WHO SPECIFICATIONS AND EVALUATIONS FOR PUBLIC HEALTH PESTICIDES

ISOCYCLOSERAM

World Health Organization

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DISCLAIMER[1]

WHO specifications are developed with the basic objective of promoting, as far as practicable, the manufacture, distribution and use of pesticides that meet basic quality requirements.

Compliance with the specifications does not constitute an endorsement or warranty of the fitness of a particular pesticide for a particular purpose, including its suitability for the control of any given pest, or its suitability for use in a particular area. Owing to the complexity of the problems involved, the suitability of pesticides for a particular purpose and the content of the labelling instructions must be decided at the national or provincial level.

Furthermore, pesticides which are manufactured to comply with these specifications are not exempted from any safety regulation or other legal or administrative provision applicable to their manufacture, sale, transportation, storage, handling, preparation and/or use.

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Additionally, WHO wishes to alert users to the fact that improper storage, handling, preparation and/or use of pesticides can result in either a lowering or complete loss of safety and/or efficacy.

WHO is not responsible, and does not accept any liability, for the testing of pesticides for compliance with the specifications, nor for any methods recommended and/or used for testing compliance. As a result, WHO does not in any way warrant or represent that any pesticide claimed to comply with a WHO specification actually does so.

[1] This disclaimer applies to all specifications published by WHO.

INTRODUCTION

WHO establishes and publishes specifications[1] for technical material and related formulations of public health pesticides with the objective that these specifications may be used to provide an international point of reference against which products can be judged either for regulatory purposes or in commercial dealings.

From 2002, the development of WHO specifications follows the **New Procedure**, described in the "Manual on the development and use of FAO and WHO specifications for chemical pesticides." This **New Procedure** follows a formal and transparent evaluation process. It describes the minimum data package, the procedure and evaluation applied by WHO and the experts of the FAO/WHO Joint Meeting on Pesticide Specifications (JMPS).

WHO specifications now only apply to products for which the technical materials have been evaluated. Consequently, from the year 2002 onwards, the publication of WHO specifications under the **New Procedure** has changed. Every specification consists now of two parts, namely the specifications and the evaluation report(s):

Part One: The Specification of the technical material and the related formulations of the pesticide in accordance with chapters 4 to 8 of the above-mentioned manual.

Part Two: The Evaluation Report(s) of the pesticide, reflecting the evaluation of the data package carried out by WHO and the JMPS. The data are provided by the manufacturer(s) according to the requirements of chapter 3 of the above-mentioned manual and supported by other information sources. Evaluation reports include the name(s) of the manufacturer(s) whose technical material has been evaluated. Evaluation reports on specifications developed subsequently to the original set of specifications are added in chronological order to this report.

WHO specifications under the **New Procedure** do not necessarily apply to nominally similar products of other manufacturer(s), nor to those where the active ingredient is produced by other routes of manufacture. WHO has the possibility to extend the scope of the specifications to similar products but only when the JMPS has been satisfied that the additional products are equivalent to that which formed the basis of the reference specification.

Specifications bear the date (month and year) of publication of the current version. Evaluations bear the date (year) of the meeting at which the recommendations were made by the JMPS.

[1] Publications available on the WHO Prequalification Unit – Vector Control Product Assessment Team (PQT/VCP) website: https://extranet.who.int/prequal/vector-control-products

PART ONE: SPECIFICATIONS

ISOCYCLOSERAM

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ISOCYCLOSERAM INFORMATION

ISO common name: Isocycloseram

Synonyms: SYN547407

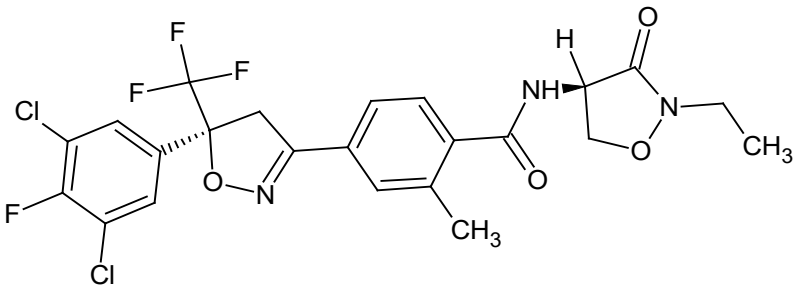
Chemical names:

IUPAC (PIN): mixture comprised of 80–100% 4-[(5*S*)-5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydro-1,2-oxazol-3-yl]-*N*-[(4*R*)-2-ethyl-3-oxo-1,2-oxazolidin-4-yl]-2-methylbenzamide and 20–0% of the (5*R*,4*R*), (5*R*,4*S*) and (5*S*,4*S*) isomers

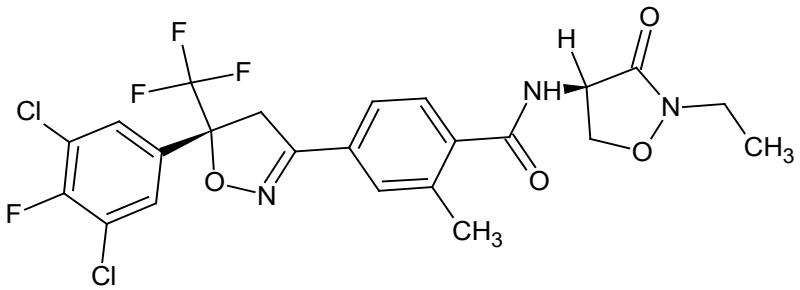
CA: 4-[5-(3,5-dichloro-4-fluorophenyl)-4,5-dihydro-5-(trifluoromethyl)-3-isoxazolyl]-*N*-(2-ethyl-3-oxo-4-isoxazolidinyl)-2-methylbenzamide

Structural formulae:

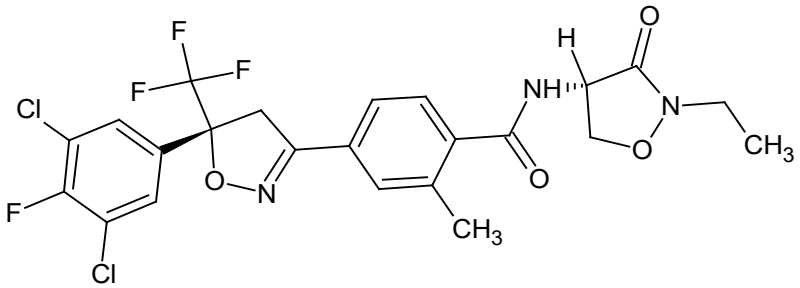
5S,4R-isomer



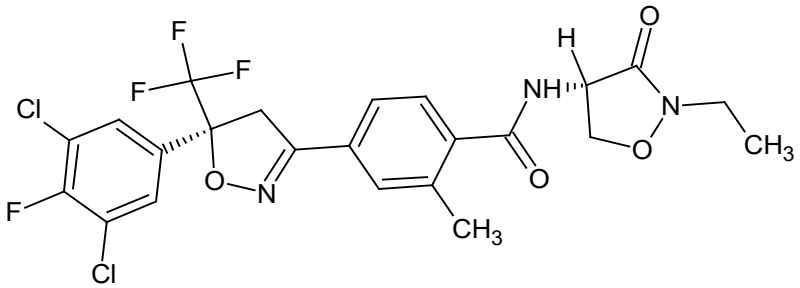
5R,4R-isomer



5R,4S-isomer



5S,4S-isomer



Molecular formula:	$C_{23}H_{19}Cl_2F_4N_3O_4$
Relative molecular mass:	548.3
CAS Registry number:	2061933-85-3
CIPAC number:	1025
Identity tests:	HPLC retention time, UV spectrum, IR spectrum.

ISOCYCLOSERAM TECHNICAL MATERIAL

WHO Specification 1025/TC (April 2025*)

This specification, which is PART ONE of this publication, is based on an evaluation of data submitted by the manufacturers whose names are listed in the evaluation reports (1025/2025.1). This specification should be applicable to TC produced by these manufacturers, but it is not an endorsement of those products nor a guarantee that they comply with the specification. The specification may not be appropriate for TC produced by other manufacturers. The evaluation reports (1025/2025.1), as PART TWO, form an integral part of this publication.

1 Description

The material shall consist of isocycloseram together with related manufacturing impurities, in the form of a white to beige powder, and shall be free from visible extraneous matter and added modifying agents, except stabilizers if required.

2 Active ingredient

2.1 Identity tests (1025/TC/M/2, CIPAC Handbook Q, p.86, 2024)

The active ingredient shall comply with an identity test and, where the identity remains in doubt, shall comply with at least one additional test.

2.2 Isocycloseram content (1025/TC/M/3, CIPAC Handbook Q, p.89, 2024)

The isocycloseram content shall be declared (not less than 960 g/kg) and, when determined, the average measured content shall not be lower than the declared minimum content.

2.3 Isocycloseram isomer ratio (1025/TC/M/2.2, CIPAC Handbook Q, p.86, 2024)

The isocycloseram 5S,4R-isomer content shall be at least 80% of the total isocycloseram content as measured under 2.2.

* Specifications may be revised and/or additional evaluations may be undertaken. Ensure the use of current versions by checking at the WHO Prequalification Unit – Vector Control Product Assessment Team (PQT/VCP) website: https://extranet.who.int/prequal/vector-control-products/specifications-new-procedure

ISOCYCLOSERAM WETTABLE POWDER IN SEALED WATER-SOLUBLE BAG

WHO Specification 1025/WP-SB (August 2025*)

This specification, which is PART ONE of this publication, is based on an evaluation of data submitted by the manufacturers whose names are listed in the evaluation reports (1025/2025.2). This specification should be applicable to relevant products of these manufacturers and those of any other formulators who use only TC from the evaluated sources. The specification is not an endorsement of those products nor a guarantee that they comply with the specification. The specification may not be appropriate for the products of other manufacturers who use TC from other sources. The evaluation reports (1025/2025.2), as PART TWO, form an integral part of this publication.

1 Description

The material shall consist of a defined quantity of a homogeneous mixture of technical isocycloseram, complying with the requirements of the WHO Specification 1025/TC in the form of a powder together with filler(s) and any other necessary formulants. It shall be in the form of a fine powder, free from visible extraneous matter and hard lumps, contained in a sealed water-soluble bag (Note 1).

2 Active ingredient

2.1 **Identity tests** (1025/WP/M/2, CIPAC Handbook Q, p.92, 2024) (Note 2)

The active ingredient shall comply with an identity test and, where the identity remains in doubt, shall comply with at least one additional test.

2.2. **Isocycloseram content** (1025/WP/M/3, CIPAC Handbook Q, p.92, 2024) (Note 2)

The isocycloseram content shall be declared (g/kg or g/L at 20 ± 2°C, Note 2) and, when determined, the average measured content shall not differ from that declared by more than the following tolerance:

Declared content, g/kg or g/l at 20 ± 2ºC	Tolerance
above 100 up to 250 Note: the upper limit is included in each range	± 6% of the declared content

3 Physical properties (Note 2)

3.1 pH range (MT 75.3, CIPAC Handbook J, p.131, 2000) (Note 3),

pH range: 6 to 9

3.2 Wettability (MT 53.3, CIPAC Handbook F, p.164, 1995)

The formulation shall be completely wetted in 1 min without swirling.

3.3 Wet sieve test (MT 185.1, CIPAC Handbook Q, p.205, 2024)

Maximum: 2% retained on a 75 µm test sieve.

* Specifications may be revised and/or additional evaluations may be undertaken. Ensure the use of current versions by checking at the WHO Prequalification Unit – Vector Control Product Assessment Team (PQT/VCP) website: https://extranet.who.int/prequal/vector-control-products/specifications-new-procedure

3.4 Suspensibility (MT 184.1, CIPAC Handbook P, p.245, 2021) (Notes 4 & 5)

The suspensibility shall be tested on a suspension containing the WP and the bag material in the actual ratio of application, prepared according to the procedure described in Note 6.

A minimum of 60% of the isocycloseram content shall be in suspension after 30 min in CIPAC Standard Water D at 25 ± 5°C.[1]

The re-suspensibility should be determined only if suspensibility is < 60%. A minimum of 95% of the isocycloseram content shall be in suspension after 30 min in CIPAC Standard Water D at 25 ± 5°C.

3.5 Persistent foam (MT 47.3, CIPAC Handbook O, p.177, 2017) (Note 7)

The persistent foam shall be tested on a suspension containing the WP and the bag material in the actual ratio of application in CIPAC Standard Water D, prepared according to the procedure described in Note 6.

Maximum: 40 mL after 1 min.

3.6 Dissolution of the bag (MT 176, CIPAC Handbook F, p.440, 1995) (Notes 2 & 8)

The dissolution of the bag shall be tested on a sample of the emptied and cleaned bag together with an appropriate proportion of the WP in CIPAC Standard Water D taken according to the procedure described in Note 8.

Flow time of the suspension: maximum 30 sec.

4 Storage stability

4.1 Stability at elevated temperature (MT 46.4, CIPAC Handbook P, p.232, 2021)

The package should be enclosed in a watertight sachet, box or any other container at 54 °C for 14 days. The determined average active ingredient content must not be lower than 95% relative to the determined average content found before storage (Note 9), and the formulation shall continue to comply with the clauses for:

- pH range (3.1),
- wettability (3.2),
- wet sieve test (3.3),
- suspensibility (3.4),
- persistent foam (3.5),
- dissolution of the bag (3.6).

None of the bags tested should show signs of leakage or rupture during normal handling, before and after storage.

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[1] For prequalified vector control products minimum values may differ in comparison to the generalized WHO specifications. The manufacturing release specifications in the WHO Public Assessment report should be used as a reference for quality control testing.

Note 1 For record keeping purposes, the suffix “SB” should be added to the formulation code (WP-SB).

Note 2 Sub-sampling.

Lay the bag on a bench and carefully open one side of the bag with a cutter, taking care not to damage the seals. Transfer the contents of the bag into a suitable flask. This material shall be used to carry out the tests for:

- active ingredient identity (2.1),
- active ingredient content (2.2),
- pH range (3.1),
- wettability (3.2),
- wet sieve test (3.3),
- suspensibility (3.4),
- persistent foam (3.5),
- dissolution of the bag (3.6).

The bag is then opened on three sides, completely cleaned from adhering powder by brushing or suction and weighed to the nearest 0.01 g. It shall be used to carry out the dissolution test (3.6). Aliquots of an aqueous solution of the bag material shall be used in the suspensibility (3.4) and persistent foam (3.5) tests.

In the case of delay of the above tests, the bag shall be stored in a watertight container (glass bottle or equivalent) to avoid any change in its properties.

Note 3 The method to be used shall be stated. If several methods are available, a referee method shall be selected.

Note 4 The formulation should be tested at the highest and lowest rates of use recommended by the supplier, provided this does not exceed the conditions given in method MT 184.1.

Note 5 Chemical assay is the only fully reliable method to measure the mass of active ingredient still in suspension. However, the simpler gravimetric method may be used on a routine basis provided that it has been shown to give equal results to those of chemical assay. In case of dispute, chemical assay shall be the referee method.

Note 6 The procedure for adding the bag material to the solution for the suspensibility and persistent foam tests should be as follows:

Prepare a stock solution of the bag material (1 mg/ml) by weighing approximately a sample (n mg) of the bag (excluding sealed parts) to the nearest mg. Dissolve this sample by stirring in the standard water used for the tests to give a final volume of n ml. Store the stock solution in a stoppered bottle before use.

Calculate the volume (V ml) of the stock solution of the bag to be added to the test suspension of the wettable powder according to the following equation:

$$V(\text{ml}) = X \times \frac{1000B}{W}$$

Where: B (g) = weight of the emptied and cleaned bag
W (g) = nominal weight of the WP contained in the bag
X (g) = weight of the WP sample used in the test

Note 7 The mass of sample to be used in the test should be specified at the highest rate recommended by the supplier. The test is to be conducted in CIPAC standard water D at 25 ± 5 °C.

Note 8 The sampling of the bag for the dissolution test should be as follows:
Lay the empty cleaned bag in its original configuration (double layer). Delineate and then cut up a test sample including part of the upper seal (5 cm) and symmetrically including the vertical seal (10 cm). If the size of the bag is less than this dimension, use the whole bag.

Carry out the dissolution test immediately to avoid any modification of the sample.

Note 9 Samples of the formulation taken before and after the accelerated storage stability test may be analysed concurrently after the test in order to reduce the analytical error.

PART TWO: EVALUATION REPORTS

ISOCYCLOSERAM

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FAO/WHO EVALUATION REPORT 1025/2025.2

Recommendations

The Meeting recommended the specification for isocycloseram WP-SB, proposed by Syngenta Crop Protection AG, as amended, should be adopted by WHO.

Appraisal

The Meeting considered data and information submitted between November 2023 and October 2024 by Syngenta Crop Protection AG in support of the development of a new specification for Isocycloseram WP-SB (wettable powder in sealed water-soluble bag).

The Manufacturer provided a data package on the physical and chemical properties of the isocycloseram WP-SB formulation to support the proposed specification. The data submitted were in accordance with the requirements of the Manual on Development and Use of FAO and WHO Specifications for Pesticides (2022, second edition).

Test results for all properties of a WP for three batches of the WP formulation were provided. Suspensibility and persistent foam were tested on three batches of WP in the presence of the water-soluble bag (SB), wettability and wet sieve in the presence of the water-soluble bag were tested in one batch.

Description

The supporting data showed the appearance of the WP formulation to be an off-white powder that does not change after storage at elevated temperatures.

Active ingredient identity and content and analytical methods

The nominal content of isocycloseram in the WP formulation is 150 g/kg. The supporting data showed that the isocycloseram content is well within the tolerance of ± 6% of the declared content in all the batches analysed.

A CIPAC method 1025/TC/- is available for the determination of isocycloseram in TC (1025/TC/- CIPAC Handbook Q, p.85, 2024) and WP formulations (CIPAC Handbook Q, p.85, 2024) (1025/WP/- CIPAC Handbook Q, p.92, 2024). Isocycloseram is determined by reverse phase HPLC-UV at 265 nm using external standardisation. For the determination of isocycloseram content in the WP-SB, an in-house method identical to the CIPAC method was used.

Relevant impurities

The are no relevant impurities identified in the WHO specification for isocycloseram TC.

The Meeting concluded that no relevant impurities need to be specified for the WP-SB formulation.

Physical-chemical properties

The physical and chemical properties were tested using the relevant CIPAC methods for each property.

For pH a range of 6 to 10 was proposed. The pH of a 1% dilution in water was measured and showed consistent results for all batches tested. The Meeting noted

that isocycloseram is hydrolytically unstable at higher pH therefore a pH clause is justified, however also noted that isocycloseram shows rapid degradation at pH>9. The Manufacturer proposed a narrower range for the clause of 6 to 9. The Meeting considered this range is supported by the available data.

Where required, physical-chemical properties were tested with and without the presence of the water-soluble bag material (SB) as outlined in the Manual on Development and Use of FAO and WHO Specifications for Pesticides (2022, second edition). The Manufacturer confirmed that the concentration of SB used in the tests was consistent with the ratio of SB to WP in the finished product.

The data for wettability (three batches tested without SB, one batch tested with SB), and dissolution of the bag (three batches) supported the proposed clauses in the specification. The Manufacturer further explained that wettability characteristics are considered inherent properties of a WP and that, as the dissolution properties of the water-soluble bag were acceptable, data tested on one batch in the presence of the SB was sufficient to show that wettability would not be adversely affected by the SB packaging.

For wet sieve, the maximum clause limit in the Manual of “maximum 2% retained on a 75µm sieve” was proposed; the Meeting noted that although the provided data (max. 0.82% for three batches without the SB, max 0.5% for one batch with the SB) showed a lower limit might be possible, the available data supported the proposed limit. Furthermore, as the dissolution properties of the water-soluble bag were acceptable, the Meeting noted the Manufacturer’s justification that the bag material would not have an impact on the wet sieve results and agreed that no further wet sieve data were required to support the clause.

For persistent foam, the maximum clause limit in the Manual of 60 mL after 1 minute was proposed, whereas the data (max. 1 mL after 1 minute for three batches tested in the presence of the SB) showed a much lower limit could be supported. The Manufacturer indicated that they had initially chosen the maximum limit of 60 mL after 1 minute, as this is a globally established standard. They noted that although the tests did not show significant foam development, foaming cannot always be completely prevented; therefore, they proposed a revised maximum limit of 40 mL after 1 minute. The Meeting accepted the revised limit.

For suspensibility, a clause of “minimum 35% of the isocycloseram content” was proposed. This was based on data from three batches tested in the presence of the SB at both the lowest and highest in-use concentration and determined using chemical assay. The suspensibility tested under these conditions ranged from 44%–56% (57%–67% after accelerated storage according to MT 46.4).

The Manufacturer also provided data on one batch which compared results by the gravimetric method with chemical assay. Suspensibility determined using the gravimetric determination was much higher (86%–88%). In all cases, re-suspensibility was tested and gave results ranging from 97%–99% (three batches including bag, chemical assay) and 102%–103% (one batch including bag, gravimetric method).

The Manufacturer indicated that the results for suspensibility show that the gravimetric determination is not an adequate acceptance criterion for a product release due to the obvious discrepancy between analytical and gravimetrical determination. The suspensibility must therefore be determined and specified analytically for Sovrenta 15WP formulation specifically.

The Manufacturer further justified that the specification clause of the minimum 35% was suggested to account for potential batch-to-batch variations, and that where suspensibility levels of less than 60% are obtained, the re-suspensibility should be tested, and that the product must show a re-suspensibility of 95%–105%. This was the case for the product tested. They also noted that, considering the specific instructions on mixing procedures, the results for suspensibility and re-suspensibility demonstrate that the product is suitable for its use in IRS programs under the given conditions and recommendations.

The Manufacturer therefore suggested a footnote in the specification which reads, “If the suspensibility is determined to be below 60%, then the re-suspensibility should be determined, where a minimum of 95% of the isocycloseram content found under 2.2.2 shall be in suspension after 30 minuntes in CIPAC Standard Water D at 30 ± 2 °C.”

The Meeting agreed that, given the potential for low initial suspensibility values, this information should be included in the main text of the specification as a principal clause rather than in a footnote, meaning that the re-suspensibility should only be tested if the initial suspensibility value is determined to be below 60%.

The Meeting acknowledged the challenges of establishing the general specification for a formulation type for which a single product has been developed and submitted. It was agreed by the Meeting and recommended that, for the purpose of the WHO specification, the generic language recommended in the FAO/WHO Manual, indicating a minimum of 60% suspensibility, coupled with the re-suspensibility clause, should be included in the WP specification for isocycloseram. The Meeting acknowledged that in product specific evaluations, regulatory authorities and or the Prequalification Programme may determine the need for differing product specific tolerances.

Storage stability

The stability of the WP-SB after the accelerated storage test (MT 46.4) was demonstrated to be acceptable and no significant adverse effects of storage of the formulated product were observed in terms of active ingredient content, pH, wettability wet sieve, suspensibility, re-suspensibility, and dissolution of the water-soluble bag.

Annex 1: References

Study number	Author(s)	Year	Study title. Study identification number. Report identification number. GLP [if GLP]. Company conducting the study
USGR210339	Perine, S.	2022	A23752B - Chemical Characterization of Batch ID 1222763, Syngenta Crop Protection, LLC, Syngenta File No. VV-937370
USGR220275	Mittapalli, R.	2022	A23752B - Chemical Characterization of Batch ID 1257375, Syngenta Crop Protection, LLC, Syngenta File No. VV-966493
USGR220274	Mittapalli, R.	2022	A23752B - Chemical Characterization of Batch ID 1257373, Syngenta Crop Protection, LLC, Syngenta File No. VV-966271
USGR220365	Schilling, W.	2023	A23752B - Content of Active Ingredient after Storage in Water Soluble Bag in PE/PET Packaging for 2 Weeks at 54°C, Syngenta Crop Protection, LLC, Syngenta File No. VV-980193
USGR220400	Schilling, W.	2023	A23752B - Content of Active Ingredient after Storage in Water Soluble Bag in PE/PET Packaging for 2 Weeks at 54°C, Syngenta Crop Protection, LLC, Syngenta File No. VV-980887
USGR220384	Schilling, W.	2023	A23752B - Content of Active Ingredient after Storage in Water Soluble Bag in PE/PET Packaging for 2 Weeks at 54°C, Syngenta Crop Protection, LLC, Syngenta File No. VV-980200
USGR220362	Schilling, W.	2023	A23752B - Physico-chemical characteristics of Batch 1222763 Syngenta Crop Protection, LLC, Syngenta File No. VV-982239
USGR220398	Schilling, W.	2023	A23752B - Physico-chemical characteristics of Batch 1257375 Syngenta Crop Protection, LLC, Syngenta File No. VV-980420
USGR220382	Schilling, W.	2023	A23752B - Physico-chemical characteristics of Batch 1257373 Syngenta Crop Protection, LLC, Syngenta File No. VV-980418
USGR220366	Schilling, W.	2023	A23752B - Physical and Technical Properties of Batch 1222763 After Storage in Water Soluble Bag in PE/PET Packaging for 2 Weeks at 54°C, Syngenta Crop Protection, LLC, Syngenta File No. VV-983504
USGR220401	Schilling, W.	2023	A23752B - Physical and Technical Properties of Batch 1257375 After Storage in Water Soluble Bag in PE/PET Packaging for 2 Weeks at 54°C, Syngenta Crop Protection, LLC, Syngenta File No. VV-983673
USGR220385	Schilling, W.	2023	A23752B - Physical and Technical Properties of Batch 1257373 After Storage in Water Soluble Bag in PE/PET Packaging for 2 Weeks at 54°C, Syngenta Crop Protection, LLC, Syngenta File No. VV-983524
300225950	Schilling, W.	2023	A23752B - Storage Stability and Shelf-Life Statement for Batch 1257373 (2 Weeks 54°C) in Water Soluble Bags in PE/PET packaging according to CIPAC MT 46.4 Syngenta Crop Protection, LLC, Syngenta File No. VV-985789
300225931	Schilling, W.	2023	A23752B - Storage Stability and Shelf-Life Statement for Batch 1222763 (2 Weeks 54°C) in Water Soluble Bags in PE/PET packaging according to CIPAC MT 46.4 , Syngenta Crop Protection, LLC, Syngenta File No. VV-985791
300226235	Schilling, W.	2023	A23752B - Storage Stability and Shelf-Life Statement for Batch 1257375 (2 Weeks 54°C) in Water Soluble Bags in PE/PET packaging according to CIPAC MT 46.4 , Syngenta Crop Protection, LLC, Syngenta File No. VV-986934

ISOCYCLOSERAM

FAO/WHO EVALUATION REPORT 1025/2025.1

Recommendations

The Meeting recommended that the specification for isocycloseram TC, proposed by Syngenta Crop Protection AG, should be adopted by WHO.

Appraisal

The Meeting considered data and information submitted in 2022–2024 by Syngenta Crop Protection AG (”Syngenta”) in support of development of a new WHO specification for isocycloseram TC. The data submitted met the requirements of the Manual on development and use of FAO and WHO specifications for chemical pesticides (2022, second edition). Isocycloseram consists of four stereoisomers, with 80–100% 5*S*,4*R*-isomer and 20–0% of the (5*R*,4*R*), (5*R*,4*S*) and (5*S*,4*S*) isomers.

The toxicology of isocycloseram was evaluated by the FAO/WHO JMPR in 2023.

Isocycloseram TC has been registered in Australia. A notice of approval has been received (APVMA, Nov 2021). Registration is being pursued in the USA.

Isocycloseram is a white to beige powder. It has a low vapour pressure. The compound has no potentially dissociating functional groups, possesses low water solubility and the octanol/water partition coefficient at pH 5-6 at 20°C is 5. The active ingredient undergoes rapid degradation by hydrolysis at pH 9 at 25°C. In simulated sunlight, there is degradation with half-life of 38.4 days at pH 4.

The manufacturer submitted confidential data on the manufacturing process, together with the manufacturing specification and 5-batch analysis data on isocycloseram TC purity and all detectable impurities at or above 1 g/kg.

The batches analyzed in the 5-batch study were produced over 3 months in 2018. The mass balance in the 5 batches ranged from 991 to 993 g/kg. The specified minimum purity of isocycloseram in the TC is 960 g/kg. The minimum purity, the isomer ratio, and the maximum limits for the impurities were supported by the 5-batch data and are statistically justified. The 5-batch study report indicates that no other significant impurities (each at or above 1 g/kg) were found in any of the 5 batches.

Based on available toxicological information, *in silico* modelling and the criteria of the Manual, the Meeting concluded that no impurities should be considered as relevant at the specified limits.

The identity of isocycloseram is confirmed by comparing the retention time in the HPLC method and by IR spectroscopy. The 5-batch analysis study was performed according to GLP guidelines. Validated in-house methods were used for the determination of isocycloseram content (reversed-phase UHPLC with UV detection) and isomer ratio (chiral UHPLC with UV detection) in the technical material. GLP analytical bridging studies were submitted, which demonstrated that in-house methods led to comparable results as CIPAC methods 1025/TC/M/3 and 1025/TC/M/2.2, respectively. Validated in-house methods (reversed-phase UHPLC with UV detection, or GC with flame ionization detection) were used for the determination of organic manufacturing impurities. Water was determined using the CIPAC method MT 30.6 (Karl Fischer

titration). All the analytical methods used in the 5-batch analysis study were adequately validated with their specificity, linearity of response, accuracy, repeatability and limits of detection and quantification (for impurities).

Test methods for determination of physical-chemical properties of the technical active ingredient were essentially OECD and CIPAC methods, as indicated in the supporting data.

Isocycloseram is of low toxicity following acute exposure. The acute oral median lethal dose (LD_{50}) is greater than 4500 mg/kg bw in female rats and the dermal LD_{50} is greater than 5000 mg/kg bw in female rats under the experimental conditions employed. Acute inhalation exposure was conducted for 4 hours nose-only in male and female rats. The combined median lethal concentration (LC_{50}) value was above 1.15 mg/L in one study (Biró, 2022) and 4.62 mg/L in another study (JMPR, 2023), the highest attainable concentration in the study. Isocycloseram was not a skin irritant to rabbits but was minimally irritating to rabbit eyes. Finally, isocycloseram obtained a positive result in a skin sensitizer murine local lymph node assay (LLNA) in mice but a negative result in the less sensitive Buehler test in guinea pigs.

JMPR selected a point of departure (POD) to derive an acute reference dose (ARfD) from an acute neurotoxicity study in rats with a NOAEL of 50 mg/kg and a LOAEL of 200 mg/kg based on decreased body weight gain, reduced food consumption and transiently depressed activity. This study was considered appropriate by JMPR for the route of duration of exposure and for the population of concern. An uncertainty factor of 100X (10X for interspecies extrapolation and 10X for intraspecies variation) is applied to establish the ARfD of 0.5 mg/kg bw (JMPR, 2023).

JMPR reported on an 18-month carcinogenicity study in mice and a chronic (24-month) carcinogenicity study in rat that support establishing a POD of 2 mg/kg/day to derive the acceptable daily intake (ADI). The mouse carcinogenicity study review identified a NOAEL of 1.7 mg/kg/day from the LOAEL of 6.7 mg/kg/day based on increased plasma cell infiltration in the mesenteric lymph nodes. The rat carcinogenicity study review identified a NOAEL of 2.3 mg/kg/day from the LOAEL of 7.0 mg/kg/day based on histopathological findings in the testes and epididymis in males. JMPR considered these studies appropriate for the route of exposure and duration and for the population of concern. JMPR has established an ADI at 0 – 0.02 mg/kg bw/day from the two chronic carcinogenicity studies in mice and rats and the safety factor of 100X (10X for interspecies extrapolation and 10X for intraspecies variation) (JMPR, 2023).

Isocycloseram was not considered carcinogenic in mice or rats and is unlikely to be genotoxic based on the chronic carcinogenicity and genotoxic studies according to JMPR (2023). Furthermore, JMPR also concluded that isocycloseram is not teratogenic (2023).

The Meeting concluded that the specifications for isocycloseram TC, proposed by Syngenta Crop Protection AG, should be adopted by WHO.

Supporting Information
for
Evaluation Report 1025/2025

Uses

Isocycloseram is a new broad spectrum insecticide belonging to the chemical group of isoxazolines. Isocycloseram binds to a site on the GABA receptor, resulting in a block of inhibitory neurotransmission, hyperexcitation, and death of target insects, and the mode of action is classified by the Insecticide Resistance Action Committee as a Group 30 insecticide (GABA-gated chloride channel allosteric modulators). It is used in public health against mosquitos.

Identity of the active ingredient

ISO common name

Isocycloseram

Synonyms

SYN547407

Chemical names

IUPAC (PIN)

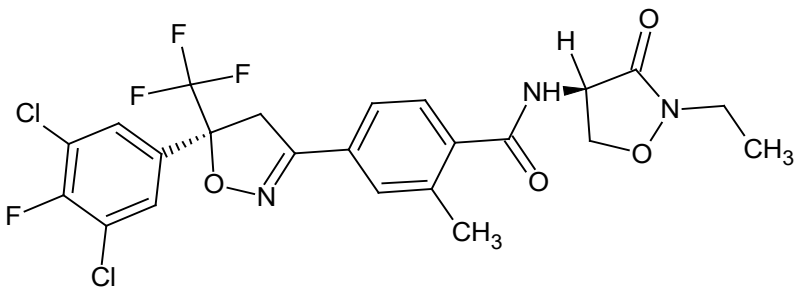
mixture comprised of 80–100% 4-[(5*S*)-5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydro-1,2-oxazol-3-yl]-*N*-[(4*R*)-2-ethyl-3-oxo-1,2-oxazolidin-4-yl]-2-methylbenzamide and 20–0% of the (5*R*,4*R*), (5*R*,4*S*) and (5*S*,4*S*) isomers

CA

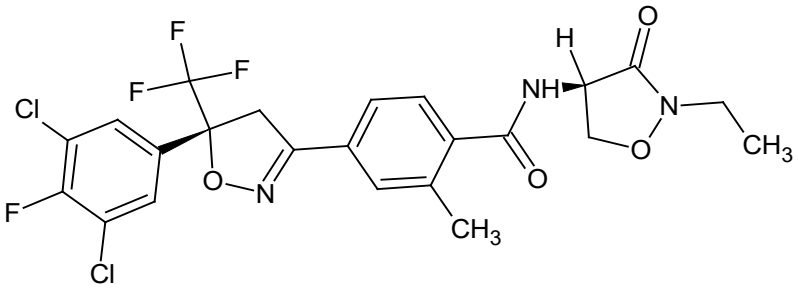
4-[5-(3,5-dichloro-4-fluorophenyl)-4,5-dihydro-5-(trifluoromethyl)-3-isoxazolyl]-*N*-(2-ethyl-3-oxo-4-isoxazolidinyl)-2-methylbenzamide

Structural formulae

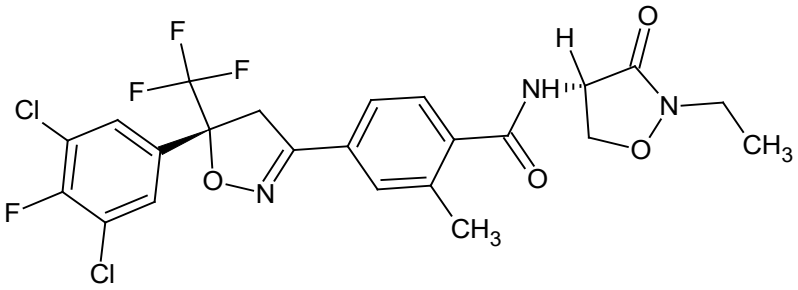
5S,4R-isomer



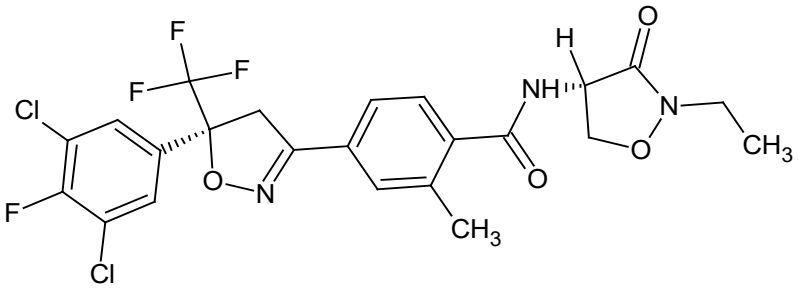
5R,4R-isomer



5R,4S-isomer



5S,4S-isomer



Molecular formula

$C_{23}H_{19}Cl_2F_4N_3O_4$

Relative molecular mass

548.3

CAS Registry number

2061933-85-3

CIPAC number

1025

Identity tests

HPLC retention time, UV spectrum, IR spectrum.

Physico-chemical properties of isocycloseram

Table 1. Physico-chemical properties of pure isocycloseram

Parameter	Value(s) and conditions	Purity %	Method reference (and technique if the reference gives more than one)	Study number
Vapour pressure	< 6.2 · 10^{-6} Pa at 20 °C < 6.2 · 10^{-6} Pa at 25 °C	98.4	OECD 104 (2006) gas saturation method	Vijayakumar (2017) SMG14076, GLP
Melting point.	138.9 °C, at 100.1 to 103.0 kPa	98.4	OECD 102 (1995) differential scanning calorimetry (DSC)	O'Connor (2017) QD17QM, GLP
Temperature of decomposition	The test item was determined to decompose from approximately 212°C (485 K) at 102.0 to 103.0 kPa. Decomposition was observed both in air and under a nitrogen atmosphere	98.4	OECD 103 (1995) differential scanning calorimetry (DSC)	O'Connor (2017) SG92NR, GLP
Solubility in water	1.2 mg / l (pure water, pH=6) at 20°C No Potential dissociating functional groups. Therefore, no other pH ranges measured	98.4	OECD 105 (1995) column elution method	Halarnakar (2017) SMG14120, GLP
Octanol/water partition coefficient	log P_{ow} = 5.0 (pH=5.4) at 20°C	98.4	OECD 107 (1995) shake-flask method	Halarnakar (2017) SMG14121, GLP
Hydrolysis characteristics	At pH 4, SYN547407 was relatively stable with $DegT_{50}$ values of 1290, 759, 350 and 140 days at 25, 50, 60 and 70°C, respectively. Degradation of SYN547407 was slightly faster at pH 7 than pH 4. $DegT_{50}$ values of 262, 9.81, 3.14 and 1.03 days were obtained at 25, 50, 60 and 70°C, respectively. Degradation at pH 9 was rapid resulting in $DegT_{50}$ values of 5.41, 1.36 and 0.348 days at 10, 25 and 35°C, respectively.	97.4-99.7 (chemical purity); 97.4-99.3 (radiochemical purity)	OECD 111 (2004)	Adam (2019) 20160233, GLP
Photolysis characteristics	Photo-degradation of SYN547407 in pH 4 buffer solution was slow as a result of direct photolysis. A half-life ($DegT_{50}$) of 38.4 days was determined in continuously irradiated samples under the light of the Suntest. This was calculated to be equivalent to 233.9 days of Tokyo spring sunlight at 35°N and of 72.4 days of summer sunlight at 30 to 50°N.	98.9-99.2 (chemical purity); 97.5-99.1 (radiochemical purity)	OECD 316 (2008)	Wijnties, (2021) 20160284, GLP

Dissociation characteristics	No Potential dissociating functional groups No experimental evaluation due to low water solubility	98.4	OECD 112 (1981)	O'Connor (2017) YJ47SY, GLP
Solubility in organic solvents	See for technical grade			

Table 2. Chemical composition and properties of isocycloseram technical materials (TC and/or TK)

Manufacturing process, maximum limits for impurities ³ 1 g/kg, 5 batch analysis data	Confidential information supplied and held on file by WHO. Mass balances were 99.1 -99.3% and percentages of unknowns were 0.7 - 0.9%.
Declared minimum isocycloseram content	960 g/kg
Relevant impurities ³ 1 g/kg and maximum limits for them	None
Relevant impurities < 1 g/kg and maximum limits for them:	None
Stabilisers or other additives and maximum limits for them:	None

Parameter	Value and conditions	Purity%	Method reference	Study number
Melting temperature range of the TC and/or TK	135.3°C	96.9	OECD 102 DSC	B J O'Connor (2017) VV-466832
Solubility in organic solvents	at 25°C: acetone 270 g/l methanol 75 g/l dichloromethane 400 g/l octanol 17 g/l ethyl acetate 190 g/l toluene 33 g/l hexane 39 mg/l	96.9	Similar to CIPAC MT 157.3 flask method	C Vijayakumar (2017) VV-466922

Hazard summary

The toxicology of isocycloseram was evaluated by the FAO/WHO JMPR in 2023.

The JMPR concluded that the results of the long-term studies in rats and mice and a series of studies designed to evaluate genotoxicity indicated that isocycloseram is unlikely to pose a carcinogenic hazard to humans. An ADI of 0-0.02 mg/kg bw was allocated on the basis of the NOAEL using a 100-fold safety factor.

Formulations

The main formulation type available is WP.

Methods of analysis and testing

The analytical methods for the active ingredient in TC are validated in-house methods. Isocycloseram content is determined by reversed-phase UHPLC with UV detection, while the isomer ratio is determined by chiral UHPLC with UV detection. GLP analytical bridging studies were submitted, which demonstrated that in-house methods led to

comparable results as CIPAC methods 1025/TC/M/3 and 1025/TC/M/2.2, respectively.

The methods for determination of impurities are based on reversed-phase UHPLC with UV detection, or GC with flame ionization detection, and are adequately validated.

Test methods for determination of physico-chemical properties of the technical active ingredient were essentially OECD and CIPAC methods, as indicated in the supporting data.

Containers and packaging

No special requirements for containers and packaging have been identified.

Expression of the active ingredient

The active ingredient is expressed as isocycloseram.

Annex 1: Hazard Summary Provided by the Proposer

Notes.

(i) The proposer has confirmed that the toxicological and ecotoxicological data included in the summary below were derived from isocycloseram having impurity profiles similar to that referred to in the table above.

(ii) The conclusions expressed in the summary below are those of the proposer, unless otherwise specified.

Table 3. Toxicology profile of the isocycloseram technical material, based on acute toxicity, irritation and sensitization.

Species	Test	Purity%	Guideline, duration, doses and conditions	Result [(isomer/form)]	Study number
Rat (Crl:WI); (female)	oral	96.9	OECD425 (2008), GLP Dose levels: 1750 or 5000 mg/kg 14 day observation period	LD_{50} >5000 mg/kg bw	Tarcai (2016) VV-466679
Rat (SD); (males and females)	oral	96.9	P.R. of China GB/T 15670.3-2017 Dose levels: 464, 1000, 2150, 4640 or 5000 mg/kg 14 day observation period	LD_{50} = 4569 mg/kg bw	Xue (2021) VV-924284
Rat (Crl:WI); (males and females)	dermal	96.9	OECD402 (1987), GLP Dose levels: 5000 mg/kg 14 day observation period	LD_{50} >5000 mg/kg bw	Tarcia (2016) VV-466714
Rat (SD); (males and females)	dermal	96.9	P.R. of China GB/T 15670.5-2017 Dose levels: 5000 mg/kg 14 day observation period	LD_{50} >5000 mg/kg bw	Xue (2021) VV-937895
Rat (Crl:WI); (males and females)	inhalation	96.9	OECD403 (2009), GLP 4h nose only exposure, MMAD approx.3.38 µm 14 day observation period	LC_{50} = >4.62mg/L	Rosos-Matting (2016) VV-467437
Rabbit (NZW); (male)	skin irritation	98.4	OECD404 (2002), GLP Dose levels: 0.5g per animal 72hr observation period	Not irritating	Matting (2015) VV-413103
Rabbit (JW); (male)	skin irritation	96.9	P.R. of China GB/T 15670.7-2017 Dose levels: 0.5g per animal 72hr observation period	Not irritating	Xue (2021) VV-937896
Rabbit (NZW); (male)	eye irritation	98.4	OECD405 (2012), GLP Dose levels: 0.1g per left eye 72hr observation period	Minimal irritant	Matting (2015) VV-413102
Chicken eye	eye irritation	98	OECD438 (2013), GLP Dose levels: 30mg per eye 4hr observation period	Not classified as a severe irritant and not classified as non-irritant	Váliczkó (2014) VV-410146
Rabbit (JW); (male)	eye irritation	96.9	P.R. of China GB/T 15670.8-2017 Dose levels: 0.1g per right eye 72hr observation period	Slight irritant	Xue (2021) VV-937897
Mouse (CBA/Ca); (Female)	skin sensitisation	96.9	OECD429 (2010), GLP Dose levels: 10, 25, 50% (w/w) in acetone/olive oil 4:1	Skin sensitization potential	Pooles (2016) VV-466882
Guinea Pig (Dunkin Hartley); (male)	skin sensitisation	96.9	P.R. of China GB/T 15670.9-2017 Dose levels: 50% w/w in corn oil	Not a skin sensitiser	Xue (2021) VV-937898

Table 4. Toxicology profile of the isocycloseram technical material based on repeated administration (subacute to chronic)

Species	Test	Purity %	Guideline, duration, doses and conditions	Result [(isomer/form)]	Study number
Rat (Crl:WI), (males and females)	Short term toxicity	98	OECD407 (2008), GLP 28 day dietary oral Dose levels: 0, 50, 200, 350 or 500 ppm (males) or 0, 50, 700, 800 or 1000 ppm (females) 5/sex/group	NOAEL = 50 ppm (4.3mg/kg (male), 4.5mg/kg (female))	Dymarkowska (2017) VV-467799
Mouse (Crl:CD-1); (males and females)	Short term toxicity	98	OECD407 (2008); GLP 28 day dietary oral Dose levels: 0, 100, 300, 700 or 1000 ppm 5/sex/group	NOAEL = 100 ppm (17.4mg/kg (male), 20.9mg/kg (female))	Dymarkowska (2015) VV-467980
Dog (Beagle); (males and females)	Short term toxicity	98	OECD409 (1998), GLP 28 day capsule oral Dose levels: 0, 10, 50 and 150/80 mg/kg (males) or 0, 10, 35 and 70 mg/kg (females) 3/sex/group	NOAEL = 10mg/kg	Robertson (2019) VV-719063
Rat (Crl:WI); (males and females)	Short term toxicity	98.4	OECD408 (1998), GLP 13 week dietary oral Dose levels: 0, 50, 150 or 300 ppm (equivalent to 0, 3.9, 11.2, and 22.0 mg/kg in males and 0, 4.4, 13.4, and 24.0 mg/kg in females)	NOAEL = 50 ppm in males (3.9mg/kg), 150ppm in females (13.4mg/kg)	Laidlaw (2019) VV-472306

Species	Test	Purity %	Guideline, duration, doses and conditions	Result [(isomer/form)]	Study number
			10/sex/group		
Mouse (CRL:CD-1); (males and females)	Short term toxicity	98.4	OECD408 (1998), GLP 13 week dietary oral Dose levels: 0, 50, 300 or 700 ppm (equivalent to 0, 8.0, 48.8 and 117 mg/kg in males and 0, 9.9, 51.6 and 140 mg/kg in females) 10/sex/group	NOAEL = 50 ppm equating to 8.0 mg/kg bw/day in males and 9.9 mg/kg bw/day in females	Laidlaw (2019) VV-472418
Dog (Beagle); (males and females)	Short term toxicity	96.9	OECD409 (1998), GLP 13 week capsule oral Dose levels: 0, 5, 15 and 35/25 mg/kg 4/sex/group	NOAEL = 15 mg/kg	Robertson (2019) VV-718750
Rat (RccHan™:WIST); (males and females)	Short term dermal toxicity	96.9	OECD410 (1981), GLP 4 week dermal Dose levels: 0, 100, 300 and 1000 mg/kg 10/sex/group	NOAEL = 100 mg/kg	Cooper (2019) VV-619265
Rat (Crl:WI); (males and females)	Carcinogenicity	96.9	OECD453 (2009), GLP 104 Week dietary oral Dose levels: 0, 20, 50 or 150 ppm (equivalent to 0, 0.9, 2.3 and 7.0 mg/kg in males and 0, 1.2, 3.0 and 9.2 mg/kg for females) 52/sex/group	NOAEL = 50 ppm (2.3/3.0 mg/kg for males/females respectively)	Strepka (2019) VV-716659

Species	Test	Purity %	Guideline, duration, doses and conditions	Result [(isomer/form)]	Study number
Mouse (CRL:CD-1); (males and females)	Carcinogenicity	96.9	OECD451 (2009) 80 Week dietary oral Dose levels: 0, 15, 60 or 200 ppm (equivalent to 0, 1.7, 6.7 and 23.1 mg/kg in males and 0, 1.8, 7.1 and 24.4 mg/kg for females) 50/sex/group	NOAEL = 15 ppm (1.7/1.8 mg/kg for males/females respectively)	Strepka (2019) VV-716634
Rat (Crl:WI); (males and females)	Reproductive toxicity, enhanced 1-generation	98.4	OECD415 (1983) Oral gavage Dose levels: 0, 7.5, 15, and 45/60 mg/kg (males), 0, 3.5, 7.5, and 15 mg/kg (females) 24/sex/group	NOAEL: Reproductive 45/60 mg/kg (males) and 15 mg/kg (females) Systemic 7.5 mg/kg (males and females)	Penn (2018) VV-471049
Rat (Crl:WI); (males and females)	Reproductive toxicity, 2-generation	96.9	OECD416 (2001) Dietary oral Dose levels: 0, 1.5, 4, and 12 mg/kg 24/sex/group	NOAEL: Reproductive 12 mg/kg Systemic 4 mg/kg	Britton, King (2019) VV-471790
Rat (Crl:WI); (female)	Developmental toxicity dose ranger finding	96-97	No guideline Oral gavage Dose levels: 0, 3.5, 7.5, and 15 mg/kg 10/group	NOAEL: Not assigned in this study type	Britton (2015) VV-411304
Rat (Crl:WI); (female)	Developmental toxicity	96.9	OECD414 (2001), GLP Oral gavage Dose levels: 0, 3.5, 7.5, and 15 mg/kg 22/group	NOAEL: Maternal 15 mg/kg Embryo-Fetal 15 mg/kg	Blunt, Fincher (2019) VV-472253 Wolton, French (2020) VV-882864

Species	Test	Purity %	Guideline, duration, doses and conditions	Result [(isomer/form)]	Study number
					DeSesso, Williams (2019) VV-882865
Rabbit (NZW); (female)	Developmental toxicity dose ranger finding	>96	No guideline Oral gavage Dose levels: 0, 7.5, 15, and 30 mg/kg 10/group	NOAEL: Not assigned in this study type	Blunt (2015) VV-411667
Rabbit (NZW); (female)	Developmental toxicity	96.9	OECD414 (2001) Oral gavage Dose levels: 0, 3.5, 7.5, and 15 mg/kg 22/group	NOAEL: Maternal 15 mg/kg Embryo-Fetal 15 mg/kg	Pottle (2017) VV-468197
Rat (RccHan™: WIST); (males and females)	Acute neurotoxicity	98.4	OECD424 (1997) Oral gavage Dose levels: 0, 50, 200, and 1000 mg/kg 10/sex/group	NOAEL: General Toxicity 50 mg/kg Neurotoxicity 1000 mg/kg	Cocker (2016) VV-466670
Rat (RccHan™: WIST); (males and females)	90 day neurotoxicity	96.9	OECD424 (1997) Dietary oral Dose levels: 0, 50, 150, 300 ppm 10/sex/group	NOAEL: General Toxicity and Neurotoxicity 300ppm (24.8 and 32.7 mg/kg for males and females respectively)	Froud (2019) VV-619064

Table 5. Mutagenicity profile of the isocycloseram technical material based on in vitro and in vivo tests

Species	Test	Purity%	Guideline, duration, doses and conditions	Result [(isomer/form)]	Study number
Salmonella typhimurium strains TA1535, TA1537, TA98, and TA100, and the Escherichia coli strains	Bacterial Reverse Gene Mutation (in vitro)	96.9	3-5000 µg/plate ±S9-mix (Exp I&II) DMSO OECD471 (1997), GLP	Negative	Chang (2016) VV-465073

Species	Test	Purity%	Guideline, duration, doses and conditions	Result [(isomer/form)]	Study number
WP2 uvrA pKM101 and WP2 pKM101					
Salmonella typhimurium strains TA1535, TA1537, TA98, and TA100, and the Escherichia coli strains WP2 uvrA pKM101 and WP2 pKM101	Bacterial Reverse Gene Mutation (in vitro)	96.1	3-5000 µg/plate ±S9-mix (Exp I) 33-5000 µg/plate ±S9-mix (Exp II) 33-5000 µg/plate -S9-mix (Exp III) DMSO OECD471 (1997), GLP	Negative	Chang (2019) VV-619413
Mouse lymphoma L5178Y Tk +/- cells	Mammalian Gene Mutation (in vitro)	96.9	1-125 µg/mL ±S9-mix (Exp I) 1.9-77.5 µg/mL ±S9-mix (Exp II) DMSO OECD490 (2015)	Non-mutagenic	Wollny (2016) VV 465417
Mouse lymphoma L5178Y Tk +/- cells	Mammalian Gene Mutation (in vitro)	96.1	0.9-80 µg/mL ±S9-mix (Exp I) 3.13-80 µg/mL +S9-mix (Exp II) 3.2-75 µg/mL +S9-mix (Exp III) DMSO OECD490 (2016)	Non-mutagenic	Sokolowski (2019) VV-719550
Human lymphocytes	Chromosomal aberration (in vitro)	96.9	4.3-5160 µg/mL ±S9-mix (Exp I) 2.1-322.5 µg/mL -S9 mix (Exp II) DMSO OECD473 (2014)	Non-clastogenic	Chang (2016) VV-465554
Rat (CRL:WI); (male)	Micronucleus formation (in vivo)	96.9	500, 1250, 2000 mg/kg bw/day 0.5% (w/v) CMC with 0.1% (v/v) Tween 80 OECD474 (1997)	Neither clastogenic nor aneugenic	Dunton (2016) VV 465063

Table 6. Ecotoxicology profile of the isocycloseram technical material

Species	Test	Purity%	Guideline, duration, doses and conditions	Result [(isomer/form)]	Study number
Colinus virginianus [Bobwhite quail]	Acute toxicity	96.9	OECD Guideline 223. 2000 mg/kg bw limit dose	LD50 > 2000 mg/kg bw	VV-465340
Anas platyrhynchos [Mallard duck]	Acute toxicity	96.9	OECD Guideline 223. 2000 mg/kg bw limit dose	LD50 > 2000 mg/kg bw	VV-465876
Serinus Canaria [Canary]	Acute toxicity	96.9	OECD Guideline 223. 1500 mg/kg bw limit dose	LD50 > 1500 mg/kg bw	VV-470612
Colinus virginianus [Bobwhite quail]	Short term dietary	96.9	U.S. EPA 850.2200, OECD Guideline 205. 5-day dietary study, 562, 1000, 1780, 3160, 5620 mg/kg	LC50 > 5620 mg/kg	VV-465340
Anas platyrhynchos [Mallard duck]	Short term dietary	96.9	U.S. EPA 850.2200, OECD Guideline 205. 5-day dietary study, 562, 1000, 1780, 3160, 5620 mg/kg	LC50 = 2000 mg/kg	VV-468375
Colinus virginianus [Bobwhite quail]	Chronic toxicity	96.9	U.S. EPA 850.2300, OECD Guideline 206. 21-week reproductive study, 100, 320, 1000 mg/kg	NOEC = 320 mg/kg equivalent to 21.6 mg/kg bw/d	VV-470611
Anas platyrhynchos [Mallard duck]	Chronic toxicity	96.9	U.S. EPA 850.2300, OECD Guideline 206. 21-week reproductive study, 100, 320, 1000 mg/kg	NOEC = 100 mg/kg equivalent to 14.6 mg/kg bw/d	VV-470610
Oncorhynchus mykiss [rainbow trout]	Acute toxicity	96.9	U.S. EPA 850.1075, OECD Guideline 203, 96 hr acute test 0.066, 0.12, 0.23, 0.42 and 0.94 mg/L	LC50 = 0.13 mg/L	VV-470111
Pimephales promelas [fathead minnow]	Acute toxicity	96.9	U.S. EPA 850.1075, OECD Guideline 203, 96 hr acute test 0.058, 0.14, 0.23, 0.48 and 0.62 mg/L	LC50 = 0.33 mg/L	VV-469970
Cyprinodon variegatus [sheepshead minnow]	Acute toxicity	96.9	U.S. EPA 850.1075, OECD Guideline 203, 96 hr acute test 0.064, 0.14, 0.27, 0.54 and 0.94 mg/L	LC50 = 0.29 mg/L	VV-470108
Cyprinus carpio [carp]	Acute toxicity	96.9	U.S. EPA 850.1075, OECD Guideline 203, 96 hr acute test 0.057, 0.12, 0.24, 0.47 and 0.97 mg/L	LC50 = 0.37 mg/L	VV-470076
Pimephales promelas [fathead minnow]	Chronic toxicity	96.9	U.S. EPA 850.1400, OECD Guideline 210, 28-day early life-stage toxicity test, 0.013, 0.027, 0.048, 0.11 and 0.22 mg/L	NOEC = 0.11 mg/L	VV-470291

Cyprinodon variegatus [sheepshead minnow]	Chronic toxicity	96.9	U.S. EPA 850.1400, OECD Guideline 210, 28-day early life-stage toxicity test, 0.0037, 0.0081, 0.018, 0.052 and 0.13 mg/L	NOEC = 0.0081 mg/L	VV-469971
Daphnia magna [water flea]	Acute toxicity	96.9	U.S. EPA 850.1010, OECD Guideline 202, 48 hr acute toxicity 0.0035, 0.0089, 0.021, 0.052, 0.14, 0.53 and 0.91 mg/L	EC50 = 0.52 mg/L	VV-470284
Crassostrea virginica [Eastern oyster]	Acute toxicity	96.9	U.S. EPA 850.1025, 96 hr acute toxicity 0.0057, 0.016, 0.031, 0.056, 0.19 and 0.50 mg/L	EC50 = 0.083 mg/L	VV-469923
Mysidopsis bahia [mysid shrimp]	Acute toxicity	96.9	U.S. EPA 850.1035, 96 hr acute toxicity 0.003, 0.0064, 0.013, 0.026, 0.053 and 0.12 ug/L	LC50 = 0.018 ug/L	VV-846361
Hyalella azteca [freshwater amphipod]	Acute toxicity	96.9	U.S. EPA 850.1020, OECD Guideline 202, JMAFF 2-7-5, 96 hr acute toxicity 0.032, 0.095, 0.27, 0.82, 2.5 and 9.2 ug/L	LC50 = 0.041 ug/L	VV-868235
Chironomus riparius [midge]	Acute toxicity	96.9	OECD Guideline 235, 48 hr acute toxicity 0.0011, 0.0023, 0.0056, 0.014, 0.038 and 0.096 ug/L	LC50 = 0.015 ug/L	VV-866777
Caecidotea communis [water louse]	Acute toxicity	96.9	U.S. EPA 850.1020, U.S. EPA 850.1000, 96 hr acute toxicity 0.038, 0.058, 0.099, 0.170 and 0.26 ug/L	EC50 = 0.15 ug/L	VV-890842
Brachionus calyciflorus [freshwater rotifer]	Acute toxicity	96.9	U.S. EPA 850.1000, ASTM E 1440-91, 24 hr acute toxicity 1.3, 1.8, 7.2, 20, 66, 220 and 810 ug/L	EC50 > 810 ug/L	VV-889418
Hexagenia limbate [mayfly]	Acute toxicity	96.9	U.S. EPA 850.1000, OECD Guideline 235, 48 hr acute toxicity <0.015, 0.032, 0.084, 0.23, 0.60 and 1.5 ug/L	EC50 = 0.32 ug/L	VV-888013
Pycnopsyche gentilis [caddisfly]	Acute toxicity	96.9	U.S. EPA 850.1000, OECD Guideline 235, 48 hr acute toxicity <0.015, 0.027, 0.071, 0.19, 0.51 and 1.4 ug/L	EC50 = 0.49 ug/L	VV-878602
Faxonius virilis [Northern crayfish]	Acute toxicity	96.9	U.S. EPA 850.1000, 96 hr acute toxicity 0.22, 0.49, 0.98, 2.1 and 3.6 ug/L	EC50 = 1.6 ug/L	VV-888912
Palaemonetes paludosus [grass shrimp]	Acute toxicity	96.9	U.S. EPA 850.1000, U.S. EPA 850.1045, 96 hr acute toxicity 0.058, 0.14, 0.37, 0.91 and 2.2 ug/L	EC50 = 0.25 ug/L	VV-889404
Thamnocephalus platyurus [Fairy shrimp]	Acute toxicity	96.9	U.S. EPA 850.1000, U.S. EPA 850.1035, 96 hr acute	EC50 = 0.26 ug/L	VV-892711

			toxicity 0.028, 0.074, 0.22, 0.69, 2.3, 6.9 and 21 ug/L		
Daphnia magna [water flea]	Chronic toxicity	96.9	U.S. EPA 850.1300, OECD Guideline 211, 21-day static renewal, 0.031, 0.063, 0.13, 0.24, and 0.5 ug/L	NOEC = 0.063 ug/L	VV-740015
Daphnia magna [water flea]	Chronic toxicity	96.9	U.S. EPA 850.1300, OECD Guideline 211, 21-day static renewal, 0.0092, 0.015, 0.03, 0.064, 0.13 and 0.24 ug/L	NOEC = 0.03 ug/L	VV-869410
Mysidopsis bahia [mysid shrimp]	Chronic toxicity	96.9	U.S. EPA 850.1350, 28-day flow-through, 0.00052, 0.001, 0.0023, 0.0042 and 0.0074 ug/L	NOEC = 0.001 ug/L	VV-846373
Hyalella azteca [freshwater amphipod]	Chronic toxicity	96.9	U.S. EPA 100.4, US EPA 850.1770 (in preparation), 42-day intermittent-renewal, 0.019, 0.051, 0.13, 0.31, 0.77 and 2.1 ug/kg dw	NOEC = 0.77 ug/kg dw	VV-869054
Leptocheirus plumulosus [estuarine amphipod]	Chronic toxicity	96.9	U.S. EPA 600/R-01/020, 21-day intermittent-renewal, 0.21, 0.38, 0.79, 1.7 and 3.0 ug/kg dw	NOEC = 1.7 ug/kg dw	VV-846384
Chironomus dilutus [midge]	Chronic toxicity	96.9	U.S. EPA 100.5, US EPA 850.1760 (in preparation), 60-day intermittent-renewal, 0.018, 0.046, 0.12, 0.39 and 1.1 ug/kg dw	NOEC = 0.39 ug/kg dw	VV-890854
Chironomus riparius [midge]	Chronic toxicity	96.9	OECD 218, 28-day static, 0.085, 0.18, 0.34, 0.68, 1.5 and 2.7 ug/kg dw	NOEC = 0.68 ug/kg dw	VV-893580
Pseudokirchneriella subcapitata [green algae]	Chronic toxicity	96.9	U.S. EPA 850.4500, OECD 201; 96 hr algal growth inhibition assay. 0.041, 0.061, 0.11, 0.24 and 0.78 mg/L	96hr ErC50 > 0.78 mg/L	VV-469976
Navicula pelliculosa [freshwater diatom]	Chronic toxicity	96.9	U.S. EPA 850.4500, OECD 201; 96 hr algal growth inhibition assay. 0.023, 0.042, 0.090, 0.21 and 0.61 mg/L	96hr ErC50 > 0.61 mg/L	VV-469967
Skeletonema costatum [marine diatom]	Chronic toxicity	96.9	U.S. EPA 850.4500, OECD 201; 96 hr algal growth inhibition assay. 0.023, 0.044, 0.093, 0.21 and 0.54 mg/L	96hr ErC50 = 029 mg/L	VV-469997
Anabaena flos-aquae [freshwater cyanobacterium]	Chronic toxicity	96.9	U.S. EPA 850.4550, OECD 201; 96 hr freshwater cyanobacterium growth inhibition assay. 0.033, 0.050, 0.11, 0.29 and 0.69 mg/L	96hr ErC50 > 0.69 mg/L	VV-470238

Lemna gibba [Duckweed]	Chronic toxicity	96.9	U.S. EPA 850.4400, OECD 221; 7-day static renewal. 0.080, 0.13, 0.24, 0.50 and 1.2 mg/L	7d ErC50 > 1.2 mg/L	VV-469969
Eisenia andrei [earthworm]	Acute toxicity	96.9	OECD 207; 14d acute toxicity test 62.5, 125, 250, 500 and 1000 mg/kg dry soil	LC50 > 1000 mg/kg dw	VV-466604
*Eisenia fetida [*earthworm]	Chronic toxicity	96.9	OECD 222; 28d chronic toxicity test 0.625, 1.25, 2.5, 5.0 and 10.0 mg/kg dry soil	NOEC = 10 mg/kg dw	VV-412931
Soil Microflora	Nitrogen and Carbon Transformation	96.9	OECD 216, OECD 217; 28d chronic transformation test 0.5 and 4.95 mg/kg dry soil	NOEC = 4.95 mg/kg dw	VV-466609
Activated sludge	Respiration inhibition test	96.9	OECD 209, ISO 8192; 3-h inhibition test 10, 32, 100, 320 and 1000 mg/L	NOEC = 100 mg/L	VV-467858
Folsomia candida [Collembola]	Chronic toxicity	96.9	OECD 232; 28-day toxicity test 0.009, 0.016, 0.029, 0.053, 0.095, 0.171, 0.309, 0.556 and 1.0 mg/kg dw	NOEC = 0.095 mg/kg dw	VV-412444
Hypoaspis aculeifer [predatory mite]	Chronic toxicity	96.9	OECD 226; 14-day toxicity test 0.009, 0.016, 0.029, 0.053, 0.095, 0.171, 0.309, 0.556 and 1.0 mg/kg dw	NOEC = 0.171 mg/kg dw	VV-412437
Apis mellifera [honeybee]	Acute toxicity	96.9	OECD 213, OECD 214; 96h acute oral and contact toxicity test. 0.04, 0.09, 0.21, 0.47 and 0.99 ug/bee (oral test). 0.04, 0.09, 0.20, 0.45 and 1.0 ug/bee (contact test).	72-h oral LD50 = 0.28 ug/bee 96-h contact LD50 = 0.26 ug/bee	VV-466340
Bombus terrestris [bumblebee]	Acute toxicity	96.9	OECD 246, OECD 247; 48h acute oral and contact toxicity test. 0.16, 0.32, 0.64, 1.35 and 2.57 ug/bee (oral test). 1.3, 2.2, 3.6, 6.0 and 10 ug/bee (contact test).	48-h oral LD50 = 0.35 ug/bee 48-h contact LD50 >10 ug/bee	VV-900003
Apis mellifera [honeybee]	Chronic toxicity	96.9	Based on OECD guideline proposal (2016); 10-day laboratory adult feeding test. 0.07, 0.13, 0.25, 0.5 and 1.0 mg/kg feeding solution	NOEC = 0.13 mg/kg diet NOEDD 0.0034 ug/bee/day	VV-462082
Apis mellifera [honeybee]	Larval toxicity test (single exposure)	96.9	OECD 237; 7-day larval toxicity test (single exposure). 0.02, 0.07, 0.22, 0.67 and 2.0 mg/kg diet	LD50 = 0.08 ug/larvae LC50 = 2.42 mg/kg diet	VV-467266

Apis mellifera [honeybee]	Larval toxicity test (repeat exposure through adult emergence)	96.9	OECD Draft guidance 20 July 2015; 22-day repeat exposure through feeding larval toxicity test. 0.0123, 0.0370, 0.111, 0.333 and 1.0 mg/kg diet	22d NOEC = 0.111 mg/kg diet 22d NOED = 0.0171 ug/larvae per developmental period	VV-467145

Annex 2: References

Study number	Author(s)	Year	Study title. Study identification number. Report identification number. GLP [if GLP]. Company conducting the study.
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