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Australian Pesticides and Veterinary Medicines Authority

Public Release Summary

on the evaluation of the active constituent isocycloseram in the product Simodis Plinazolin Technology Insecticide

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Preface

The Australian Pesticides and Veterinary Medicines Authority (APVMA) is the Australian Government regulator responsible for assessing and approving agricultural and veterinary chemical products prior to their sale and use in Australia. Before approving an active constituent and/or registering a product, the APVMA must be satisfied that the statutory criteria, including the safety, efficacy, trade, and labelling criteria, have been met. The information and technical data required by the APVMA to assess the statutory criteria of new chemical products, and the methods of assessment, must be consistent with accepted scientific principles and processes. Details are outlined on the APVMA website.

The APVMA has a policy of encouraging transparency in its activities and seeking community involvement in decision making. Part of that process is the publication of Public Release Summaries for products containing new active constituents. This Public Release Summary is intended as a brief overview of the assessment that has been conducted by the APVMA and of the specialist advice received from advisory agencies, including other Australian Government agencies and State departments of primary industries. It has been deliberately presented in a manner that is likely to be informative to the widest possible audience to encourage public comment.

About this document

This Public Release Summary indicates that the APVMA is considering an application for registration of an agricultural or veterinary chemical. It provides a summary of the APVMA's assessment, which may include details of:

- the toxicology of both the active constituent and product
- the residues and trade assessment
- occupational exposure aspects
- environmental fate, toxicity, potential exposure and hazard
- efficacy and target crop safety.

Comment is sought from interested stakeholders on the information contained within this document.

Making a submission

In accordance with sections 12 and 13 of the Agvet Code, the APVMA invites any person to submit a relevant written submission as to whether the application for registration of Simodis Plinazolin Technology Insecticide should be granted. Submissions should relate only to matters that the APVMA is required, by legislation, to take into account in deciding whether to grant the application. These matters include aspects of public health, occupational health and safety, chemistry and manufacture, residues in food, environmental safety, trade, and efficacy and target crop safety. Submissions should state the grounds on which they are based. Comments received that address issues outside the relevant matters cannot be considered by the APVMA.

Submissions must be received by the APVMA by close of business on 1 November 2022 and be directed to the contact listed below. All submissions to the APVMA will be acknowledged in writing via email or by post.

Relevant comments will be considered by the APVMA in deciding whether the product should be registered and in determining appropriate conditions of registration and product labelling.

When making a submission please include:

- contact name
- company or organisation name (if relevant)
- email or postal address (if available)
- the date you made the submission.

Please note: submissions will be published on the APVMA's website, unless you have asked for the submission to remain confidential, or if the APVMA chooses at its discretion not to publish any submissions received (refer to the public consultation coversheet).

Please lodge your submission using the public consultation coversheet, which provides options for how your submission will be published.

Note that all APVMA documents are subject to the access provisions of the *Freedom of Information Act 1982* and may be required to be released under that Act should a request for access be made.

Unless you request for your submission to remain confidential, the APVMA may release your submission to the applicant for comment.

Written submissions should be addressed to:

Case Management and Administration Unit

Australian Pesticides and Veterinary Medicines Authority

GPO Box 3262

Sydney NSW 2001

Phone: +61 2 6770 2300

Email: casemanagement@apvma.gov.au

Further information

Further information can be obtained via the contact details provided above.

Copies of technical evaluation reports covering chemistry, efficacy and safety, toxicology, occupational health and safety aspects, residues in food and environmental aspects are available from the APVMA on request.

Further information on Public Release Summaries can be found on the APVMA website.

Introduction

This publication provides a summary of the data reviewed and an outline of the regulatory considerations for the proposed registration of Simodis Plinazolin Technology Insecticide, containing the active constituent, isocycloseram.

Applicant

Syngenta Australia Pty Ltd.

Purpose of application

Syngenta Australia Pty Ltd has applied to the APVMA for registration of the new product Simodis Plinazolin Technology Insecticide, containing 100 g/L, as dispersable concentrate of the active constituent isocycloseram.

This publication provides a summary of the data reviewed and an outline of the regulatory considerations for the proposed registration of the product Simodis Plinazolin Technology Insecticide containing the active constituent isocycloseram.

Proposed claims and use pattern

For the control of certain insect and mite pests in vegetables.

Mode of action

Isocycloseram is a member of the isoxazoline chemical family and belongs to a new IRAC Mode of Action Group 30 (IRAC 2021). It acts at the gamma-aminobutyric acid (GABA) receptor as an antagonist with a novel mode of action.

The compound works on all insect and mite stages, via contact and/or ingestion. Symptoms include paralysis and inactivity. As the compound is metabolised very slowly in the target pest, and the mechanism of action is also slow, pests will assimilate doses beyond the toxic dose before symptoms set in, making the product a very effective insecticide/miticide against crop pests. To date, no cross-resistance to other modes of action has been identified.

Overseas registrations

At this stage, there are no approvals for this active constituent, or any product registrations anywhere in the world.

Registration of products containing isocycloseram will be sought in North America, South America, China and Asia. The products are being developed globally across key market segments for the control of stinkbug,

lepidoptera, and sucking pests in rice, soya, corn, vegetables and specialty crops; and wireworm as a seed treatment in broadacre cereals, corn and cotton.

Chemistry and manufacture

Active constituent

The isocycloseram technical active constituent is manufactured overseas. Details of the chemical name, structure, and physicochemical properties of isocycloseram active constituent are listed below (Tables 1 to 2).

Isocycloseram was approved in 2021 (approval number 89440) as a new active constituent. However, there are no products containing isocycloseram currently registered.

Table 1: Nomenclature and structural formula of the isocycloseram active constituent

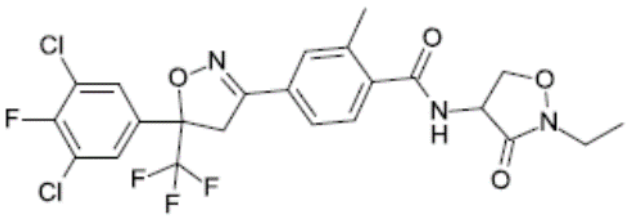
Common name (ISO):	Isocycloseram
IUPAC name:	A mixture comprised of 80-100% 4-[(5S)-5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydro-1,2-oxazol-3-yl]-N-((4R)-2-ethyl-3-oxo-1,2-oxazolidin-4-yl)-2-methylbenzamide and 20-0% of the (5R,4R), (5R,4S) and (5S,4S) isomers.
CAS name:	Benzamide, 4-[5-(3,5-dichloro-4-fluorophenyl)-4,5-dihydro-5-(trifluoromethyl)-3-isoxazolyl]-N-(2-ethyl-3-oxo-4-isoxazolidinyl)-2-methyl-
Manufacturer's code number:	SYN547407
CAS registry number:	2061933-85-3
Molecular formula:	C23H19Cl2F4N3O4
Molecular weight:	548.3 gmol-1
Structural formula:	

Table 2: Key physicochemical properties of isocycloseram

Appearance and odour:	Off-white solid powder with a sweetish odour
Melting point:	138.9 °C (for pure active ingredient, PAI, with 98.4% w/w purity) 135.3 °C (for technical grade active ingredient, TGAI, with 96.9% w/w purity)
Boiling point:	Decomposes from approximately 212 °C (for PAI) Decomposes from approximately 178 °C (for TGAI)
Specific gravity (20 °C)	1.45 (for PAI) 1.53 (for TGAI)
Solubility in water:	1.2 mg/L at 20 °C (for PAI and TGAI)
Organic solvent solubility:	**For TGAI at 25 °C** **Solubilitv** — **Solvents** 400 g/L — Dichloromethane 270 g/L — Acetone 190 g/L — Ethyl acetate 75 g/L — Methanol 33 g/L — Toluene 17 g/L — Octanol 39 mg/L — Hexane
Dissociation constant:	No dissociation observed between pH 2 and 12 at 20 °C (for PAI)
PH:	6.81 (1% w/v aqueous dispersion at 20°C for TGAI)
Octanol/water partition coefficient (Log K_{ow}):	5.0 at 20°C for PAI 4.9 at 25°C for TGAI
Vapour pressure:	<6.2×10^{-6} Pa at 20 and 25 °C (for PAI)
Henry's law constant:	2.83×10^{-3} Pa m^3/mol at 25 °C (calculated, for PAI)
UV/VIS absorption spectra:	

	Wavelength [nm]	Absorbance	Molar extinction coefficient [L mol^{-1} cm^{-1}]
Neutral solution (methanol)	265	0.6325	25004
	290	0.1617	6392
Acidic solution (90:10 v/v methanol: 1 N HCl)	265	0.5725	22632
	290	0.1241	4906
Basic solution (90:10 v/v methanol: 1 N NaOH)	265	0.5657	22363
	290	0.1286	5084

Stability:	The active (PAI or TGAI) was stable at 54 °C for 2 weeks, or at 20 °C for 12 months when stored in either a conductive PE bag or a paper/PETP/Al/PE bag
Safety properties:	Not flammable, and no explosive and oxidizing properties available Slight corrosion to tin plate, but no corrosion to galvanised sheet metal, sheet steel, stainless steel (for TGAI)

Isocycloseram is an off-white powder at room temperature, with a melting point of 135 to 138 °C, and very low vapour pressure. It has very low water solubility, while being soluble or very soluble in aromatic hydrocarbon solvents and polar organic solvents. The partition coefficient ($log_{10}K_{OW}$) is above 3, indicating a potential to partition into fatty or organic matrices from water. Isocycloseram has good safety properties, not being oxidising or reducing, or corrosive to most materials, although slight corrosion of tinplated steel was observed. The technical active constituent is expected to be stable for at least two years under normal storage conditions.

Formulated product

The product Simodis Plinazolin Technology Insecticide will be manufactured overseas. Tables 3 and 4 outline some key aspects of the formulation and physicochemical properties of the product.

Table 3: Key aspects of the formulation of Simodis Plinazolin Technology Insecticide

Distinguishing name:	Simodis Plinazolin Technology Insecticide
Formulation type:	Dispersible Concentrate (DC)
Active constituent concentration:	100 g/L isocycloseram

Table 4: Physicochemical properties of Simodis Plinazolin Technology Insecticide

Physical form:	Light brown to dark brown clear liquid with a pungent odour
pH (1% in DI water):	4.3
Specific gravity:	1.0819 at 20 °C
Viscosity:	14.0 mPa.s at shear rate from 200 to 120 s-1 at 20 °C
Surface tension	45.13 mN/m (3% in pure water at 20 °C) 51.00 mN/m (0.1% in pure water at 20 °C)
Persistent foam:	16 mL foam after 1 minute for the dilution of 0.1% in CIPAC Standard Water A/D 58 mL foam after 1 minute for the dilution of 3.0% in CIPAC Standard Water A/D
Dispersion stability:	No cream, no oil, or no sediment for dilution of 0.1% in CIPAC Standard Water A/D after 0.5 hour 0.05 mL cream; no oil, or no sediment for the dilution of 3.0% in CIPAC Standard Water A/D after 0.5 hour
Safety properties:	This product is not expected to be flammable, explosive, or oxidizing under normal use conditions, and is non-corrosive to the HDPE packaging. The liquid product has a relatively high flash point and auto-ignition temperature of 110 °C and 410 °C, respectively
Storage stability:	The product was stable for 2 weeks at 54 °C when stored in the proposed HDPE packaging and in PET containers, as well as in laminated paper/PET/Al/PE bags

Recommendations

The APVMA Chemistry section has evaluated the chemistry of the isocycloseram active constituent and the associated product Simodis Plinazolin Technology Insecticide including the physicochemical properties, identification, manufacturing process, quality control procedures, stability data, batch analysis results and analytical methods, and found them to be acceptable.

The available storage stability data indicate that the formulated product is expected to remain stable for at least 2 years when stored under normal conditions.

Based on a review of the chemistry and manufacturing details, the registration of Simodis Plinazolin Technology Insecticide and approval of the isocycloseram active constituent, are supported from a chemistry perspective.

Toxicological assessment

A full package of toxicological data for isocycloseram was submitted by the applicant, which was sufficient to assess the toxicity of isocycloseram.

Evaluation of toxicology

Chemical class

Isocycloseram is an isoxazoline insecticide (IRAC Group 30) with a novel GABA-gate chloride antagonist as biochemical mode of action. It works by contact and feeding in insects and mites and is characterised by long residual effects on the leaf surface, but only moderate knockdown effects.

Pharmacokinetics

Metabolism studies in rats showed that isocycloseram was readily absorbed following oral administration with extensive metabolism. The parent compound accounted for <3.5% of the dose in bile, faeces and plasma, and was not detected in urine. The excretion pattern (mainly via bile and faeces, and to lesser extent, via urine) following multiple oral administrations was similar to that following a single oral administration, indicating there were no changes to elimination or metabolic pathways. Tissue clearance of isocycloseram was incomplete after 72 and 168 hours, with 5.5 to 12% of administered radioactivity remaining in tissues. The primary biotransformation pathway of isocycloseram in rats involved ring opening of the isoxazole ring, ring opening and cleavage of the oxazolidinone ring, oxidative defluorination, and glucuronic acid conjugation. The overall weight of evidence suggests that identified isocycloseram metabolites are unlikely to be genotoxic in an adequate range of *in vitro* and *in vivo* genotoxicity studies.

Dermal absorption studies with a concentrated formulation of 200 g/L SC product and at a range of dilutions in *in vitro* studies on human and rat skin, and in rat *in vivo* studies confirmed that dermal absorption of isocycloseram in humans can be anticipated to be low: 2.2% for concentrated formulation, and 20% for a diluted formulation.

Acute toxicity (active constituent)

Isocycloseram was of very low oral, low dermal and low acute inhalational toxicity. It was not an irritant of rabbit skin but was identified as slightly irritating to the eyes of rabbits and has potential to be a skin sensitiser.

Acute toxicity (product)

Simodis Plinazolin Technology Insecticide has very low acute toxicity by oral and inhalation routes, and low acute toxicity by dermal route. It is not irritant to skin or have potential to be a skin sensitiser, however, it is moderately irritant to the eyes.

Repeat-dose toxicity

The short-term toxicity of isocycloseram was investigated in rats, mice, and dogs via dietary or capsule administration, and in rats via dermal exposure. In general, signs of toxicity across species included increased erythrocyte products, adrenal gland toxicity, and effects on body weight.

In mice, following 28-day dietary exposure, the no observed adverse effect level (NOAEL) was 17 mg/kg bw/day, based on microscopic changes in the liver, spleen, duodenum and adrenal gland at the next highest dose, with signs of a compensatory increase in erythrocyte products. In a 13-week oral toxicity study in mice, the NOAEL was 8 mg/kg bw/day, based on effects on body weight, increased erythrocyte production, and adrenal and liver toxicity at higher doses.

In rats, the NOAEL in a 28-day dietary study was 50 ppm, equal to 4.3 mg/kg bw/day, based on the presence of clinical signs consistent with neurotoxicity, reduced body weight gain, lymphocytic leucocytosis, minimal evidence of hepatic or renal toxicity in females, and adrenal gland toxicity in both sexes. In a 13-week dietary study in rats, the NOAEL was 50 ppm in males (equal to 3.9 mg/kg bw/day) based on adrenal gland toxicity, and tubular degeneration of the rat male testis followed by reduced sperm counts in epididymis.

In dogs, the NOAEL in a 28-day oral capsule study was considered to be 10 mg/kg bw/d, based on signs of overt toxicity at the next highest dose. The reliability of this NOAEL was considered to be reduced due to the problems associated with poor dose-ranging selection used in the study. In a 13-week oral toxicity study in dogs, the NOAEL was considered to be 5 mg/kg bw/d, based on effects on body weight parameters at 15 mg/kg bw/d. There was no notable evidence of neurotoxicity detected at any dose.

In a 28-day dermal toxicity study in rats, the NOAEL was 100 mg/kg bw/d, based on hypertrophy and vacuolation of the adrenal gland zona fasciculata, small intestinal vacuolation in females, increased erythrocyte production demand, leucocytosis, and reduced body weight change at ≥300 mg/kg bw/d. There was no notable evidence of neurotoxicity detected in this study.

Chronic toxicity and carcinogenicity

Two chronic toxicity studies were conducted using isocycloseram: an 80-week study in mice, and a 2-year study in rats. The overall NOAEL for toxicity was 1.7 mg/kg bw/d in males and 1.8 mg/kg bw/d in female mice, based on lymphatic and non-lymphatic plasmacytosis in both males and females.

No evidence of carcinogenicity was observed in rats. Body weight reduction in females, hepatotoxicity manifesting as centrilobular hepatocellular vacuolation, and effects in the testis of males were observed at the highest dose tested (150 ppm, equivalent to 7.0 mg/kg bw/d in males and 9.3 mg/kg bw/d in females). The NOAEL was 2.3 mg/kg bw/d in male, and 3.0 mg/kg bw/d in female rats.

Reproductive and developmental toxicity

In a 1-generation study in rats, isocycloseram was administered daily via oral gavage. While there were observed effects on male reproductive organs including tubular degeneration in the testes, there were no observed effects on sperm motility, concentration, or morphology, nor any effects on mating. There was no

effect on reproductive performance, mating behaviour, conception, or pup development. Signs of systemic toxicity included tubular degeneration in the testes, and liver vacuolation in male rats, in addition to epithelial vacuolation in the duodenum and jejunum in both males and females. The NOAEL for reproductive performance was 45/60 mg/kg bw/d in males, and 15 mg/kg bw/d in females, the highest dose tested. The NOAEL for systemic toxicity was 7.5 mg/kg bw/d.

In a 2-generation dietary study, the NOAEL for reproductive performance was 12 mg/kg bw/d, the highest dose tested, based on the lack of adverse effects on mating behaviour, conception, or pup development. The NOAEL for systemic toxicity was set at 4 mg/kg bw/d, based on the epithelial vacuolation in the duodenum and jejunum in males and females, and centrilobular hepatocyte vacuolation in the liver and testicular toxicity in males.

In a developmental toxicity study in rats, skeletal malformation (bifid sternum in 2 foetuses from 2 separate litters) was observed at the highest dose tested (15 mg/kg bw/d). The NOAEL for maternal toxicity in rats was 15 mg/kg bw/d, and NOAEL for foetal developmental toxicity was 7.5 mg/kg bw/d. In a developmental toxicity study in rabbits, the NOAEL for maternal toxicity and for foetal toxicity was 15 mg/kg bw/day, the highest dose tested.

Genotoxicity

In *in vitro* genotoxicity tests and *in vivo* chromosomal aberration tests in rats, isocycloseram produced negative results. Isocycloseram is unlikely to be genotoxic.

Neurotoxicity/immunotoxicity

The neurotoxicity studies on isocycloseram produced no evidence to support neurotoxicity. The NOAEL for general neurotoxicity was 24.8/32.7 mg/kg bw/d in males and females respectively, the highest dose tested. These are supported by the lack of signs of neurotoxicity in repeat dose studies.

No data were available on immunotoxicity. In an 80-week dietary study in mice, plasmacytosis was observed at, and above 60 ppm in the diet. While APVMA agrees that the observed plasmacytosis is unlikely to be due to immunodeficiency, without further immunological mechanistic data, the test-article associated modulation of T- and B-cell function cannot be mechanistically excluded, based on the available data.

Toxicity of metabolites and/or impurities

The potential *in vitro* mutagenicity of the main technical impurities was tested in a battery of genotoxicity studies. The overall weight-of-evidence indicates that isocycloseram and its known impurities are unlikely to be genotoxic.

Health-based guidance values and poisons scheduling

Poisons Standard

Isocycloseram is included in Schedule 6 of the Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP).

Health-based guidance values

Acceptable daily intake

An acceptable daily intake (ADI) for isocycloseram was established at 0.02 mg/kg bw/d, based on a NOAEL of 1.7 mg/kg bw/d in male, and 1.8 mg/kg bw/d in females from an 80-week dietary study in mice. The NOAEL was based on lymphatic and non-lymphatic plasmacytosis in males and females, at the next higher dose. The ADI includes a 100-fold uncertainty factor incorporating differences in toxicodynamics and toxicokinectics between and within species.

Acute reference dose

An acute reference dose (ARfD) has been established for isocycloseram at 0.08 mg/kg bw/d for women of child-bearing age based, on a NOAEL of 7.5 mg/kg bw/d, identified based on an increased incidence of bifid sternum in rats, which may be attributable to a single exposure to isocycloseram at 15 mg/kg bw/d in a rat developmental toxicity study. In the absence of any chemical specific data to adjust the uncertainty factor for extrapolation from laboratory animals to humans, or take account of differences in human responses, a default, 100-fold uncertainty factor was applied to the NOAEL.

Recommendations

There are no objections on human health grounds to the approval of isocycloseram.

There are no objections on human health grounds to the registration of the product Simodis Plinazolin Technology Insecticide containing 100 g/L of isocycloseram when the product is used as directed on the label safety directions and appropriate PPE are worn.

Residues assessment

Metabolism, analytical methodology, residue trial data, fate in storage, and trade aspects have been considered for isocycloseram.

Metabolism

Metabolism studies for isocycloseram (SYN547407) were conducted on primary crops (tomato, mustard greens, rice and soybeans), confined rotational crops (lettuce, radish and wheat) and target animals (lactating goats and laying hens). The studies were conducted with compound radiolabelled with 14C at 3 different positions.

Parent isocycloseram was detected as the most abundant component in all tomato samples, ranging from 51% TRR to 95% TRR.

For mustard greens, parent isocycloseram was the most abundant component in samples from foliar applications, ranging from 75% TRR to 99% TRR. Parent was also detected as the most abundant component in immature mustard greens samples from in-furrow application of methylphenyl- and oxoisoxazolidinyl-labelled experiments, ranging from 38% TRR to 45% TRR, but was less abundant in the mature sample of the halophenyl-labelled experiment, accounting for 2.3% TRR.

Parent isocycloseram was detected as the most abundant component in all commodities from rice, ranging from 62% to 96% TRR.

Parent isocycloseram was detected as the most abundant component in soybean forage samples, ranging from 42% TRR to 67% TRR. Isocycloseram was also detected at low levels in soy hay and bean samples, ranging from 2.1% TRR to 15% TRR, except for the soybean samples from the oxoisoxazolidinyl-labelled experiment, and hay samples from the methylphenyl-labelled experiment in which isocycloseram was not detected.

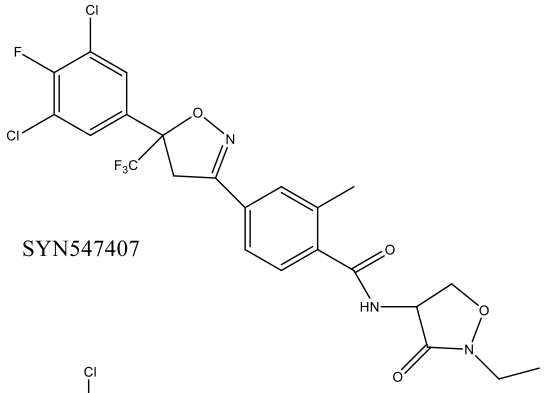
Metabolite SYN549431 was identified at up to 15% TRR in tomato leaves, 25% TRR in rice hay and 10% TRR in soybean forage and hay. While this metabolite was observed in the submitted residue field trials conducted on vegetables, the residue level was generally <10% when compared to the residue level of parent isocycloseram.

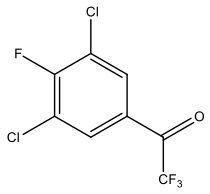
In the confined rotational crop study, parent isocycloseram was identified as the most abundant component in 30 DAT wheat hay (34% TRR, 0.025 mg/kg), 30 DAT wheat straw (31% TRR, 0.021 mg/kg), 120 DAT wheat hay (42% TRR, 0.008 mg/kg), 120 DAT wheat straw (51% TRR, 0.008 mg/kg), 273 DAT wheat straw (34% TRR, 0.006 mg/kg), and radish roots (54% TRR, 0.007 mg/kg). It was not identified in other analysed commodities.

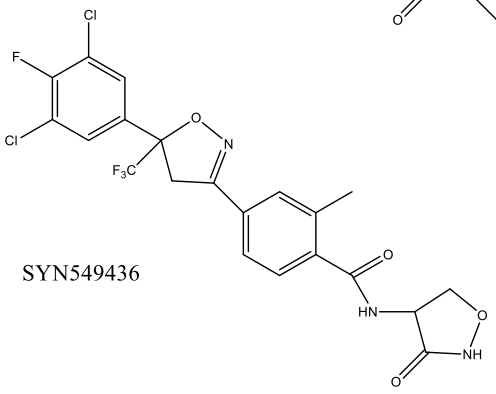
In the lactating goat metabolism studies, parent isocycloseram was the most abundant component detected in all samples analysed, accounting for 22% to 93% TRR and absolute residues of up to 7.4 mg/kg. Similarly in the laying hen metabolism studies, parent was detected as the most abundant component in all samples analysed, ranging from 8.6% TRR to 64% TRR.

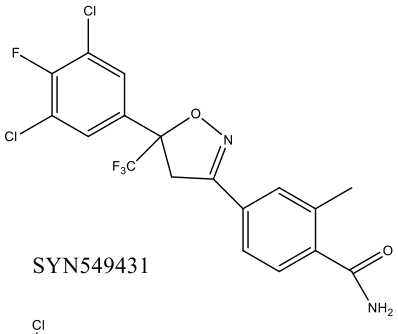
Metabolites in the goat forming more than 10% of TRR were SYN548569 (up to 22% in liver), SYN549544 (up to 14% in liver) and SYN549436 (up to 21% in liver). Metabolism in hens was more complex with several more metabolites forming more than 10% TRR in different matrices (the highest TRR for a metabolite was 29.7% for SYN549431 in hen muscle).

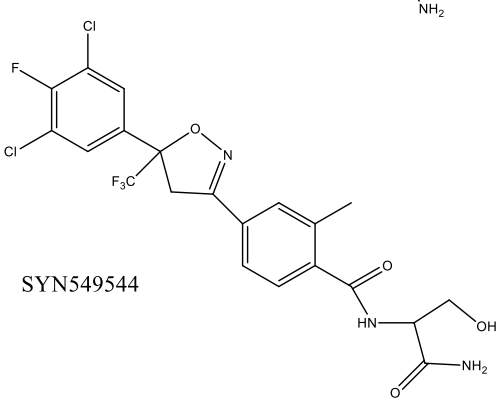
Structures of isocycloseram (SYN547407) and its main metabolites:











Analytical methods and storage stability

In the Australian vegetable trials provided by the applicant, sample extraction and determination of residues of isocycloseram and its metabolites was performed according to the analytical method: “Analytical Method GRM072.10B for the Determination of SYN547407 and its Metabolites SYN549431 and SYN548569 in Crops” Syngenta Report No. GRM072.10B, March 2018.

Isocycloseram and its metabolites (SYN549431 and SYN548569) were extracted from a blended, homogeneous sample with acetonitrile/water. An aliquot of the extract was diluted with acetonitrile/water and

analysed by LC-MS/MS. Quantitation was via external matrix-matched standards. The LOQ was 0.01 mg/kg for each analyte/matrix, the LOD was 0.003 mg/kg. The calibration curves obtained for all analytes and matrices were linear with coefficients of determination (R2) ≥0.995. Similar methods were used in the supporting overseas residue studies. Recoveries from fortified samples were generally within acceptable limits.

In the dairy cattle animal transfer study provided by the applicant, residues of isocycloseram (and metabolites SYN549431, SYN548569, SYN549436, and SYN549544) were determined using high-performance liquid chromatography (HPLC)/mass spectrometry (MS)/MS) following Syngenta analytical method GRM072.01A, with modifications by Smithers (Jutson, 2020).

Residues of isocycloseram and SYN549431 in milk, skim milk, cream, and muscle were extracted by homogenisation in acetonitrile/water. Extracts were centrifuged and filtered through an Oasis Prime SPE cartridge, prior to analysis by LC-MS/MS.

Residues of isocycloseram and SYN549431 in fat were extracted by homogenisation in hexane. The extract was centrifuged, and liquid/liquid partitioned with acetonitrile/acetone. The acetonitrile/acetone layer (bottom) was collected and diluted and filtered prior to analysis by LC-MS/MS.

Residues of isocycloseram, SYN549431, SYN548569, SYN549436, and SYN549544 in liver and kidney were extracted by homogenisation in acetonitrile water. The extract was centrifuged, and the supernatant collected. The post extraction solids (PES) were further extracted by refluxing in isopropanol/1 N HCl. The mixture was cooled to room temperature and pH adjusted to 5 to 7 by addition of 3 N NaOH. The neutralised sample was combined with the initial extract and centrifuged prior to analysis by LC-MS/MS.

The LOQ was 0.01 mg/kg for each analyte. Samples fortified during the course of this study resulted in measured concentrations generally within acceptance criteria (i.e., 70 to 120% and RSD <20%).

The same method was used in the laying hen transfer study, again with recoveries from fortified control samples generally within acceptable limits.

Stability of residues in stored analytical samples

Storage stability of residues (parent SYN547407, SYN549431 and SYN548569) has been demonstrated to be satisfactory for at least 2 years in various representative crop commodities [lettuce (high water/leafy), cereal grain (high starch), soybean (high oil), dried bean (high protein), whole orange (high acid), potato (root crop), straw (dry crop) and coffee].

In the residue trials submitted, all samples were maintained under freezer conditions, (i.e.–18°C) prior to analysis and tested within 697 days of collection. This is acceptable for the purposes of the current application.

Residue definition

Parent compound was generally the major component in the plant metabolism studies and the available residue field trials and is therefore a suitable marker for misuse. An enforcement definition of parent

compound only is recommended for commodities of plant origin. Given that the other metabolites were generally found at <10% TRR in edible commodities, or at a low overall concentration in mg eq/kg, a definition of parent compound only is also suitable for commodities of plant origin for dietary exposure assessment.

Parent compound is the most suitable marker for misuse, as it was the predominant component in the target animal metabolism studies and is recommended as the enforcement residue definition for commodities of animal origin. As metabolites SYN548569, SYN549544 and SYN549436 were observed as significant residues in cattle liver and kidney in the lactating cow transfer study, it is considered prudent to include these metabolites with the parent compound into the residue definition for dietary risk assessment.

Residues in food and animal feeds

Brassica vegetables

In an Australian study, residues of parent in cabbage (3), broccoli (1), cauliflower (1) and Brussels sprouts (1) at 3 days after the last of 3 applications at 30 g ai/ha (1× proposed) were <0.003, 0.003, 0.02, 0.03, 0.08, and 0.09 mg/kg.

In a North American study, residues of parent in cabbage (with wrapper leaves), broccoli, cauliflower and Brussels sprouts at 2 to 3 days after the last of 3 applications at 60 g ai/ha (2× proposed) were 0.20, 0.35, 0.44 and 0.80 mg/kg. Scaled for the proposed application rate, residues are 0.10, 0.18, 0.22 and 0.40 mg/kg.

The combined dataset for MRL estimation is <0.003, 0.003, 0.02, 0.03, 0.08, 0.09, 0.10, 0.18, 0.22 and 0.40 mg/kg. The OECD MRL calculator recommends an MRL of 0.7 mg/kg (STMR= 0.086 mg/kg, unrounded, n= 10).

An MRL of 0.7 mg/kg is recommended for isocycloseram on VB 0040 Brassica (cole or cabbage) vegetables, head cabbages, and flowerhead brassicas in conjunction with a 3-day harvest withholding period.

Brassica leafy vegetables

Residues of parent in leafy vegetables (mustard greens, lettuce and spinach) in North American trials at 2 to 5 days after the last of 3 applications at 60 g ai/ha (2× proposed) were 0.224, 0.441, 2.632 and 2.816 mg/kg. Scaled for application rate, residues were 0.11, 0.22, 1.3 and 1.4 mg/kg. The OECD MRL calculator recommends an MRL of 4 mg/kg, noting a high uncertainty due to the small dataset (STMR= 0.769 mg/kg, unrounded, n= 4).

It is noted that the highest residue at a 1-day PHI was 6.547 mg/kg or 3.274 mg/kg when scaled for application rate, which is within the suggested MRL. Given also that 3 applications were made in the trials, when a maximum of 2 are proposed, it is recommended that an MRL of 4 mg/kg be established for isocycloseram on VL 0054 Brassica leafy vegetables in conjunction with a 3-day harvest withholding period.

Bulb vegetables

Residues of parent in bulb onions from Australian trials at 6 to 8 days after the last application at 60 g ai/ha (2× proposed) were <0.003 mg/kg (n= 3). Residues in leeks and spring onions were 0.03, 0.15, 0.18, 0.22, 0.22, 0.26, 0.35 and 0.59 mg/kg. Scaled for application rate, residues were 0.03, 0.11, 0.14, 0.17, 0.17, 0.20, 0.26 and 0.44 mg/kg.

Residues of parent in bulb onions from North American trials at 6 to 9 days after the last application at approximately 120 g ai/ha (4× proposed) were <0.01 mg/kg (n= 10). Residues in green onions were 0.19, 0.20, 0.24, 0.28, 0.31 and 0.52 mg/kg. Scaled for application rate, residues were 0.07, 0.07, 0.09, 0.10, 0.12 and 0.19 mg/kg.

The combined data set for bulb onions is <0.01 mg/kg (n= 13). Bulb onions are the representative crop for the bulb onion crop subgroup, which also includes garlic and shallots. An MRL of *0.01 mg/kg is recommended for isocycloseram on the crop subgroup VA 2031 Bulb onions, in conjunction with a 7-day harvest withholding period.

The combined dataset for green onions is 0.03, 0.07, 0.07, 0.09, 0.10, 0.11, 0.12, 0.14, 0.17, 0.17, 0.19, 0.20, 0.26 and 0.44 mg/kg. Spring onions are the representative crop for the Green Onion subgroup. The OECD MRL calculator recommends an MRL of 0.6 mg/kg (STMR= 0.129 mg/kg, unrounded, n= 14). An MRL of 0.6 mg/kg is recommended for isocycloseram on VA 2032 Green Onions, in conjunction with a 7-day harvest withholding period.

Fruiting vegetables, cucurbits

Residues of parent in cucurbits [rockmelon (3), zucchini (2) and cucumber (3)] in Australian trials at 1 day after the last application at 75 g ai/ha (2.5× proposed) or at 7.5 g ai/100 L (for cucumber) were <0.003, 0.01, 0.02, 0.03, 0.04, 0.04, 0.06 and 0.06 mg/kg. Scaled for application rate, residues were <0.003, 0.01, 0.01, 0.02, 0.02, 0.02, 0.03 and 0.04 mg/kg.

Residues of parent in cucurbits (cantaloupe, cucumber and summer squash) in North American trials at 1 day after the last application at 60 g ai/ha (2× proposed) were 0.01, 0.08 and 0.09 mg/kg. Scaled for application rate, residues were 0.01, 0.06 and 0.07 mg/kg.

The combined dataset for MRL recommendation is <0.003, 0.01, 0.01, 0.01, 0.02, 0.02, 0.02, 0.03, 0.04, 0.06 and 0.07 mg/kg. The OECD MRL calculator recommends an MRL of 0.15 mg/kg (STMR= 0.021 mg/kg, unrounded, n= 11).

An MRL of 0.2 mg/kg is recommended for isocycloseram on VC 0045 Fruiting vegetables, cucurbits in conjunction with a 1-day withholding period.

Use in both field and protected grown cucurbits is proposed. As the studies included trials in protected cropping situations, the proposed use on protected grown crops is supported.

Fruiting vegetables, other than cucurbits

Residues of parent in field and protected tomatoes in Australian trials at 1-day after the last application at 75 g ai/ha (2.5× proposed) or 7.5 g ai/100 L were 0.01, 0.02, 0.05, 0.05 and 0.08 mg/kg. Scaled for the proposed application, rate residues were 0.003, 0.01, 0.03, 0.03 and 0.05 mg/kg.

Residues of parent in field and protected capsicums in Australian trials at 1-day after the last application at 75 g ai/ha (2.5× proposed) or 7.5 g ai/100 L were 0.01, 0.01, 0.02 and 0.07 mg/kg. Scaled for the proposed application rate, residues were 0.004, 0.01, 0.01 and 0.04 mg/kg.

Residues of parent in tomatoes in North American trials at 1-day after the last application at 120 g ai/ha (4× proposed) were 0.02, 0.05, 0.06, 0.08, 0.09, 0.10, 0.11, 0.11, 0.11, 0.12, 0.13, 0.15, 0.17, 0.22, 0.25 and 0.33 mg/kg. Scaled for the proposed application rate, residues were 0.01, 0.02, 0.02, 0.03, 0.04, 0.04, 0.04, 0.04, 0.04, 0.05, 0.05, 0.05, 0.07, 0.08, 0.09 and 0.13 mg/kg.

Residues of parent in peppers in North American trials at 1-day after the last application at 120 g ai/ha (4× proposed) were 0.04, 0.06, 0.08, 0.09, 0.10, 0.10, 0.11, 0.13, 0.14, 0.16, 0.17, 0.18, 0.18, 0.21, 0.35 and 0.40 mg/kg. Scaled for the proposed application rate, residues were 0.01, 0.02, 0.03, 0.04, 0.04, 0.04, 0.04, 0.05, 0.05, 0.06, 0.06, 0.07, 0.07, 0.08, 0.13 and 0.15 mg/kg.

Residues of parent in eggplants in North American trials at 1-day after the last application at 120 g ai/ha (4× proposed) were 0.03, 0.03, 0.04 and 0.06 mg/kg. Scaled for the proposed application rate, residues were 0.01, 0.01, 0.01 and 0.02 mg/kg.

The dataset will be combined for MRL estimation, noting that the high residues were similar in tomatoes and peppers. The combined dataset is 0.003, 0.004, 0.01, 0.01, 0.01, 0.01, 0.01, 0.01, 0.01, 0.01, 0.02, 0.02, 0.02, 0.02, 0.03, 0.03, 0.03, 0.03, 0.04, 0.04, 0.04, 0.04, 0.04, 0.04, 0.04, 0.04, 0.04, 0.04, 0.05, 0.05, 0.05, 0.05, 0.05, 0.05, 0.06, 0.06, 0.07, 0.07, 0.07, 0.08, 0.08, 0.09, 0.13, 0.13 and 0.15 mg/kg. The OECD MRL calculator recommends an MRL of 0.2 mg/kg (STMR= 0.039 mg/kg, unrounded, n= 45).

An MRL of 0.2 mg/kg is recommended for isocycloseram on VO 0050 Fruiting vegetables, other than cucurbits, in conjunction with a 1-day harvest withholding period.

Use in both field and protected grown fruiting vegetables is proposed. As the studies included trials in protected cropping situations, the proposed use on protected grown crops is supported.

Tomato pomace

Tomato pomace is a feed for livestock in Australia. Processing factors for parent in dry tomato pomace in the two Australian trials were 8.7× and 10.6×. Significantly higher processing factors to dry pomace were observed in the North American trials at 53.0× and 90.1×.

Applying the highest processing factor in the Australian trials to the tomato HR of 0.125 mg/kg (unrounded) gives a HR-P of 1.33 mg/kg. An MRL of 2 mg/kg is recommended for isocycloseram on Tomato pomace, dry.

The median residue in tomatoes was 0.041 mg/kg (unrounded). The STMR-P for estimation of livestock dietary burden is 0.40 mg/kg dry weight (using the average processing factor from the two Australian trials, 9.65×).

Crop rotation

The maximum application rate to crops grown in rotational situations is 2×30 g ai/ha.

In the confined rotational crop metabolism study, the highest TRR (by combustion) was 0.086 mg/kg in wheat hay from a 30-day plant back interval after application to bare soil at approximately 360 g ai/ha. The estimated total residue after 2 applications at 45 g ai/ha is 0.022 mg/kg. Given this is a total radioactive residue comprising several components (parent was 34.0% TRR in the 30-day PBI wheat hay sample) and noting that in-practice the application will also be intercepted by the crop, it is considered that the potential for residues in rotational crops is low. Plant-back intervals for residue management purposes, or an “All other foods” MRL to cover potential residues in following crops are not considered to be necessary.

It is noted that the confined rotational crop metabolism study involved compound labelled at one position only so may not reveal all metabolites. However, a residue definition of parent compound only has been recommended for plant commodities, noting also that the estimated total residue in rotational crops based on the study is low.

Residues in animal commodities

The following grazing restraint has been proposed which will ensure there is no direct feeding of vegetable crops to livestock: “DO NOT USE TREATED CROP, CROP WASTE OR PRODUCE FOR STOCK FOOD”.

Tomato pomace is a feed for mammalian livestock in Australia fed at 10% of the diet. The maximum livestock dietary burdens for beef and dairy cattle are each 0.04 ppm.

A dairy cattle animal transfer study was provided. The feeding study was conducted with lactating dairy cows to determine the magnitude of the residues of isocycloseram and metabolites SYN549431, SYN548569, SYN549436, and SYN549544 in milk and tissues, during or following oral exposure to the active ingredient at target dose levels corresponding to 4.40 mg/kg, 13.2 mg/kg, and 44.0 mg/kg in feed (dry weight basis) daily for 28 consecutive days.

Estimated residues in tissues and milk for a livestock dietary burden of 0.04 ppm extrapolated from the residues observed from the 4.40 ppm level in the feeding study are summarised in Table 5.

Table 5: Cattle

Feeding level (ppm)	Milk	Muscle	Liver	Kidney	Fat
					Parent Isocycloseram residue (mg/kg)
4.40 (feeding study)	0.0181	<0.01	0.0257	<0.01	0.0575
0.04 – beef, estimated burden	-	<0.01	<0.01	<0.01	<0.01
0.04 – dairy, estimated burden	<0.01	-	-	-	-
Recommended MRLs	*0.01 (milks)	*0.01 (meat - in fat)		*0.01 (offal)	-

Note: residues of all metabolites analysed for in the dairy cattle transfer study would also be <0.01 in all tissues and milk for a dietary burden of 0.04 ppm.

The following MRLs are recommended:

MO 0105 Edible offal (mammalian): *0.01 mg/kg

MM 0095 Meat (mammalian) [in the fat]:*0.01 mg/kg

ML 0106 Milks: *0.01 mg/kg

Poultry commodity MRLs will also be recommended at the LOQ noting there are no proposed uses on significant feeds for poultry. The following MRLs are recommended:

PE 0112 Eggs: *0.01 mg/kg

PM 0110 Poultry meat [in the fat]: *0.01 mg/kg

PO 0111 Poultry, edible offal of: *0.01 mg/kg

For dietary exposure assessment a combined LOQ of 0.05 mg/kg in parent equivalents will be used for each commodity (LOQ for each component is 0.01 mg/kg, molecular weights are 548.3 for parent, 261.0 for SYN548569, 520.3 for SYN549436 and 522.3 for SYN549544).

Spray drift

The product will be applied with coarse droplets by boom spray to vegetables. There is a label restraint against aerial and vertical sprayer application.

In the dairy cattle transfer study, the maximum parent residue after dosing at 4.40 ppm was 0.0575 mg/kg. The regulatory acceptable level (RAL) for livestock areas, which is in this case the feeding level for residues in fat to be at the LOQ of 0.01 mg/kg, is 0.77 ppm.

If a RAL of 0.77 ppm is used in the APVMA Spray Drift Risk Assessment Tool, then mandatory buffer zones are not required for livestock areas for protection of international trade.

Dietary risk assessment

The chronic dietary exposure to isocycloseram is estimated by the National Estimated Daily Intake (NEDI) calculation encompassing all registered/temporary uses of the chemical and the mean daily dietary consumption data derived primarily from the 2011–12 National Nutritional and Physical Activity Survey. The NEDI calculation is made in accordance with WHO Guidelines and is a conservative estimate of dietary exposure to chemical residues in food. The NEDI for isocycloseram is equivalent to <5% of the ADI. It is concluded that the chronic dietary exposure to isocycloseram is acceptable.

The acute dietary exposure is estimated by the National Estimated Short-Term Intake (NESTI) calculation. The NESTI calculations are made in accordance with the deterministic method used by the JMPR with 97.5th percentile food consumption data derived primarily from the 2011–12 National Nutritional and Physical Activity Survey. NESTI calculations are conservative estimates of short-term exposure (24-hour period) to chemical residues in food. The highest acute dietary intake was estimated at <50% of the ARfD which is for females of childbearing age. It is concluded that the acute dietary exposure is acceptable.

Recommendations

The following amendments are required to be made to the APVMA MRL Standard (Table 5).

Table 6: Amendments to the APVMA MRL Standard

Amendments to Table 1		
Compound	**Food**	**MRL (mg/kg)**
Add:		
Isocycloseram		
VB 0040	Brassica (cole or cabbage) vegetables, head cabbages, flowerhead brassicas	0.7
VL 0054	Brassica leafy vegetables	4
VA 2031	Bulb onions	*0.01
MO 0105	Edible offal (mammalian)	*0.01
PE 0112	Eggs	*0.01
VC 0045	Fruiting vegetables, cucurbits	0.2
VO 0050	Fruiting vegetables, other than cucurbits	0.2
VA 2032	Green onions	0.6

MM 0095	Meat (mammalian) [in the fat]	*0.01
ML 0106	Milks	*0.01
PM 0110	Poultry meat [in the fat]	*0.01
PO 0111	Poultry, edible offal of	*0.01

Amendments to Table 3	
Compound	**Residue**
Add:	
Isocycloseram	Commodities of plant origin: Isocycloseram
	Commodities of animal origin for enforcement: Isocycloseram
	Commodities of animal origin for dietary exposure assessment: Sum of isocycloseram, 1-(3,5-dichloro-4-fluoro-phenyl)-2,2,2-trifluoroethanone (SYN548569), 4-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydro-1,2-oxazol-3-yl)-2-methyl-N-(3-oxo-1,2-oxazolidin-4-yl)benzamide (SYN549436) and N-(1-amino-3-hydroxy-1-oxopropan-2-yl)-4-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydro-1,2-oxazol-3-yl)-2-methylbenzamide (SYN549544), expressed as isocycloseram

Amendments to Table 4		
Compound	**Animal feed commodity**	**MRL (mg/kg)**
Add:		
Isocycloseram		
	Tomato pomace, dry	2

Assessment of overseas trade aspects of residues in food

The vegetable crops on the draft label are not considered to be major export commodities and animal commodity MRLs have been recommended at the LOQ of the analytical method. The risk to trade is low.

Work health and safety assessment

Health hazards

Simodis Plinazolin Technology Insecticide has very low acute toxicity by oral and inhalation routes, and low acute toxicity by dermal route. It is not irritant to skin or have potential to be a skin sensitiser, however, it is moderately irritant to the eyes.

Occupational exposure

Exposure during use

Simodis Plinazolin Technology Insecticide is a dispersible concentrate (DC) formulation, which will be applied at a maximum rate of 300 mL product/ha (i.e. 30 g ai/ha) for use as a foliar spray on brassicas, cucurbits and fruiting vegetables for control of various insects and mites. It is intended to be applied by ground boom and handheld application equipment. Workers may be exposed to the product from dermal and/or inhalation routes during mixing, loading and application.

Risks from exposure during use of Simodis Plinazolin Technology Insecticide were considered using the US EPA OPHEC (2020) calculator. Risks were very low for workers mixing, loading and applying the product while wearing recommended personal protective equipment.

Exposure during re-entry or rehandling

Growers and their workers may also be exposed to the dried product when they re-enter treated areas for inspection and farming activities. Re-entry exposures have been estimated using the US EPA OPREC (2017) calculator. There were no systemic risks identified for re-entry into treated areas, however as there is an acute risk associated with exposure to the product, a re-entry statement is required on the label.

Public exposure

The product is intended for professional use and is not expected to be handled by members of the public. An assessment of risks associated with unintended bystander exposure to spray drift was determined, and no buffer zones were required.

Recommendations

The following first aid instructions, safety directions and precautionary (warning) statements are recommended for the product label.

First aid instructions

If poisoning occurs, contact a doctor or Poisons Information Centre. Phone Australia 131126; New Zealand 0800 764 766.

Safety directions

Will irritate the eyes. Avoid contact with eyes. When opening the container, mixing and preparing spray and using the prepared spray, wear cotton overalls buttoned to the neck and wrist (or equivalent clothing) and goggles or safety glasses. Wash hands after use. After each day's use, wash goggles or safety glasses and contaminated clothing.

Precautionary (warning) statements

WARNING – suspected of damaging the unborn child

Re-entry Statement

DO NOT allow entry into treated areas until spray has dried. If prior entry is required wear cotton overalls buttoned to the neck and wrist (or equivalent clothing). Clothing must be laundered after each day's use.

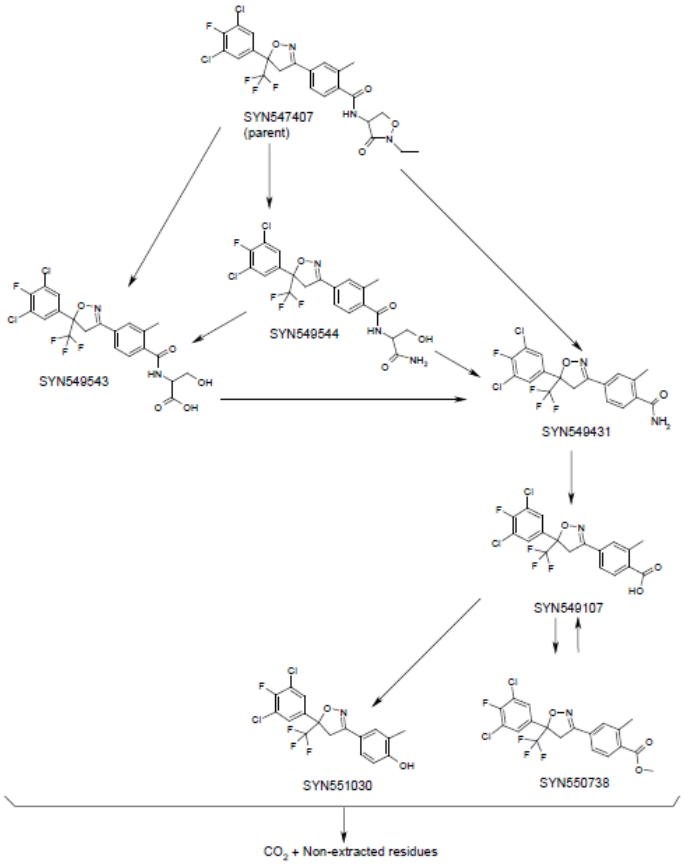
Environmental assessment

Fate and behaviour in the environment

Soil

Irradiation in the soil photolysis experiments with isocycloseram resulted in slow degradation in both dry and moist soils, with DT_{50} values of 46 and 61 days, respectively. There was no significant degradation found in the dark control samples. Extrapolated half-lives to natural sunlight conditions at 30 to 50°N corresponded to 85 and 112 days in dry and moist soils, respectively.

Isocycloseram was applied to nine soils in two laboratory studies as the active constituent under aerobic conditions, at 20°C in the dark, and its degradation rate evaluated. In all soils, degradation was described by first order kinetics (SFO). In one study (5 soils), $DegT_{50}$ values ranged from 56 to 293 days. In all soils in this study, isocycloseram degraded primarily via the opening of the oxoisoxazolidinyl ring to form either SYN549543 or SYN549544. Further hydrolysis of the amide in SYN549544 could also result in further formation of the carboxylic acid SYN549543. Elimination of the oxoisoxazolidinyl moiety yielded the primary amide, SYN549431. Further amide hydrolysis yielded the carboxylic acid, SYN549107. Methylation of SYN549107 yielded the methyl ester, SYN550738. Decarboxylation of the acid SYN549107 yielded the phenol metabolite, SYN551030. The proposed degradation pathway is shown graphically below.



In the second aerobic soil metabolisms study on four Brazilian soils, $DegT_{50}$ values ranged from 244 to 723 days. Combining the full data set, the geometric mean aerobic soil $DegT_{50}$ is 186 days. There were two major metabolites exceeding 10% AR, SYN549107 was formed at a maximum 26%. In separate laboratory testing on five soils, this metabolite degraded following first order kinetics in all except one soil. Modelling DT_{50} values ranged from 72 to 314 days (geomean 147 days). SYN550738 was formed at a maximum 11%. Degradation was biphasic in four of the five soils, and modelling DT_{50} values ranged from 19 to 360 days (geometric mean 60 days).

Under anaerobic soil conditions (one study, 4 soils), isocycloseram was less persistent with $DegT_{50}$ values all modelled following SFO kinetics and ranging from 37 to132 days (geomean 56 days). Under anaerobic conditions, isocycloseram is degraded by four principal transformation reactions: opening of the isoxazoline and oxoisoxazolidine rings via reduction and hydrolysis, cleavage of the β-hydroxy ketone moiety resulting from opening of the isoxazoline ring, ketone reduction, and amide hydrolysis.

A single field dissipation study from a site in Germany was provided. This study considered two treatments to bare soil with one plot remaining uncovered, and a second plot covered by a layer of sand following application, to minimise surface loss processes. In both cases, dissipation/degradation was best described by biphasic kinetics, and the FOMC model was applied in determining final values. Results were similar for modelling $DegT_{50}$ values, which were 452 to 470 days for the covered and uncovered plots, respectively. Residues of isocycloseram were retained in the top 30 cm soil layer. The SYN549107 metabolite was found at the highest levels, but still only at a maximum 3.5 g/ha at 533 DAT, which is <10% parent equivalent.

The mobility of isocycloseram and its major soil metabolites was tested with standard batch equilibrium studies. Freundlich KF values for isocycloseram (13 soils from 3 studies) ranged from 62 to 601 L/kg (KFOC 5890 to 21565 L/kg) indicating isocycloseram is unlikely to be significantly mobile in a soil environment. A positive relationship between KF and soil organic carbon was apparent, and regression derived KF values for 1%, 2% and 5% soil organic carbon are 51, 101 and 254 mL/g, respectively (mean 1/n 0.87). The two major soil metabolites were tested on six soils. Mean KF values for SYN549107 and SYN550738 were 31 and 3119 L/kg, respectively.

Water and sediment

Isocycloseram was stable in aqueous solution at pH 4 (DT_{50}>1000 days) and pH 7 (DT_{50} 262 days) at 25°C. At pH 9, isocycloseram hydrolysed quickly, and the DT_{50} values at 10°C and 25°C were 5.4 days and 1.4 days, respectively. The photolytic degradation was tested in a pH 4 buffer. Isocycloseram degraded slowly via cleavage of the oxoisoxazolidinyl ring forming the amide (SYN549431). Additionally, several minor degradates (<5% AR) were detected together with low amounts (≤5.8% AR) of radioactive carbon dioxide in the irradiated samples. Under continuous irradiation, the DT_{50} was 35 days, which corresponded to 72 and 234 days under midsummer sunlight (30 to 50°N) and Tokyo spring sunlight (35°C), respectively.

When applied to aerobic water-sediment systems that were incubated in the dark, isocycloseram was not persistent, with water DT_{50} values of 2.4 to 7.8 days, and whole system half-lives from 14 to 303 days. A total of 14 metabolites were identified of which eight were present at ≥10% AR in the total system. Three metabolites exceeded 10% AR in the water compartment (SYN549546 13%, SYN550602 12%, SYN550603 13%) and five metabolites exceeded 10% AR in the sediment compartment (SYN549433 10%, SYN550737 19%, SYN550602 22%, SYN550455 22%, SYN549546 28%).

When applied to anaerobic water-sediment systems that were incubated in the dark, isocycloseram was not persistent, with water DT_{50} values of 1.9 to 4.1 days and whole system half-lives of 2.2 to 5.2 days. A total of 13 were present at ≥10% AR in the total system. Eleven metabolites exceeded 10% AR in the water compartment (SYN549546 27%, SYN548569 47%, SYN549110 44%, SYN549557 35%, SYN550603 20%, SYN550321 18%, SYN551203 21%, SYN551415 20%, SYN551057 13%, SYN549433 10%, SYN551441 12%) and two metabolites exceeded 10% AR in the sediment compartment (SYN549546 53%, SYN548569 10%).

Isocycloseram is not readily biodegradable.

Air

Standard modelling was undertaken to predict the atmospheric half-life of isocycloseram through reaction with hydroxyl radicals. The DT_{50} from reaction with hydroxyl radicals is 6.2 hours (12h-day). Isocycloseram is not volatile (vapour pressure <6.2×10-6 Pa), so is not expected to partition to the atmospheric compartment and will not be subject to long-range transport thought the air.

Effects and associated risks to non-target species

Terrestrial vertebrates

Following gavage administration, isocycloseram had low acute toxicity to mammals (LD50>5000 mg ac/kg bw, *Rattus norvegicus*) and birds (LD50>2000 mg ac/kg bw, several species). However, short-term dietary exposure of birds resulted in an LDD50 of 528 mg ac/kg bw/d in one species (Anas platyrhynchos). The formulation does not enhance the toxicity to terrestrial vertebrates.

Following long-term dietary administration in reproduction studies, there was a significant reduction in the number of eggs laid at 86 mg ac/kg bw/d (NOEC 26 mg ac/kg bw/d, *Colinus virginianus*) and significant reductions in offspring survival, egg-shell thickness, and weights of 14-day old survivors at 53 mg ac/kg bw/d (NOEC 15 mg ac/kg bw/d, *Anas platyrhynchos*). In mammals, no adverse effects were observed in a two-generation reproductive toxicity study with the rat (NOEL 12 mg ac/kg bw/d, *Rattus norvegicus*).

Risks of isocycloseram to terrestrial vertebrates were determined to be acceptable under realistic, worst-case scenarios of dietary exposure within the treatment area at the maximum exposure rate. No protection statements are therefore required.

There were clear effects on avian reproduction to endpoints potentially affected by estrogen/androgen/thyroid/steroidogenesis (E,A,T,S) endocrine disrupting chemicals (egg production and embryo viability). However, risks to birds from dietary exposure were determined to be acceptable when considering these endpoints.

A food chain assessment indicated that any accumulated residues in earthworms or fish will not reach levels harmful to predators under the proposed conditions of use. Isocycloseram has low potential for accumulation in mammalian and fish tissue; therefore, it is expected that there will be no biomagnification up the food chain.

Aquatic species

Isocycloseram has high toxicity to fish (lowest LC50 0.13 mg ac/L, Oncorhynchus mykiss), acute invertebrates (lowest LC50 0.000018 mg ac/L, *Americamysis bahia*), sediment dwellers (lowest LC50 0.000015 mg ac/L, *Chironomus riparius*), and algae (lowest ErC50 0.27 mg ac/L, *Skeletonema costatum*), and moderate toxicity to aquatic plants (ErC50>1.2 mg ac/L, *Lemna gibba*). The representative DC formulation was not more toxic than technical isocycloseram to fish or algae; however, a notable increase in toxicity was observed in aquatic invertebrates (from EC50 0.52 to 0.017 mg ac/L, Daphnia magna). A protection statement is advised to identify the high toxicity of isocycloseram to aquatic species.

Following long-term exposure to isocycloseram, decreased growth of fish fry was observed at concentrations as low as 0.018 mg ac/L (NOEC 0.0081 mg ac/L, *Cyprinodon variegatus*). Parental survival and reproduction of aquatic invertebrates decreased in a dose-dependent manner (lowest EC10 0.0000024 mg ac/L, *Americamysis bahia*). Reduced growth of sediment dwellers was observed at concentrations as low as 0.00031 mg ac/kg dry sediment (NOEC 0.00077 mg ac/kg dry sediment, *Hyalella azteca*).

Mortality of aquatic invertebrates following acute exposure was determined to be the effect of greatest concern in aquatic systems due to the very high toxicity of isocycloseram and its low persistence in the water phase. Based on a species sensitivity distribution (SSD) of the acute toxicity values for 12 aquatic invertebrate species (including sediment dwellers), the best-fit HC5 was determined to be 0.011 µg ac/L, which was set as the regulatory acceptable level (RAL) in water. For the sediment phase, the RAL was set at 0.77 µg ac/kg dry sediment based on the *Hyalella azteca* NOEC.

A runoff assessment was performed which considered seasonal rainfall and site characteristics that are typical of horticultural and citrus growing regions of Australia. Acceptable risks could be concluded in most regions, provided that the product is not applied when a runoff event can be expected soon after application. Timing restrictions are required in Mackay/Whitsunday, where the product must not be applied to bulb vegetables in August-December, or to leafy vegetables in October-November.

To mitigate spray drift risks to aquatic species, a buffer zone of 350 metres is advised for a coarse spray quality and low boom height.

Bees and other non-target arthropods

Isocycloseram is toxic to adult bees (*Apis mellifera*) by contact exposure (LD50 0.26 µg ac/bee) and oral exposure (LD50 0.28 µg ac/bee), and very toxic to bee larvae (LD50 0.080 µg ac/bee). The representative DC formulation was approximately equivalent in toxicity. Following long-term dietary exposure to isocycloseram, there were significant effects on mortality of adult bees at daily dietary doses as low as 0.0050 µg ac/bee/d (NOEDD 0.0034 µg/bee/d), while emergence of bee larvae on day 22 was reduced in a dose dependent manner (ED10 0.018 µg/larvae/development period).

In semi-field studies, a representative DC formulation was applied to flowering *Phacelia tanacetifolia* or *Fagopyrum esculentum* after bee flight at rates ranging from 60 to 120 g ac/ha. No adverse effects were observed on adult mortality, foraging activity, or colony health in buckwheat; however, brood development was negatively impacted at 120 g ac/ha in *Phacelia* (NOER 90 g ac/ha). Considering the highest application

rate is equivalent to 30 g ac/ha, no adverse effects on bees are expected under field conditions provided the product is applied after bee flight.

In Tier 1 (glass plate) laboratory tests, fresh-dried residues of a representative DC formulation of isocycloseram were very toxic to the indicator species of predatory arthropods (LR50 0.0059 g ac/ha, *Typhlodromus pyri*) and parasitic arthropods (LR50 0.43 g ac/ha, *Aphidius rhopalosiphi*). There is no information available on the toxicity of isocycloseram to other arthropod species or under more realistic conditions. Based on the high toxicity observed in the laboratory tests, use of the product is not considered to be compatible with integrated pest management (IPM) programs utilising ground-dwelling arthropods.

Soil organisms

Isocycloseram has low toxicity to soil macro-organisms such as earthworms (LC50corr >500 mg ac/kg dry soil, Eisenia fetida). Following long-term exposure, reproduction of soil macro-organisms was inhibited in a dose-dependent manner in two of three test species (lowest EC10 0.11 mg ac/kg dry soil, *Hypoaspis acuifer*). The S-enantiomers of the major soil metabolites SYN549107 and SYN550738 were less toxic than the parent substance. Isocycloseram did not adversely affect soil processes such as nitrogen transformation at the highest tested concentration (NOEC 5.0 mg ac/kg dry soil). The representative DC formulation was not more toxic to soil organisms than technical isocycloseram.

Risks of isocycloseram to soil organisms were determined to be acceptable under the realistic worst-case scenario of a direct overspray of soil without interception at the maximum exposure rate. Therefore, no protection statements are required for soil organisms.

Non-target terrestrial plants

The effects of an SC formulation of isocycloseram on ten crop species were examined following a pre-emergent (seedling emergence) and post-emergent (vegetative vigour) spray application. The highest rate tested in both studies was 814 g ac/ha, and no effects on any species were observed in the vegetative vigour study. In the seedling emergence study, no effects were observed in 8 of the 10 species. The most sensitive plant was *Beta vulgaris* with a NOER of 90 g ac/ha due to effects on dry weight at rates higher than this. For this species, the ER25 was empirically estimated to be 814 g ac/ha, the highest tested rate.

Risks of isocycloseram to non-target terrestrial plants were determined to be acceptable under the realistic worst-case scenario of direct exposure at the maximum exposure rate. Therefore, no protection statements are required for non-target terrestrial plants.

Recommendations

In considering the environmental safety of the proposed use of Simodis Plinazolin Technology Insecticide, the APVMA had regard to the toxicity of the active constituent in relation to relevant organisms and ecosystems. Based on the available information, the APVMA can be satisfied that the proposed use of the product is unlikely to have an unintended effect that is harmful to animals, plants or things or to the environment.

Efficacy and safety assessment

Proposed product use pattern

Proposed uses for Simodis Plinazolin technology Insecticide (abbreviated to Simodis herein) are for the control of various insect and mite pests in brassica vegetables, leafy vegetables, fruiting vegetables, cucurbits and bulb vegetables. It will be applied by ground boom at the same rate of 30 g ai/ha (300 mL/ha) per spray application, for all crops and pest species. No aerial or vertical sprayer application uses are being sought. A maximum of 2 applications per crop, with a minimum retreatment interval of 7-days, is proposed for all target pests and crop types. Use of an appropriate adjuvant with Simodis is recommended to ensure thorough coverage of the target crop.

Efficacy and target crop safety

Efficacy and crop safety was assessed in brassica vegetables, bulb vegetables, cucurbits and fruiting vegetables in 45 Australian field trials, conducted in Queensland, New South Wales, Victoria, Western Australia, South Australia and Tasmania, between 2017 and 2020. Six field trials were also conducted in fruiting vegetables overseas (Korea, Vietnam and Bangladesh). All trials used appropriate experimental designs, locations, timing, methods of spray application and pest assessment methodology, with 3 or 4 replicates. The trial data was analysed using appropriate statistical tests.

Efficacy assessments were made by comparing numbers of insects or mites on Simodis treated plants alongside plants treated with several registered industry standards (applied at label rates) and an untreated control. In some trials, the incidence of pest damage to fruit and/or foliage was also assessed. Assessments were made before treatment and at varying intervals after treatment. In most trials, two consecutive spray applications were made (range= 1 to 4), approximately 1 or 2 weeks apart. Efficacy of a range of Simodis rates were tested, with or without a spray adjuvant and using various droplet sizes.

Phytotoxicity was assessed by scoring the percentage of the total area of fruit or foliage affected by chlorosis and/or necrosis, on a scale ranging from 0 (nil effect) to 100 (complete loss of crop). Other phytotoxicity symptoms or plot differences were recorded if present.

Efficacy

Brassica vegetables and Brassica leafy vegetables

Proposed uses for Simodis in brassica vegetables and brassica leafy vegetables are:

- control of Diamondback moth (DBM) (*Plutella xylostella*) and Cabbage white butterfly (*Pieris rapae*)
- suppression of Heliothis (*Helicoverpa* spp.).

Data from 11 trials, conducted in various brassica vegetables (Brussel Sprouts, Broccoli, Cauliflower and Cabbage), were provided to support the label claim. Simodis was applied at 25, 50, 100, 200 or 300 mL/ha and compared to industry standards applied at the recommended label rate. In all trials and target pests, levels of control/suppression achieved by Simodis was equivalent to, or greater than, industry standards

containing spirotetramat, flubendiamide, indoxacarb, chlorantraniliprole, emamectin benzoate, fipronil and spinetoram. A significant reduction in total numbers of DBM and Cabbage White butterfly larvae and suppression of *Heliothis* larvae was observed at 300 mL/ha. As per the other proposed lepidopteran control claims, the label recommends mixing Simodis with a non-ionic surfactant (Agral 600 SL) at 10 mL/100 L of spray mixture to ensure thorough spray coverage. A maximum of two spray applications per crop, with a minimum spray interval of 7 days, is recommended on the label. Label comments also recommend commencing spray applications once local economic thresholds have been achieved based on crop monitoring. Sprays are to be applied at egg hatch or very soon afterwards, to target young larvae and avoid treatment of established populations dominated by large larvae.

Bulb vegetables

Proposed uses of Simodis in bulb vegetables are:

- suppression of onion thrips (*Thrips tabaci*) and plague thrips (*Thrips imaginis*).

Data from nine field trials on onion thrips and one trial on plague thrips were submitted to support the label claims. Rates of Simodis tested ranged from 150 to 750 mL/ha. Efficacy was compared with industry standards containing spirotetramat or methidathion applied at recommended label rates. Overall, the results were consistent with Simodis applied at the proposed label rates achieving levels of thrips suppression equivalent to the industry standards, but this was dependent on the adjuvant used and application of two spray applications. Although efficacy of Simodis was equivalent to industry standards, the applicant has chosen to register the product in bulb vegetables for “suppression only” of onion thrips and plague thrips. As with other proposed uses, the label recommends mixing Simodis with specific adjuvants at 60 mL/100 L of spray mixture. A maximum of two spray applications per crop, with a minimum spray interval of 7 days, is recommended on the label.

Cucurbits

Proposed uses in cucurbits are:

- control of Two-spotted Mite (*Tetranychus urticae*) and Cucumber Moth (*Diaphania indica*)
- suppression of Broad Mite (*Polyphagotarsonemus latus*) and Bean Red Spider Mite (*Tetranychus ludeni*), Western Flower Thrips (*Frankliniella occidentalis*), Tomato Thrips (*Frankliniella schultzei*), Melon Thrips (*Thrips palmi*), Plague Thrips (*Thrips imaginis*) and Heliothis (*Helicoverpa spp.*).

Data from 10 Australian efficacy trials, conducted in various cucurbit crops (cucumber, pumpkin, watermelon and zucchini), supported these uses. Simodis was applied at various rates to determine efficacy against cucurbit pests, ranging from 25 to 750 mL/ha. For the control/suppression of mites and thrips, Simodis was equivalent to, if not superior to, several industry standards containing the actives spirotetramat, emamectin benzoate, spinetoram, abamectin, bifenazate, cyantraniliprole+ diafenthiuron, propargite and diafenthiuron. For control/suppression of cucumber moth and *Heliothis*, Simodis was equivalent to registered insecticides containing cyantraniliprole+ diafenthiuron, spinetoram, emamectin benzoate, chlorantraniliprole, flubendiamide and lambda-cyhalothrin+ chlorantraniliprole. As with other proposed uses, the label recommends mixing Simodis with specific adjuvants at a rate of 10 mL per 100 L of spray mixture. A

maximum of two spray applications per crop, with a minimum spray interval of 7 days, is recommended on the label.

Fruiting vegetables

Proposed uses in Fruiting vegetables are:

- control of Two-spotted Mite (*Tetranychus urticae*) and Broad Mite (*Polyphagotarsonemus latus*)
- suppression of Tomato Russet Mite (*Aculops lycopersici*), Western Flower Thrips (*Frankliniella occidentalis*), Tomato Thrips (*Frankliniella schultzei*), Melon Thrips (*Thrips palmi*), Plague Thrips (*Thrips imaginis*) and Heliothis (*Helicoverpa spp.*).

Data from 19 efficacy trials conducted in Australia and overseas in various fruiting vegetable crops (tomato, capsicum, chilli and eggplant) supported these uses. Simodis was applied at various rates to determine efficacy against fruiting vegetable pests, ranging from 50 to 1200 mL/ha. When applied at the proposed label rates, Simodis was equivalent to, if not superior to, all industry standards tested alongside, including those containing the actives spirotetramat, emamectin benzoate, spinetoram, abamectin, bifenazate, cyantraniliprole+ diafenthiuron, propargite and diafenthiuron. As with other proposed uses, the label recommends mixing Simodis with specific adjuvants at a rate of 10 mL per 100 L of spray mixture. A maximum of two spray applications per crop, with a minimum spray interval of 7 days, is recommended on the label.

Crop safety

Nil phytotoxicity was observed in all efficacy trials, for all crops tested and for all rates of Simodis applied. For brassica vegetables, the maximum rate of Simodis used in 9 efficacy trials was 300 mL/ha (1× the proposed label rate). Data submitted for residue trials also confirmed crop safety of Simodis when applied in brassica vegetables at 2× the proposed label rate. For bulb vegetables, the maximum application rate used in efficacy trials was 2.5× in 3 trials. Data from a further 11 residues trials confirmed crop safety of Simodis when applied in onions, leeks and spring onions at up to 4× the proposed label rates. For cucurbits, crop safety was assessed in 10 efficacy trials in five types of cucurbits with the maximum rate applied being 2.5× in 4 trials. Data from another 8 residue trials confirmed crop safety of Simodis applied in cucurbits (rockmelon, zucchini and cucumber) at up to 4× proposed label rate. For fruiting vegetables, crop safety was assessed in 19 efficacy trials (13 in Australia) in 4 types of fruiting vegetables, with a maximum rate of 2.5× in 5 Australian trials and 4× in one overseas trial. A further 9 residue trials confirmed crop safety of Simodis when applied at up to 4× the proposed maximum label rate to fruiting vegetables (tomatoes, capsicum).

Resistance management

The active constituent in Simodis, isocycloseram, has a mode of action corresponding to Group 30 of the international insecticide mode of action scheme (IRAC 2021). Isocycloseram represents the first registration of a Group 30 insecticide for use in field crops in Australia. To date, no cross-resistance to active constituents with other modes of action has been identified. Therefore, Simodis will provide growers with a useful control agent, with a different mode of action, for rotation in resistance management programs. The proposed label contains a standard Insecticide Resistance Warning with advice on strategies to avoid or delay the selection of resistant insects. To manage insecticide resistance, users are advised not to apply

sequential applications of Simodis and, if retreatment is required, to rotate with an active constituent with a different mode of action. The label also refers users to follow specific CropLife resistance management strategies for each pest, where applicable.

Recommendations

The results of the field trials confirmed efficacy and crop safety for the proposed product, when used according to label directions.

The APVMA has no objections on efficacy and target-crop safety grounds to the registration of Simodis Plinazolin Technology Insecticide.

Spray drift assessment

Regulatory Acceptable Levels (RALs) were established by each risk area in order to calculate the appropriate spray drift buffer zones for Simodis Plinazolin Technology Insecticide (Table 6).

Table 7: Summary of RALs for Simodis Plinazolin Technology Insecticide

Sensitive area	Regulatory Acceptable Level	
	Level of active	Units
Bystander	476	g/ha
Livestock	0.77	ppm
Aquatic	0.011	µg/L
Pollinator	43	g/ha
Vegetation	407	µg/L

Buffer zones calculated by the APVMA Spray Drift Risk Assessment Tool (SDRAT) using the above RALs, were incorporated into the Simodis Plinazolin Technology Insecticide label spray drift instructions (see Labelling Requirements below).

Labelling requirements

POISON

KEEP OUT OF REACH OF CHILDREN
READ SAFETY DIRECTIONS BEFORE OPENING OR USING

Simodis®

PLINAZOLIN® technology Insecticide

syngenta®

ACTIVE CONSTITUENT: 100 g/L ISOCYCLOSERAM

GROUP	30	INSECTICIDE

For control of certain insect and mite pests in Vegetables as per the Directions for Use

1 to 5 LITRES

DC	Formulation Type **Dispersible Concentrate**

Directions for use

Restraints:

DO NOT apply by aircraft

DO NOT apply by a vertical sprayer

DO NOT apply if heavy rains or storms that are likely to cause runoff are forecast within 3 days

DO NOT apply to bulb vegetables in Mackay/Whitsunday in August to end of December

DO NOT apply to leafy vegetables in Mackay/Whitsunday in October to end of November

DO NOT irrigate to the point of water runoff for at least 3 days after application

DO NOT apply more than 2 applications of SIMODIS® per crop

DO NOT apply to nursery crops

Spray Drift Restraints:

Specific definitions for terms used in this section of the label can be found at apvma.gov.au/spraydrift.

DO NOT allow bystanders to come into contact with the spray cloud.

DO NOT apply in a manner that may cause an unacceptable impact to native vegetation, agricultural crops, landscaped gardens and aquaculture production, or cause contamination of plant or livestock commodities, outside the application site from spray drift. The buffer zones in the buffer zone table below provide guidance but may not be sufficient in all situations. Wherever possible, correctly use application equipment designed to reduce spray drift and apply when the wind direction is away from these sensitive areas.

DO NOT apply unless the wind speed is between 3 and 20 kilometres per hour at the application site during the time of application.

DO NOT apply if there are hazardous surface temperature inversion conditions present at the application site during the time of application. Surface temperature inversion conditions exist most evenings one to two hours before sunset and persist until one to two hours after sunrise.

DO NOT apply by a boom sprayer unless the following requirements are met:

Spray droplets are not smaller than a coarse spray droplet size category.

Minimum distances between the application site and downwind sensitive areas are observed (see ‘Mandatory downwind buffer zones’ section of the following table titled ‘Buffer zones for boom sprayers’).

Buffer zones for boom sprayers

Application rate	Boom height above the target canopy	Mandatory downwind buffer zones				
		Natural aquatic areas	Vegetation areas	Bystander areas	Pollinator areas	Livestock areas
Up to 300 mL/ha	0.5 m or lower	350 metres	0 metres	0 metres	0 metres	0 metres

Crop	Pest	Rate	Critical Comments
Brassica vegetables (Broccoli, Broccolini, Brussels Sprouts, Cabbage, Cauliflower, Kohlrabi) Brassica leafy vegetables including Bok Choy, Chinese Broccoli (Gai Lum/Gai Lan/Kai Lan), Chinese Cabbage (Pet Sai/Wombok/Haksukai), Choy Sum, Gai Choy/Am Soy/Kai Choy, Kale, Mibuna, Mustard (Leafy) including Indian Mustard and Mustard Spinach (Komatsuma), Pak Choy, Tat Soy	Diamondback Moth (*Plutella xylostella*), Cabbage White Butterfly (*Pieris rapae*) Suppression of: Heliothis (*Helicoverpa spp.*)	300 mL/ha plus adjuvant Δ	Monitor crops and commence SIMODIS® applications immediately once local economic spray thresholds are reached. Apply at egg hatch or very soon after egg hatch to target young larvae. Avoid applying SIMODIS® to established populations dominated by large, late instar larvae. Continue to monitor crops and make subsequent applications as required. DO NOT re-apply within 7 days of a previous SIMODIS® spray. DO NOT apply more than 2 applications per crop. Ensure thorough coverage of the target crop – refer to the Application section in General instructions. Δ Always add a specified non-ionic surfactant – refer to the Adjuvant section in General instructions. Note: This use is subject to a CropLife resistance management strategy. Refer to www.croplife.org.au for more information.

Crop	Pest	Rate	Critical Comments
Bulb vegetables (including Garlic, Onion Bulb, Spring Onion and Leeks)	Suppression of Onion Thrips (*Thrips tabaci*), Plague Thrips (*Thrips imaginis*)	300 mL/ha plus adjuvant Δ	Monitor crops and commence SIMODIS® applications once local economic spray thresholds are reached. Continue to monitor crops and make subsequent applications as required. DO NOT re-apply within 7 days of a previous SIMODIS® spray. DO NOT apply more than 2 applications per crop. Ensure thorough coverage of the target crop – refer to the Application section in General instructions. Δ Always add a specified adjuvant – refer to the Adjuvant section in General instructions.

Crop	Pest	Rate	Critical Comments
Cucurbits Open field only	Two-spotted Mite (*Tetranychus urticae*), Suppression of Broad Mite (*Polyphagotarsonemus latus*), Bean Red Spider Mite (*Tetranychus ludeni*)	300 mL/ha plus adjuvant Δ	Monitor crops and commence SIMODIS® applications immediately once local economic spray thresholds are reached. Best results will be achieved when spray is applied to low mite populations. Avoid applying SIMODIS® to high established mite populations. Use the higher application rate where extended residual control is required. To manage insecticide resistance, DO NOT apply sequential applications of SIMODIS® for mite control. If retreatment is required, apply a miticide from a different chemical group, before using SIMODIS® again. DO NOT apply more than 2 applications per crop. Ensure thorough coverage of the target crop – refer to the Application section in General instructions. Δ Always add a specified non-ionic surfactant – refer to the Adjuvant section in General instructions.

Crop	Pest	Rate	Critical Comments
	Cucumber Moth (Diaphania indica) Suppression of Western Flower Thrips (Frankliniella occidentalis), Tomato Thrips (Frankliniella schultzei), Melon Thrips (Thrips palmi), Plague Thrips (Thrips imaginis), Heliothis (Helicoverpa spp.)		Monitor crops and commence SIMODIS® applications once local economic spray thresholds are reached. Heliothis: Apply at egg hatch or very soon after egg hatch to target young larvae. Continue to monitor crops and make subsequent applications as necessary. DO NOT re-apply within 7 days of a previous SIMODIS® spray. DO NOT apply more than 2 applications per crop. Ensure thorough coverage of the target crop – refer to the Application section in General instructions. Δ Always add a specified non-ionic surfactant – refer to the Adjuvant section in General instructions. Note: This use is subject to a CropLife resistance management strategy. Refer to www.croplife.org.au for more information.

Crop	Pest	Rate	Critical Comments
Fruiting Vegetables (including Capsicum, Chilli, Eggplant and Tomato) Open field only	Two-spotted Mite (*Tetranychus urticae*), Broad Mite (*Polyphagotarsonemus latus*) Suppression of Tomato Russet Mite (*Aculops lycopersici*), Western Flower Thrips (*Frankliniella occidentalis*), Tomato Thrips (*Frankliniella schultzei*). Melon Thrips (*Thrips palmi*), Plague Thrips *(Thrips imaginis),* Heliothis (*Helicoverpa* spp.)	300 mL/ha plus adjuvant [Δ]	Monitor crops and commence SIMODIS® applications once local economic spray thresholds are reached. Best results will be achieved when spray is applied to low mite populations. Avoid applying SIMODIS® to high, established mite populations. Heliothis: Apply at egg hatch or very soon after egg hatch to target young larvae. To manage insecticide resistance, DO NOT apply sequential applications of SIMODIS® for mite control. If retreatment is required, apply a miticide from a different chemical group, before using SIMODIS® again. For thrips and Heliothis, continue to monitor crops and make subsequent applications as necessary. DO NOT re-apply within 7 days of a previous SIMODIS® spray. DO NOT apply more than 2 applications per crop. Ensure thorough coverage of the target crop – refer to the Application section in General instructions. [A]lways add a specified non-ionic surfactant – refer to the Adjuvant section in General instructions. Note: This use is subject to a CropLife resistance management strategy. Refer to www.croplife.org.au for more information.

Not to be used for any purpose, or in any manner, contrary to this label unless authorised under appropriate legislation

Withholding periods

Brassica Vegetables, Brassica Leafy Vegetables

Harvest: Do not harvest for 3 days after application

Grazing: Do not use treated crop, crop waste or produce for stock food

Bulb Vegetables

Do not harvest for 7 days after application

Cucurbits and Fruiting Vegetables

Harvest: Do not harvest for 1 day after application

Grazing: Do not use treated crop, crop waste or produce for stock food

General instructions

Mixing

SIMODIS® PLINAZOLIN® technology Insecticide is a Dispersible Concentrate (DC) formulation that mixes readily with water and is applied as a foliar spray.

Measure the required amount SIMODIS®, add to the partly filled spray tank, and then add the remainder of the water.

Adjuvant

Vegetables (except bulb vegetables): Apply SIMODIS® with a non-ionic adjuvant such as AGRAL® Spray Adjuvant Δ at 10 mL per 100 L of spray mixture.

Bulb vegetables (including bulb onions, garlic, spring onions and leeks): Apply SIMODIS® with Maxx Organosilicone Surfactant*Δ at 60 mL per 100 L of spray mixture.

Δ or other specified adjuvant – refer to Syngenta Australia Pty Ltd representative for information

Application

Thorough coverage of the target area is essential. Apply in sufficient water and adjust water volumes according to the crop growth stage. Use suitable application parameters (nozzles, pressure, boom height, speed, etc.) to ensure thorough and even coverage. Use only COARSE spray droplets according to nozzle manufacturers specifications that refer to the ASAE S572 standard or the BCPC guideline.

Compatibility

SIMODIS® may be mixed with the following crop protection products: ORONDIS® Flexi Fungicide, AMISTAR® 250 SC Fungicide, AGRAL® Spray Adjuvant, ADIGOR® Spray Adjuvant and Maxx Organosilicone Surfactant*. For the latest information on the compatibility of SIMODIS® with other products, contact your local Syngenta representative.

Insecticide Resistance Warning	GROUP	30	INSECTICIDE

For insecticide resistance management, SIMODIS® PLINAZOLIN® technology Insecticide is a Group 30 insecticide. Some naturally occurring insect biotypes resistant to SIMODIS® and other Group 30 insecticides may exist through normal genetic variability in any insect population. The resistant individuals can eventually dominate the insect population if SIMODIS® or other Group 30 insecticides are used repeatedly. The effectiveness of SIMODIS® on resistant individuals could be significantly reduced. Since occurrence of resistant individuals is difficult to detect prior to use, Syngenta Australia Pty Ltd accepts no liability for any losses that may result from the failure SIMODIS® to control resistant insects. For further information contact your local supplier, Syngenta representative or local agricultural department agronomist.

In order to avoid or delay the selection of resistant insects, Group 30 insecticides should be used as part of an insecticide resistance management (IRM) strategy which incorporates the following:

Insecticides from the same mode of action group should not be used to treat successive generations of the target pest.

Multiple applications of SIMODIS® and other products containing Group 30 insecticides may be applied successively but only when targeting a single generation of the target insect.

DO NOT apply sequential applications of SIMODIS® for mite control. If retreatment is required, apply a miticide from a different chemical group before using SIMODIS® again.

If more than one application of an insecticide is required to control successive generations of the target pest then alternative insecticides with different modes of action should be utilised in rotation with SIMODIS®.

Where possible incorporate alternative methods of pest control as part of an integrated pest management (IPM) approach.

Precautions

Re-entry Period: DO NOT allow entry into treated areas until spray has dried. If prior entry is required wear cotton overalls buttoned to the neck and wrist (or equivalent clothing). Clothing must be laundered after each day's use.

Protection of honeybees

Toxic to bees and harmful to bee brood. DO NOT apply to crops from the onset of flowering until flowering is complete unless the application is made in the time period between 2 hours prior to sunset and 8 hours prior to sunrise. DO NOT allow spray drift to flowering weeds or flowering crops in the vicinity of the treatment area. Before spraying, notify beekeepers to move hives to a safe location with an untreated source of nectar and pollen, if there is potential for managed hives to be affected by the spray or spray drift.

Integrated pest management

Toxic to beneficial arthropods. Not compatible with integrated pest management (IPM) programs utilising beneficial arthropods. Minimise spray drift to reduce harmful effects on beneficial arthropods in non-crop areas.

Protection of wildlife, fish, crustaceans and environment

Very toxic to aquatic life. DO NOT contaminate wetlands or watercourses with this product or used containers.

Storage and disposal

Store in the closed original container in a cool, well-ventilated area. DO NOT store for prolonged periods in direct sunlight.

Non-refillable containers: Triple rinse containers before disposal. Add rinsings to treatment tank. DO NOT dispose of undiluted chemicals on site. If recycling, replace cap and return clean containers to recycler or designated collection point. If not recycling, break, crush or puncture and deliver empty packaging for appropriate disposal to an approved waste management facility. If an approved waste management facility is not available bury the empty packaging 500 mm below the surface in a disposal pit specifically marked and set up for this purpose, clear of waterways, desirable vegetation and tree roots, in compliance with relevant Local, State or Territory government regulations. DO NOT burn empty containers or product.

Refillable containers: Empty contents fully into application equipment. Close all valves and return to point of supply for refill or storage.

Safety directions

Will irritate the eyes. Avoid contact with eyes. When opening the container, mixing and preparing spray and using the prepared spray, wear cotton overalls buttoned to the neck and wrist (or equivalent clothing) and goggles or safety glasses.

Wash hands after use. After each day’s use wash goggles or safety glasses and contaminated clothing.

First aid

If poisoning occurs contact a doctor or Poisons Information Centre. Phone 131 126.

WARNING - Suspected of damaging the unborn child.

Acronyms and abbreviations

Shortened term	Full term
ac	Active constituent
ADI	Acceptable daily intake (for humans)
ai	Active ingredient
ARfD	Acute reference dose
bw	Bodyweight
d	Day
DAT	Days after treatment
DT_{50}	Time taken for 50% of the concentration to dissipate
EC_{50}	Concentration at which 50% of the test population are immobilised
E_rC_{50}	Concentration at which the rate of growth of 50% of the test population is impacted
g	Gram
h	Hour
ha	Hectare
HPLC	High pressure liquid chromatography *or* high-performance liquid chromatography
IPM	Integrated pest management
in vitro	Outside the living body and in an artificial environment
in vivo	Inside the living body of a plant or animal
kg	Kilogram
K_{OC}	Organic carbon partitioning coefficient
L	Litre
LC_{50}	concentration that kills 50% of the test population of organisms
LD_{50}	dosage of chemical that kills 50% of the test population of organisms
LOD	Limit of Detection – level at which residues can be detected
Log K_{OW}	Log to base 10 of octanol water partitioning co-efficient, synonym P_{OW}
LOQ	Limit of Quantitation – level at which residues can be quantified

Shortened term	Full term
mg	Milligram
mL	Millilitre
MRL	Maximum residue limit
MSDS	Material safety data sheet
NEDI	National estimated daily intake
NESTI	National Estimated Short-Term Intake
ng	Nanogram
NOAEL	No observed adverse effect level
PPE	Personal protective equipment
ppm	Parts per million
s	Second
SC	Suspension concentrate
µg	Microgram

Glossary

Term	Description
Active constituent	The substance that is primarily responsible for the effect produced by a chemical product
Acute	Having rapid onset and of short duration
Carcinogenicity	The ability to cause cancer
Chronic	Of long duration
Codex MRL	Internationally published standard maximum residue limit
Desorption	Removal of a material from or through a surface
Efficacy	Production of the desired effect
Formulation	A combination of both active and inactive constituents to form the end use product
Genotoxicity	The ability to damage genetic material
Henry's law constant	A gas law that states that the amount of dissolved gas in a liquid is proportional to its partial pressure above the liquid
Hydrophobic	Repels water
IUPAC name	International Union of Pure and Applied Chemistry naming scheme for organic compounds
Leaching	Removal of a compound by use of a solvent
Metabolism	The chemical processes that maintain living organisms
Photodegradation	Breakdown of chemicals due to the action of light
Photolysis	Breakdown of chemicals due to the action of light
Subcutaneous	Under the skin
Toxicokinetics	The study of the movement of toxins through the body
Toxicology	The study of the nature and effects of poisons

References

Insecticide Resistance Action Committee (IRAC), 2021. *IRAC mode of action classification scheme, issued September 2021, v. 10.1*, IRAC website.