toxicity to the Grass Shrimp (Palaemonetes paludosus) Under Static-Renewal Conditions, DACO: 9.3.4,IIA 8.3.1.3

3246184 2021, SYN547407 - Acute Toxicity to the Northern Crayfish (Faxonius virilis) Under Static-Renewal Conditions, DACO: 9.3.4,IIA 8.3.1.3

3246185 2021, SYN547407 - Acute Toxicity to the Beavertail Fairy Shrimp (Thamnocephalus platyurus) Under Static-Renewal Conditions, DACO: 9.3.4,IIA 8.3.1.3

3246186 2020, SYN547407 - Acute Toxicity to Freshwater Amphipods (Hyalella azteca) Under Static-Renewal Conditions, DACO: 9.3.4,IIA 8.3.1.3

3246187 2020, SYN547407 - Chronic Toxicity Test with Water Fleas (Daphnia magna) Under Static-Renewal Conditions, DACO: 9.3.3,IIA 8.3.2.1

3246188 2019, SYN547407 - Chronic Toxicity Test with Water Fleas (Daphnia magna) Under Static-Renewal Conditions, DACO: 9.3.3,IIA 8.3.2.1

3246189 2018, SYN547407 - 96-Hour Toxicity Test with the Freshwater Green Alga, Pseudokirchneriella subcapitata, DACO: 9.8.2,9.8.3,IIA 8.4

3246190 2018, SYN547407 - 96-Hour Toxicity Test with the Freshwater Cyanobacterium, Anabaena flos-aquae, DACO: 9.8.2,9.8.3,IIA 8.4

3246191 2018, SYN547407 - 96-Hour Toxicity Test with the Freshwater Diatom, Navicula pelliculosa, DACO: 9.8.2,9.8.3,IIA 8.4

3246192 2021, SYN547407 - Toxicity Test with Sediment-Dwelling Midges (Chironomus riparius) Under Static Conditions, Following OECD Guideline 218, DACO: 9.9,IIA 8.5.2

3246193 2021, SYN547407 - Life-Cycle Toxicity Test Exposing Midges (Chironomus dilutus) to a Test Substance Applied to Sediment Under Intermittent-Renewal Conditions Following EPA Test Methods, DACO: 9.9,IIA 8.5.2

3246194 2019, SYN547407 - 28-Day Toxicity Test Exposing Estuarine Amphipods (Leptocheirus plumulosus) to a Test Substance Applied to Sediment Under Intermittent-Renewal Conditions Following EPA Test Methods, DACO: 9.9,IIA 8.5.2

3246195 2019, SYN547407 - 42-Day Toxicity Test Exposing Freshwater Amphipods (Hyalella azteca) to a Test Substance Applied to Sediment Under Intermittent-Renewal Conditions Following EPA Test Methods, DACO: 9.9,IIA 8.5.2

3246196 2018, SYN547407 - 7-Day Toxicity Test with Duckweed (Lemna gibba), DACO: 9.8.5,IIA 8.6

3246197 2017, SYN547407 - Assessment of Effects on the Adult Honey Bee, Apis mellifera L., in a 10 Day Chronic Feeding Test under Laboratory Conditions, DACO: 9.2.4.2,IIA 8.7.1

3246198 2021, Isocycloseram - Acute toxicity to the bumblebee Bombus terrestris L. under laboratory conditions, DACO: 9.2.4.1,9.2.4.2,IIA 8.7.1,IIA 8.7.2

3246199 2016, SYN547407 - Acute Oral and Contact Toxicity to the Honey Bee, Apis mellifera L. under Laboratory Conditions, DACO: 9.2.4.1,9.2.4.2,IIA 8.7.1,IIA 8.7.2

3246200 2021, SYN549106 - Acute Toxicity to the Honeybee Apis mellifera L under Laboratory Conditions, DACO: 9.2.4.1,9.2.4.2,IIA 8.7.1,IIA 8.7.2

3246206 2017, SYN547407 - Honey bee (Apis mellifera L.) Larval Toxicity Test (Repeated Exposure through to Adult Emergence), DACO: 9.2.4.3,IIA 8.7.4

3246207 2017, SYN547407 - Honey bee (Apis mellifera L.) Larval Toxicity Test (Single Exposure), DACO: 9.2.4.3,IIA 8.7.4

3246209 2020, Isocycloseram DC (A21708E) - A Rate-Response Laboratory Study to Determine the Effects of Fresh Residues on the Parasitic Wasp Aphidius rhopalosiphi (Hymenoptera, Braconidae), DACO: 9.2.6,IIA 8.8.1.1

3246210 2020, Isocycloseram DC (A21708E) - A Rate-Response Laboratory Study to Determine the Effects of Fresh Residues on the Predatory Mite Typhlodromus pyri (Acari: Phytoseiidae), DACO: 9.2.5,IIA 8.8.1.2

3246211 2020, SYN547407 - A Laboratory Test to Determine the Effects of Fresh Residues on the Predatory Mite Hypoaspis aculeifer (Acari, Laelapidae), DACO: 9.2.5,IIA 8.8.1.2

3246212 2020, SYN547950 - Effects on the Reproduction of the Predatory Mite Hypoaspis aculeifer, DACO: 9.2.5,IIA 8.8.1.2

3246213 2020, SYN549433 - Effects on the Reproduction of the Predatory Mite Hypoaspis aculeifer, DACO: 9.2.5,IIA 8.8.1.2

3246214 2020, SYN550918 - Effects on the Reproduction of the Predatory Mite Hypoaspis aculeifer, DACO: 9.2.5,IIA 8.8.1.2

3246215 2015, SYN547407 - A Laboratory Test to Determine the Effects of Fresh Residues on the Springtail Folsomia candida (Collembola, Isotomidae), DACO: 9.2.5,9.2.7,IIA 8.8.1.3,IIA 8.8.2.5

3246216 2016, SYN547407 - Acute Toxicity to the Earthworm Eisenia andrei in Artificial Soil, DACO: 9.2.3.1,IIA 8.9.1

3246217 2015, SYN547407 tech - Earthworm Reproduction Test (Eisenia fetida), DACO: 9.2.3.1,IIA 8.9.2

3420155 2022, Syngenta Response to EPAs Request for Additional Information on Non-Systemic Properties of Isocycloseram and Other Pollinator Risk Assessment Considerations, DACO: 8.6,9.9

3448476 2023, [14C]SYN547407 - Bioaccumulation in Bluegill Sunfish (Lepomis macrochirus): Aqueous Exposure, DACO: 9.5.6

3633672 2023, Isocycloseram DC (A21708E) - A Rate-Response Extended Laboratory Study to Determine the Effects of Fresh Residues on the Predatory Mite Typhlodromus pyri (Acari: Phytoseiidae), DACO: 9.2.5

3633674 2023, Isocycloseram DC (A21708E) - A Rate-Response Extended Laboratory Study to Determine the Effects of Fresh Residues on the Parasitic Wasp Aphidius rhopalosiphi (Hymenoptera, Braconidae), DACO: 9.2.6

4.0 Value

PMRA Document Number	Reference
3246583	2021, Isocycloseram A22128 (A22128E) - Document M-III, Section 7 - Efficacy Data and Information - Canada, DACO: 1.1,10.2.1,10.2.2,10.2.3.1, 10.2.3.2,10.2.3.3,10.2.3.4,10.3.1,10.3.2,10.4,10.5.1,10.5.2,10.5.4,10.6,12.7,5.2, Document M,IIIA 1.6,IIIA 3.1,IIIA 3.2,IIIA 3.3.1,IIIA 3.3.2,IIIA 3.3.3,IIIA 3.4,IIIA 3.5,IIIA 3.6,IIIA 3.7.1,IIIA 3.9,IIIA 6.1.2,IIIA 6.1.3,IIIA 6.2.1,IIIA 6.2.2,IIIA 6.2.3,IIIA 6.3,IIIA 6.4.1,IIIA 6.4.2,IIIA 6.4.3,IIIA 6.5,IIIA 6.6
3246588	2020, Isocycloseram Technology (1.0%) Cockroach Gel Bait - Oriental Cockroach, DACO: 10.2.3.3,10.2.3.4,IIIA 6.1.2,IIIA 6.1.3
3246589	2020, Isocycloseram Technology (1.0%) Cockroach Gel Bait - American Cockroach, DACO: 10.2.3.3,10.2.3.4,IIIA 6.1.2,IIIA 6.1.3
3246590	2020, Performance of Isocycloseram (Isocycloseram) (A22128E) Bait Against a Low Density of Cockroaches, DACO: 10.2.3.3,10.2.3.4,IIIA 6.1.2,IIIA 6.1.3
3246591	2020, Performance of Isocycloseram (Isocycloseram) (A22128E) Bait Against a Low Density of Cockroaches, DACO: 10.2.3.3,10.2.3.4,IIIA 6.1.2,IIIA 6.1.3
3246592	2020, Performance of Isocycloseram (Isocycloseram) (A22128E) Bait Against a Low Density of Cockroaches, DACO: 10.2.3.3,10.2.3.4,IIIA 6.1.2,IIIA 6.1.3
3246593	2020, Performance of Isocycloseram (Isocycloseram) (A22128E) Bait Against a Low Density of Cockroaches, DACO: 10.2.3.3,10.2.3.4,IIIA 6.1.2,IIIA 6.1.3
3246594	2020, Performance of Isocycloseram (Isocycloseram) (A22128E) Bait Against a Low Density of American Cockroaches, DACO: 10.2.3.3,10.2.3.4,IIIA 6.1.2,IIIA 6.1.3
3246595	2020, Performance of Isocycloseram (Isocycloseram) (A22128E) Bait Against a High Density of Cockroaches, DACO: 10.2.3.3,10.2.3.4,IIIA 6.1.2,IIIA 6.1.3
3246596	2020, Performance of Aged Isocycloseram (Isocycloseram) (A22128E) Bait Against German Cockroaches, DACO: 10.2.3.3,10.2.3.4,IIIA 6.1.2,IIIA 6.1.3
3246597	2020, Efficacy of Isocycloseram (Isocycloseram) (A22128E) Bait Against a High Density of Turkestan Cockroaches, DACO: 10.2.3.3,10.2.3.4,IIIA 6.1.2,IIIA 6.1.3
3246598	2020, Efficacy of Isocycloseram (Isocycloseram) (A22128E) Bait Against a High Density of Oriental Cockroaches, DACO: 10.2.3.3,10.2.3.4,IIIA 6.1.2,IIIA 6.1.3
3246599	2020, Efficacy of Isocycloseram (Isocycloseram) (A22128E) Bait Against a High Density of German Cockroaches, DACO: 10.2.3.3,10.2.3.4,IIIA 6.1.2,IIIA 6.1.3

3246600 2020, Efficacy of Isocycloseram (Isocycloseram) (A22128E) Bait Against a High Density of German Cockroaches, DACO: 10.2.3.3,10.2.3.4,IIIA 6.1.2,IIIA 6.1.3

3246601 2020, Efficacy of Isocycloseram (Isocycloseram) (A22128E) Bait Against a High Density of Cockroaches, DACO: 10.2.3.3,10.2.3.4,IIIA 6.1.2,IIIA 6.1.3

3246602 2020, Efficacy of Isocycloseram (Isocycloseram) (A22128E) Bait Against a High Density of Cockroaches, DACO: 10.2.3.3,10.2.3.4,IIIA 6.1.2,IIIA 6.1.3

3246603 2020, Efficacy of Isocycloseram (Isocycloseram) (A22128E) Bait Against a High Density of Cockroaches, DACO: 10.2.3.3,10.2.3.4,IIIA 6.1.2,IIIA 6.1.3

3246604 2021, Isocycloseram (A22128E) - Efficacy Data to Support Use of Isocycloseram Gel Bait for the Control of Cockroaches, DACO: 10.2.3.4,IIIA 6.1.3

3246606 2020, Isocycloseram Technology (1.0%) Cockroach Gel Bait - German Cockroach, DACO: 10.2.3.3,10.2.3.4,IIIA 6.1.2,IIIA 6.1.3

3246607 2020, Performance of Aged Isocycloseram (Isocycloseram) (A22128E) Bait Against American Cockroaches, DACO: 10.2.3.3,10.2.3.4,IIIA 6.1.2,IIIA 6.1.3

3246608 2021, Efficacy of Isocycloseram (Isocycloseram) (A22128E) Bait Against a High Density of American Cockroaches, DACO: 10.2.3.3,10.2.3.4,IIIA 6.1.2,IIIA 6.1.3

3246639 2021, Isocycloseram A22241 ST (A22241C) Document M-III, Section 7 - Efficacy Data and Information - Canada, DACO: 10.1,10.2.1,10.2.2,10.2.3.1,10.2.3.2,10.2.3.3,10.2.3.4,10.3.1,10.3.2,10.4,10.5.1,10.5.2,10.5.4,10.6,12.7,5.2,Document M,IIIA 1.6,IIIA 3.1,IIIA 3.2,IIIA 3.3.1,IIIA 3.3.2,IIIA 3.3.3,IIIA 3.4,IIIA 3.5,IIIA 3.6,IIIA 3.7.1,IIIA 3.9,IIIA 6.1.2,IIIA 6.1.3,IIIA 6.2.1,IIIA 6.2.2,IIIA 6.2.3,IIIA 6.3,IIIA 6.4.1,IIIA 6.4.2,IIIA 6.4.3,IIIA 6.5,IIIA 6.6

3246651 2021, Isocycloseram (A22241A) for control of wireworms in barley, DACO: 10.2.3.3,10.2.3.4,IIIA 6.1.2,IIIA 6.1.3

3246652 2021, Establish LER for in-season stand establishment with Isocycloseram in Wheat and Barley, DACO: 10.2.3.3,10.2.3.4,IIIA 6.1.2,IIIA 6.1.3

3246653 2021, Evaluate Isocycloseram and Isocycloseram and Fortenza as mixture concept for White Grubs in Wheat -Pot study, DACO: 10.2.3.3,10.2.3.4,IIIA 6.1.2,IIIA 6.1.3

3246654 2021, Evaluate Isocycloseram for white grubs in Winter Wheat, DACO: 10.2.3.3,10.2.3.4,IIIA 6.1.2,IIIA 6.1.3

3246655 2021, Evaluate Isocycloseram for Wireworms in Winter Wheat, DACO: 10.2.3.3,10.2.3.4,IIIA 6.1.2,IIIA 6.1.3

3246656 2021, Evaluate Isocycloseram for Wireworms in Winter Wheat, DACO: 10.2.3.3,10.2.3.4,IIIA 6.1.2,IIIA 6.1.3

3246657 2021, Isocycloseram (A22241A) for control of wireworms in spring wheat, DACO: 10.2.3.3,10.2.3.4,IIIA 6.1.2,IIIA 6.1.3

3246658 2021, Establish LER for wireworm mortality with Isocycloseram in Wheat and Barley, DACO: 10.2.3.3,10.2.3.4,IIIA 6.1.2,IIIA 6.1.3

3246659 2021, Establish LER for in-season stand establishment with Isocycloseram in wheat and barley, DACO: 10.2.3.3,10.2.3.4,IIIA 6.1.2,IIIA 6.1.3

3319825 2022, A22241 ST - Revised Efficacy Discussion, DACO: 10.1

3319826 2022, A22241 ST Efficacy Summary Table Revised, DACO: 10.2.3.1

3319827 2018, Evaluate Isocycloseram and Isocycloseram and Fortenza as mixture concept for White Grubs in Wheat -Pot study, DACO: 10.2.3.3

3319828 2018, Evaluate Isocycloseram for white grubs in Winter Wheat, DACO: 10.2.3.3

3319829 2019, Evaluate Isocycloseram concept for White Grubs in Wheat - Pot study, DACO: 10.2.3.3

3319830 2021, Evaluate Isocycloseram for white grubs in Winter Wheat - Field Study, DACO: 10.2.3.3

3319831 2021, Evaluate Isocycloseram for white grubs in Winter Wheat - Field Study, DACO: 10.2.3.3

3246640 2021, Efficacy Summary Table - A22241 ST, DACO: 10.2.3.3,10.2.3.4,10.3.2,12.7,Document M,IIIA 6.1.2,IIIA 6.1.3,IIIA 6.2.1

3246797 2021, A23128 ST - Efficacy Summary Table, DACO: 10.2.3.3,10.2.3.4,10.3.2,12.7,Document M,IIIA 6.1.2,IIIA 6.1.3,IIIA 6.2.1

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3246804 2021, Evaluate Isocycloseram Premix Formulation vs. Solo Formulation and compare Syngenta's products to competitors for control of wireworms in cereals, DACO: 10.2.3.3,10.2.3.4,IIIA 6.1.2,IIIA 6.1.3

3246805 2021, Evaluate Isocycloseram Premix Formulation vs. Isocycloseram Solo Formulation and compare Syngenta's products to competitors for control of wireworms in cereals, DACO: 10.2.3.3,10.2.3.4,IIIA 6.1.2,IIIA 6.1.3

3246807 2021, Evaluate Isocycloseram Premix Formulation vs. Isocycloseram Solo Formulation and compare Syngenta's products to competitors for control of wireworms in cereals, DACO: 10.2.3.3,10.2.3.4,IIIA 6.1.2,IIIA 6.1.3

B. Additional information considered

i) Published information

1.0 Environment

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