World Health Organization

WHO Prequalification Programme / Vector Control Product Assessment

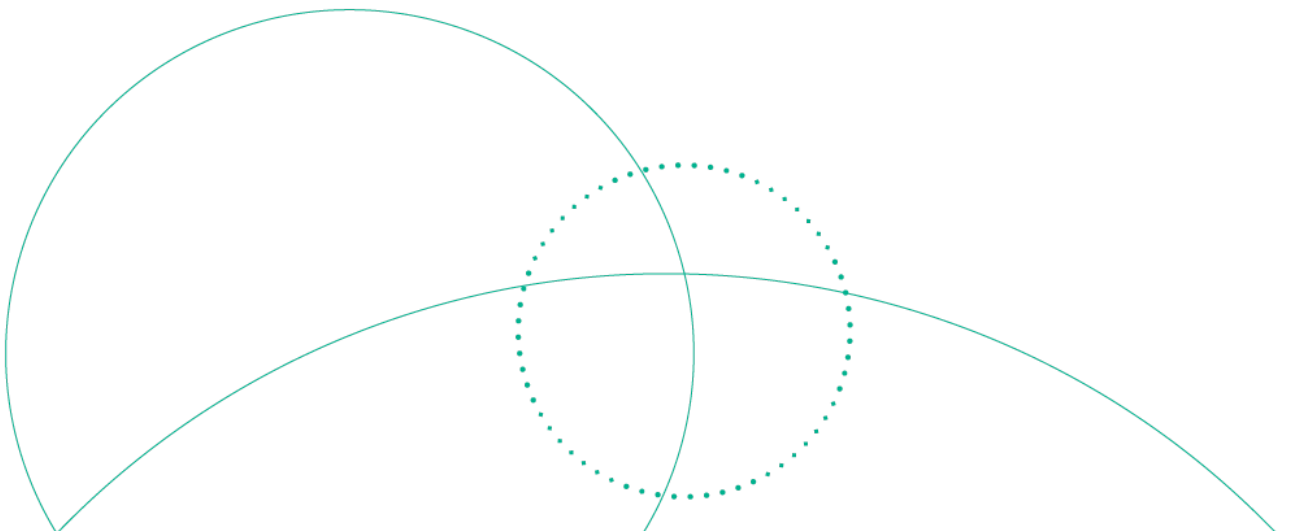
WHO Public Assessment Report: WHOPAR Part 4

SOVRENTA 15WP

(Syngenta Crop Protection AG)

P-11568

Safety Assessment



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1 Risk Assessment Summary

1.1 Introduction

The applicant, Syngenta Crop Protection AG (Switzerland), submitted a product dossier to the World Health Organization (WHO) Pre-Qualification Team, Vector Control Products Assessment Team (PQT-VCP) containing supporting data for the proposed product SOVRENTA 15WP for use as an Indoor Residual Spray (IRS). SOVRENTA 15WP is a wettable powder (WP) packaged in 200 g water soluble sachets (WSB). The active ingredient in SOVRENTA 15WP is isocycloseram at 15% w/w concentration.

1.2 Product identification

Applicant:	Syngenta Crop Protection AG (Switzerland)
Product name:	SOVRENTA 15WP
Other names:	SOVRENTA, isocycloseram WP, PLINAZOLIN technology
Active ingredient (AI):	Isocycloseram (150 g/kg)
CAS no.:	2061933-85-3
Product type:	Indoor Residual Spray
Target application rate:	120 mg AI/m^2
Spray concentration:	3 mg/ml
Volume applied:	40 ml/m^2

1.3 Active ingredient statement

Isocycloseram (CAS No. 2061933-85-3) is a new insecticide and acaricide in the isoxazolines chemical group developed by Syngenta Crop Protection AG (Switzerland). Isocycloseram produces an insecticidal effect by binding to the gamma aminobutyric acid (GABA) receptor, thereby inhibiting the neurotransmission followed by hyperexcitation and death in insects.

1.4 Summary of Findings

In this human health risk assessment, the estimated risk ratios for SOVRENTA 15WP are based on the highest spray concentration of isocycloseram (maximum concentration 120 mg AI/m^2).

The assessment supports the following conclusions:

- The existing toxicology database for SOVRENTA 15WP and isocycloseram technical is adequate for risk assessment and supports the proposed labelled uses of SOVRENTA 15WP up to a concentration of 120 mg isocycloseram/m^2.

- Applying the appropriate acute and chronic tolerable systemic doses (references doses) to the exposure assessment, all risk ratios are less than 1, hence, do not exceed the level of concern.
- The use of isocycloseram formulated as wettable powder (15% w/w, WP) and used as an indoor residual spray in the course of vector control does not present any unacceptable risk for operators, residents, residents working as operators, or to children, toddlers, infants, or newborns exposed through breast milk.
- The assessment of the submitted information supports the prequalification of the product SOVRENTA 15WP for use as an indoor residual spraying insecticide.

2 Human health risk assessment

This human health risk assessment for SOVRENTA 15WP is conducted according to the "*A Generic Risk Assessment Model for Indoor Residual Spraying of Insecticides, 2nd edition"* (GRAM) (WHO, 2018). Risk assessment involves three steps: Hazard assessment, Exposure assessment and Risk characterization.

- **Hazard assessment** is the identification of the possible toxic effects of a substance, the dose/exposure levels at which those effects occur, and the dose/exposure levels below which no adverse effects are observed. Authoritative evaluations are used as starting points for the risk assessment of insecticides. Examples of authoritative evaluations are: Joint Meeting on Pesticide Residues (JMPR), International Programme on Chemical Safety (IPCS), International Agency for Research and Cancer (IARC), United States Environmental Protection Agency (USEPA), European Food Safety Authority (EFSA).
- **Exposure assessment** is assessed in a "guideline scenario" which assumes that the insecticide is used according to the instructions given on the product label and in WHO guideline information. Conservative high-end point estimates of the default distributions are used as defaults. No account is taken of intended misuse. All relevant routes of exposure are covered.
- In **risk characterization,** estimates of exposure are compared with acceptable exposure levels previously defined in hazard assessment in all relevant exposure situations.

2.1 Hazard assessment

2.1.1 SOVRENTA 15WP

SOVRENTA 15WP is practically non-toxic via the oral route of exposure. The acute dermal toxicity study was conducted in accordance with OECD Test Guideline 402 which uses the limit dose of 2000 mg/kg/bw. No mortality or toxicity was seen at this dose; therefore, the Global Harmonization System (GHS) would place these test substances under Category 5. The applicant provided an acceptable weight of evidence postulating that the dermal LD_{50} of SOVRENTA 15WP could be higher than the experimental value and provided the necessary evidence to update the acute dermal toxicity category from Category 5 to "Not classified". It is classified as Category 4 for the inhalation route of exposure. It is not a skin irritant, but it did result in being a dermal sensitizer (GHS Category 1B) and a mild eye irritant (GHS Category 2B). Acute studies were conducted at Charles River Laboratories Hungary Kft., Hungary, following OECD guidelines and GLP regulations. Acute toxicity studies conducted with SOVRENTA 15WP are summarized in the following table.

Table 1. Acute toxicity of SOVRENTA 15WP

Route of exposure	Species	Toxicity	GHS category	Reference
Acute oral toxicity	Rat	LD_{50} > 5000 mg/kg bw	Not classified	CRL, 2022a
Acute dermal toxicity	Rat	$LD_{50} \geq$ 5000 mg/kg bw	Not classified	CRL, 2022b Syngenta, 2025
Acute inhalation toxicity	Rat	$LC_{50} \geq$ 1.15 mg/L (4 hours)	4	CRL, 2022c
Primary dermal irritation	Rabbit	Not irritant	Not classified	CRL, 2022e
Primary eye irritation	Rabbit	Mildly irritating	2B	CRL, 2022d
Skin sensitization, Local Lymph Node	Mouse	Sensitizer (EC3 19.8%)	1B	CRL, 2022f

2.1.2 Active ingredient – Isocycloseram

The product, SOVRENTA 15WP is composed of the AI, isocycloseram. This risk assessment relies heavily on toxicity studies conducted on the AI itself as the AI is the biologically active substance that produces a targeted pesticidal effect but can also have the potential to produce toxic biological effects. Isocycloseram is a new AI belonging to the chemical group isoxazolines. Toxicology studies have been evaluated by the Joint FAO/WHO Meeting on Pesticide Residues (JMPR, 2023). The toxicity profile of isocycloseram is presented in Appendix A and the complete Hazard Assessment of the AI is presented in Appendix B.

The intent of the hazard assessment of an AI (Appendix B) is to consolidate the relevant toxicological information and authoritative evaluations from national and/or international organizations and characterize the chemical as it relates to uses of VCPs. For the active ingredient, PQT/VCP relies on these authoritative evaluations, does not state specific data requirements on behalf of VCP, and focuses on the studies and endpoints applicable to the risk assessment of the use patterns of VCPs. As such, the hazard assessment is not exhaustive in its summary of publicly available information characterizing the hazard of the AI. The toxicity database of isocycloseram has adequate studies for hazard characterization.

2.1.2.1 Isocycloseram Profile Statement

Isocycloseram targets the adrenals, spleen, testes, liver and intestines in the repeat-dose rodent studies. Repeat-dose dog studies resulted in critical weight loss. No dermal or inhalation systemic toxicities were available. There is no evidence for developmental, reproductive, carcinogenic or genotoxic potential and isocycloseram is unlikely to be immunotoxic (JMPR, 2023).

2.1.2.2 Acute studies

Isocycloseram is of low toxicity following acute exposure. The acute oral has a median lethal dose (LD_{50}) greater than 4500 mg/kg bw in female rats and the dermal 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 greater than 4.62 mg/L (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.

Table 2 Acute Toxicity of Isocycloseram Technical

Route of exposure	Species	Toxicity	GHS category	Reference
Acute oral toxicity	Rat	LD_{50} = 4500 mg/kg	5	JMPR, 2023
Acute dermal toxicity	Rat	LD_{50} > 5000 mg/kg	Not classified	JMPR, 2023
Acute Inhalation (nose only)	Rat	LC_{50} > 4.62 mg/L	4	JMPR, 2023
Dermal irritation	Rabbit	Non-irritant	-	JMPR, 2023
Eye irritation	Rabbit	Minimal to slight irritant	2B	JMPR, 2023
Skin sensitization, LLNA	Mouse	Sensitizer	1A	JMPR, 2023

Skin sensitization, Maximization Test (Buehler)	Guinea Pig	Non-sensitizer		JMPR, 2023

2.1.2.3 Absorption, distribution, metabolism, and excretion

Absorption, distribution, metabolism and elimination (ADME) studies on the AI are considered and integrated into the hazard assessment. Further details on ADME for isocycloseram are available in Appendix B.

Oral absorption: Absorption via the oral route is assumed to be 100% (default value)

Dermal absorption: Based on an available *in vivo* dermal penetration "triple pack" study in rats for a formulation of isocycloseram provided in open literature, and the GRAM default value, a 10% dermal absorption value was considered appropriate for estimating risk of isocycloseram.

Inhalation absorption: Absorption via the inhalation route is assumed to be 100% that via the oral route. Due to the lack of a long-term inhalation study, the oral equivalent is used for the inhalation risk assessment.

2.1.3 Points of departure (POD) and reference doses (RfD)

2.1.3.1 Points of departure

Points of departure (PODs) (No Observed Adverse Effect Level [NOAEL]; Benchmark Dose [BMD]) are determined from the toxicological database based on the most sensitive endpoints. Once PODs are developed, safety factors (SF) and uncertainty factors (UF) are used in conjunction with the PODs to derive a safe exposure level, generally referred to as reference dose (RfD) or acceptable daily intake (ADI).

2.1.3.2 Reference doses

A reference dose (RfD) is an estimate of daily oral exposure (acute, aRfD) for a duration of 24 hours or less or chronic oral exposure (cRfD) for a duration of several months to a lifetime that is likely to be without an appreciable risk of deleterious effects during a lifetime. Both an aRfD and a cRfD can be derived from a NOAEL, LOAEL, or a benchmark dose, with uncertainty factors generally applied to reflect limitations of the data used.

Acute reference dose (aRfD)

JMPR selected aRfD from the 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 (2023). This study is appropriate 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.

aRfD = 50 mg/kg bw ÷ 100 = 0.5 mg/kg bw

Chronic reference dose (cRfD)

The 18-month carcinogenicity study in mouse and the chronic/(24-month) carcinogenicity study in rat support establishing a cRfD of 0.02 mg/kg/day. 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.

These studies are appropriate 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 cRfD.

cRfD = 2 mg/kg bw/day ÷ 100 = 0.02 mg/kg bw/day

Acceptable daily intake (ADI)

JMPR (2023) has established an acceptable daily intake at 0 – 0.02 mg/kg bw/day from the two chronic carcinogenicity studies in mouse and rat and the safety factor of 100X (10X for interspecies extrapolation and 10X for intraspecies variation).

ADI = 0.02 mg/kg bw/day

2.1.3.3 Selection of the tolerable systemic dose (TSD)

The PQT/VCP selected the aRfD of 0.5 mg/kg/day as the TSD for acute exposure (TSD_{AC}) since an aRfD for isocycloseram was established for this population.

TSD_{ac} = 0.5 mg/kg bw/day

The PQT/VCP selected the cRfD of 0.02 mg/kg bw/day as the TSD for long term (TSD) risk characterization since the appropriate studies for a cRfD were available.

TSD = 0.02 mg/kg bw/day

2.2 Exposure assessment

The second step in performing a risk assessment is to estimate exposure to the insecticide in the various groups of people potentially at risk. Exposure must take various parameters into consideration, including the route of exposure, the actual amounts of material involved, the duration of exposure in terms of both daily and annual exposure and seasonality and whether this exposure is intermittent or continuous.

Conservative, high-end point estimates of the default distributions are used as defaults in the exposure assessment. The default values may be modified by users of the models on a case-by-case basis and replaced with appropriate measured or otherwise improved point estimates or distributions, when applicable. Similarly, the application of anthropometric and physiological datasets derived from the true target population, when available, is likely to yield more accurate exposure predictions.

The exposure assessment (i.e., exposure calculations) is assessed according to the WHO-GRAM (second edition): "*Generic Risk Assessment Model for Indoor Residual Spraying of Insecticides" 2nd Edition (2018)*"

and chemical-specific data. Exposure assessment includes operators mixing and loading, application of the insecticide product by spraying and washing and maintenance of the equipment, dermal exposure through contaminated surfaces, ingestion exposure from foodstuffs on surfaces, and exposure via breast milk. In the total exposure assessments, all relevant routes and different scenarios were summed up to derive the total systemic dose. Exposure is also assessed in a "lax standard scenario" (Appendix C), which increases the anticipated exposure based on the removal of a safety factor associated with the use of personal protective equipment. This is presented for informational purposes based on its inclusion in the GRAM. WHO does not recommend the application of IRS without PPE.

SOVRENTA 15WP is a mixture containing isocycloseram (15% w/w) and other ingredients. SOVRENTA 15WP is intended to be used for malaria control as an Indoor Residual Spray (IRS). The product is wettable powder (WP) containing 150 g/kg of isocycloseram supplied in water soluble bags and will be applied exclusively on the inner walls of the houses/huts. The target application rate of the product is 120 mg isocycloseram per m^2. The volume applied per m^2 is 40 ml, hence the concentration of the spray solution is 3 mg AI/ml (120 mg/m^2: 40 ml/m^2 = 3 mg AI/ml). The most conservative aRfD and cRfD available were applied to the exposure assessment. Given that the resulting risk rations were all < 1, no further refine is necessary.

The following abbreviations and default values are used throughout the exposure assessment:

Abbreviation	Definition	Value	Data derived or Default Value
Abs-D	Dermal absorption	10%	Data derived/Default (GRAM)
Abs-P	Respiratory absorption	100%	Default (GRAM)
Abs-O	Oral absorption	100%	Default (GRAM)
AT	Average time	365 days	Default (GRAM)
AV	Average proportion of spray residue on the wall during 6 months of first-order kinetics' decay with a half-time of 60 d	0.42	Default (GRAM)
BV	Breathing volume	1.25 M^3/hr	Default (GRAM)
BW	Body weight	60 kg/adult 23.9 kg/children 10 kg/toddlers 8 kg for infants	Default (GRAM)
C_{spray}	Concentration of the AI in the spray in mg/ml	120 mg/m^2 ÷ 40 ml/m^2 = 3 mg/ml	Data derived (Applicant)
CF	Concentration of formulation mg/g (product label)	15% = 150 mg AI/g	Data derived (Applicant)
$Dose_{Mbw}$	Maternal daily dose	0.481µg/kg bw/day	Data derived (Applicant)
ED	Exposure duration	4 hours of spraying per 8 hours working day	Default (GRAM)
EF	Exposure frequency	6 days/week, 6 weeks per treatment round, 2 rounds/year=72 days/year	Default (GRAM)
ESA	Exposed skin areas	IRS: 0.33m^2 for adults; 0.26m^2 for children; 0.15m^2 for toddlers	Default (GRAM)
FHM	Fraction of hand area mouthed	0.164 – 75th percentile	Default (GRAM)
FEXS	Fraction extracted in saliva	0.57	Default (GRAM)
IR	Ingestion rate of milk	0.66 kg/day	Default (GRAM)
Lax	Lax standard scenario	1 (no protection)	Default (GRAM)
ML	Amount of insecticide (AI) handled per day	12 loads per day, 10 L tank, concentration of the	Default (GRAM)

		AI in the spray from the product label and dilution for spraying	
NOD	Number of mixing operations per day	12	Default (GRAM)
PPE	Personal protective equipment (guideline scenario)	0.1 (90% protection)	Default (GRAM)
RPE	Respiratory protection	0.1 for guideline scenario and 1.0 for lax standard scenario	Default (GRAM)
SAF	Surface area of food in contact with the shelf. Half of food items are in contact with contaminated surfaces.	0.0169, 0.0126, 0.0124 and 0.0105 m^2 for adults, children, toddlers, and infants, respectively	Default (GRAM)
Sol C	Solubility constant	0.361 for lipid-soluble	Default (GRAM)
$SysD_{TWA}$	TWA systemic dose	Calculated value	Data derived (GRAM)
$SysD_{MAX}$	Maximal systemic dose	Calculated value	Data derived (Applicant)
TC_{WALL}	Target amount of AI on the wall	120 mg /m^2	Data derived (Applicant)
Transl	Fraction translodged onto skin	8% of the amount on the surface	Default (GRAM)
UE_{SOL} / UE_{LIQ}	Unit exposure for handling	water soluble bags (0.04 mg/kg AI)	Default (GRAM)
VS_{dermal}	Volume of spray on hands	8.2 ml	Default (GRAM)

2.2.1 Occupational exposure

2.2.1.1 Operator exposure during mixing and loading of SOVRENTA 15WP

The estimated time weighted average (TWA) systemic dose from isocycloseram to operators due to potential dermal exposure from mixing and loading is calculated as follows:

$$\text{Sys-D}_{TWA} = \frac{UE_{SOL} \times PPE \times ML \times \text{Abs-D} \times EF \times 1000}{BW \times AT}$$

Table 3. Estimated long term systemic dose (TWA) to operator from dermal exposure during mixing and loading.

UE_{SOL} (mg/kg)	PPE	ML	Abs-D (%)	EF (days)	BW (kg)	AT (days)	Systemic dose (µg/kg/day)
Guideline scenario							
0.04	0.1	0.36	10	72	60.0	365	0.0005

UE_{SOL}= 0.04 mg/kg AI handling of water-soluble bags
ML = 3 g a.i/L. diluted into 10 L spray tank (3 x 10 = 30 g/10 L); 12 tank loads per day; 30 g x 12 loads = 360 g or 0.36 kg
1000 = mg to µg

The estimated maximal daily systemic dose to operators due to potential dermal exposure from mixing and loading is calculated as follows:

$$\text{Sys-D}_{MAX} = \frac{UE_{SOL} \times PPE \times ML \times \text{Abs-D} \times 1000}{BW}$$

Table 4. Estimated maximal daily systemic dose to operator from dermal exposure during mixing and loading.

UE_{SOL} (mg/kg)	PPE	ML	Abs-D (%)	BW (kg)	Systemic dose (µg/kg/day)
Guideline scenario					
0.04	0.1	0.36	10	60.0	0.002

UE_{SOL}= 0.04 mg/kg AI handling of water-soluble bags
ML = 3 g a.i/L. diluted into 10 L spray tank (3 x 10 = 30 g/10 L); 12 tank loads per day; 30 g x 12 loads = 360 g or 0.36 kg
1000 = mg to µg

2.2.1.2 Operator exposure during application, washing, and maintenance

2.2.1.2.1 Dermal exposure

The estimated TWA systemic dose of isocycloseram to operators due to potential dermal exposure during application, washing and maintenance is calculated as follows:

$$\text{Sys-D}_{TWA} = \frac{VS_{dermal} \times C_{spray} \times PPE \times EF \times Abs\text{-}D \times 1000}{BW \times AT}$$

Table 5. Estimated long-term (TWA) systemic dose to operator from dermal exposure during application, washing, and maintenance.

VS_{dermal} (ml)	C_{Spray} (mg/ml)	PPE	EF (days)	Abs-D (%)	BW (kg)	AT (days)	Systemic dose (µg/kg/day)
Guideline scenario							
8.2	3.0	0.1	72	10	60	365	0.809

VS_{dermal} = 8.2 ml
C_{spray} = Concentration of the active ingredient in the spray = 3 mg AI/ml
1000 = mg to µg

The estimated maximal systemic dose of isocycloseram to operators due to potential dermal exposure during application, washing and maintenance is calculated as follows:

$$\text{Sys-D}_{MAX} = \frac{VS_{dermal} \times C_{spray} \times PPE \times Abs\text{-}D \times 1000}{BW}$$

Table 6. Estimated maximal systemic dose to operator from dermal exposure during application, washing, and maintenance.

VS_{dermal} (ml)	C_{Spray} (mg/ml)	PPE	Abs-D (%)	BW (kg)	Systemic dose (µg/kg/day)
Guideline scenario					
8.2	3.0	0.1	10	60	4.100

VS_{dermal} = 8.2 ml
C_{spray} = Concentration of the active ingredient in the spray = 3 mg AI/ml
1000 = mg to µg

2.2.1.2.2 Inhalation exposure

The estimated TWA systemic dose of isocycloseram to operators due to potential inhalation exposure during application, washing and maintenance is calculated as follows:

$$\text{Sys-D}_{TWA} = 10^{-3} \times TC_{WALL} \times RPE \times BV \times ED \times Abs\text{-}P \times EF \times 1000$$

BW x AT

Table 7. Estimated long-term (TWA) systemic dose to operator from inhalation exposure during application, washing and maintenance.

TC_{WALL} (mg/m²)	RPE	BV (m³/hr)	ED (hours)	Abs-P (%)	EF (days)	BW (kg)	AT (days)	Systemic dose (µg/kg/day)
Guideline scenario								
120	**0.1**	**1.25**	**4**	**100**	**72**	**60**	**365**	**0.197**

TC_{WALL} = Target concentration = 120 mg/m²
1000 = mg to µg

The estimated maximal systemic dose of isocycloseram to operators due to potential inhalation exposure during application, washing and maintenance is calculated as follows:

$$\text{Sys-D}_{MAX} = \frac{10^{-3} \times TC_{WALL} \times RPE \times BV \times ED \times Abs \times 1000}{BW}$$

Table 8. Estimated maximal systemic dose to operator from inhalation exposure during application, washing and maintenance.

TC_{WALL} (mg/m2)	RPE	BV (m³/hr)	ED (hours)	Abs-P (%)	BW (kg)	Systemic dose (µg/kg/day)
Guideline scenario						
120	**0.1**	**1.25**	**4**	**100**	**60**	**1.000**

TC_{WALL} = Target concentration = 120 mg/m²
1000 = mg to µg

2.2.1.3 Total operator exposure

Estimated total systemic exposure from dermal exposure from mixing and loading and from dermal and inhalation exposure from application, washing and maintenance.

Table 9. Estimated total operator exposure from dermal and inhalation exposure.

Scenario	Dermal exposure		Inhalation exposure	Estimated systemic dose (µg/kg/day)
	Mixing/Loading (µg/kg/day)	Application/Washing/ Maintenance (µg/kg/day)	Application/Washing/ Maintenance (µg/kg/day)	
Estimated TWA				
Guideline	**0.0005**	**0.809**	**0.197**	**1.007**
Estimated maximal				
Guideline	**0.002**	**4.100**	**1.000**	**5.102**

2.2.2 Residential exposure

2.2.2.1 Dermal exposure due to touching contaminated surfaces

The estimated TWA dermal exposure due to touching contaminated surfaces is calculated. The default concentration of the insecticide on surfaces with which inhabitants are in contact is 15% of the wall target concentration.

$$\text{Sys-D}_{TWA} = \frac{0.15 \times TC_{WALL} \times AV \times Transl \times ESA \times Abs\text{-}D \times 1000}{BW}$$

The estimated maximal dermal exposure due to touching of contaminated surfaces is calculated as follows:

$$\text{Sys-D}_{MAX} = \frac{0.15 \times TC_{WALL} \times Transl \times ESA \times Abs\text{-}D \times 1000}{BW}$$

Table 10. Estimated systemic dose from dermal exposure due to touching contaminated surfaces.

Population	TC_{WALL} (mg/m²)	Transl (%)	AV	ESA (m²)	Abs-D (%)	BW (kg)	Systemic dose (µg/kg/day)
TWA scenario							
Adults	120	8	0.42	0.308	10	60	0.310
Children	120	8	0.42	0.153	10	23.9	0.387
Toddlers	120	8	0.42	0.133	10	10	0.803
Infants	120	8	0.42	0.394	10	8	2.981
Maximal scenario							
Adults	120	8	N/A	0.308	10	60	0.739
Children	120	8	N/A	0.153	10	23.9	0.922
Toddlers	120	8	N/A	0.133	10	10	1.911
Infants	120	8	N/A	0.394	10	8	7.097

AV = Average proportion of spray residue on the wall during 6 months of first order kinetic decay (default = 0.42)
Transl = Fraction translodged onto skin (default = 8%)
ESA = 0.308 m²/adults; 0.153 m²/child; 0.133 m² /toddlers and 0.394 m²/infants.
15%= Default concentration of AI on surfaces
1000 = mg to µg

2.2.2.2 Ingestion exposure from contaminated foodstuffs

The estimated TWA exposure due to ingestion of contaminated foodstuffs from surfaces is calculated. The concentration of the active ingredient on the surfaces is considered to be 30% of the target concentration on the wall immediately after the spraying.

$$\text{Sys-D}_{TWA} = \frac{0.30 \times 0.5 \times AV \times TC_{WALL} \times Transl \times SAF \times Abs\text{-}O \times 1000}{BW}$$

The estimated maximal exposure due to ingestion of contaminated foodstuffs from surfaces is calculated as follows:

$$\text{Sys-D}_{MAX} = \frac{0.30 \times 0.5 \times TC_{WALL} \times Transl \times SAF \times Abs\text{-}O \times 1000}{BW}$$

Table 11. Estimated ingestion exposure of contaminated foodstuffs from surfaces.

Population	TC_{WALL} (mg/m²)	AV	Transl (%)	SAF (m²)	Abs-O (%)	BW (kg)	Systemic dose (µg/kg/day)
TWA scenario							

Adults	**120**	**0.42**	**8**	**0.017**	**100**	**60**	**0.170**
Children	**120**	**0.42**	**8**	**0.013**	**100**	**23.9**	**0.319**
Toddlers	**120**	**0.42**	**8**	**0.012**	**100**	**10**	**0.750**
Infants	**120**	**0.42**	**8**	**0.011**	**100**	**8**	**0.794**
Maximal scenario							
Adults	**120**	**N/A**	**8**	**0.017**	**100**	**60**	**0.406**
Children	**120**	**N/A**	**8**	**0.013**	**100**	**23.9**	**0.759**
Toddlers	**120**	**N/A**	**8**	**0.012**	**100**	**10**	**1.786**
Infants	**120**	**N/A**	**8**	**0.011**	**100**	**8**	**1.890**

AV = Average proportion of spray residue on the wall during 6 months of first order kinetic decay (default = 0.42)
Transl = fraction translodgeable to foods (default = 8%) of amount present on surfaces
30% = Default concentration of AI on surfaces.

2.2.2.3 Ingestion exposure of toddlers via hand-to-mouth behavior

The estimated TWA ingestion exposure of toddlers via hand to mouth behavior is calculated as follows:

$$SysD\text{-}_{TWA} = \frac{0.15 \times AV \times TC_{WALL} \times Transl \times ESA \times F_{HM} \times F_{EXS} \times Abs\text{-}O \times 1000}{BW}$$

The estimated maximal ingestion exposure of toddlers via hand to mouth behavior is calculated as follows:

$$SysD\text{-}_{MAX} = \frac{0.15 \times TC_{WALL} \times Transl \times ESA \times F_{HM} \times F_{EXS} \times Abs\text{-}O \times 1000}{BW}$$

Table 12. Estimated ingestion exposure of toddlers via hand-to-mouth behavior.

Conc. on surface to wall target conc.	TC_{WALL} (mg/m^2)	AV	Transl (%)	ESA (m^2)	FHM	FEXS	Abs-O (%)	BW	Systemic dose (µg/kg/day)
TWA scenario									
0.15	**120**	**0.42**	**8**	**0.023**	**0.164**	**0.57**	**100**	**10**	**0.130**
Maximal scenario									
0.15	**120**	**N/A**	**8**	**0.023**	**0.164**	**0.57**	**100**	**10**	**0.310**

AV = Average proportion of spray residue on the wall during 6 months of first order kinetic decay (default = 0.42)
F_{HM} = fraction of hand area mouthed (default = 0.164 – 75th percentile)
F_{EXS} = Fraction extracted in saliva (default = 0.57)
BW = 10 kg (toddlers)
ESA = 0.023 m^2 /toddlers for hands
15%= Default concentration of AI on surfaces

2.2.2.4 Total residential exposure

Table 13. Estimated total residential systemic dose from dermal, ingestion, and hand-to-mouth exposure.				
Population	**Dermal exposure (Contaminated Surfaces) (µg/kg/day)**	**Ingestion contaminated foods (from surfaces) (µg/kg/day)**	**Hand to mouth (µg/kg/day)**	**Estimated systemic dose (ug/kg bw/day)**
TWA scenario				
Adults	**0.310**	**0.170**		**0.481**
Children	**0.387**	**0.319**		**0.706**
Toddlers	**0.803**	**0.750**	**0.130**	**1.683**
Infants	**2.981**	**0.794**		**3.775**
Maximal scenario				
Adults	**0.739**	**0.406**		**1.145**
Children	**0.922**	**0.759**		**1.681**
Toddlers	**1.911**	**1.786**	**0.310**	**4.006**
Infants	**7.097**	**1.890**		**8.987**

2.2.2.5 Combined exposure for resident operator

This represents the worst-case scenario for a resident who also works as an operator.

Combined Exposure = Total Operator Exposure + Total Residential exposure

Table 14. Combined exposure for resident operator.			
Population	**Total operator exposure (µg/kg/day)**	**Total residential exposure (µg/kg/day)**	**Total combined exposure (µg/kg/day)**
TWA exposure – guideline			
Adult	**1.007**	**0.481**	**1.488**
Maximal daily dose – guideline			
Adult	**5.102**	**1.145**	**6.247**

2.2.3 Exposure via breast milk

Newborns might be exposed to isocycloseram through the breastmilk of lactating mothers. The estimated systemic dose to the newborn is calculated based on the estimated systemic dose to the mother through residential exposure post-spraying. WHO does not approve nor recognize a scenario where a nursing or lactating mother is working as an operator, therefore, this scenario has not been evaluated.

Estimates for systemic TWA and maximal doses from exposure via breast milk are calculated as follows:

$$SysD_{TWA} = \frac{SolC \times Dose_{Mbw} \times T_{1/2} \times IR \times Abs\text{-}O}{BW}$$

Table 15. Estimated systemic dose from exposure to breast milk (residential exposure).							
Population	**SolC**	**Dose$_{Mbw}$ (adult; µg/kg bw)**	**$T_{1/2}$ (days)**	**IR (kg/day)**	**Abs-O (%)**	**BW (kg)**	**Systemic dose (µg/kg/day)**
TWA							
Newborns	**0.361**	**0.481**	**2.4**	**0.53**	**100**	**4.2**	**0.057**

Sol C = Solubility constant = 0.361 for water soluble
Dose$_{Mbw}$ = Daily dose to the mother (residential exposure)
$T_{1/2}$= First order kinetics half-life of isocycloseram ranged from 1.4 days-3.3 days. Based on available information the estimated average of 2.4 days (57 hours) was used.
IR = (default value=0.53 kg/day for the first month and 0.68 kg/day for the first 12 months

2.3 Risk characterization

The purpose of risk characterization is to examine the probability of adverse effects occurring from the use of the insecticide under defined exposure conditions. Risk characterization consists of comparing the estimate of total exposure (i.e., estimated systemic dose) with the TSD established in the hazard assessment. The TSD is the same as the ADI or the cRfD established for the active ingredients (WHO, 2018).

$$\text{Ratio} = \frac{\text{Estimated maximal daily systemic dose (µg kg bw/day)}}{\text{TSD (µg kg bw/day)}}$$

When the ratios are less than 1, the health risk is deemed acceptable. Ratios greater than 1 may indicate possible health risks, in which case steps may be taken to reduce the risk, such as changing the recommended operational conditions or the amount of active ingredient in the technical product. A risk benefit analysis in which the risks of potential toxicity are compared with potential health benefits (disease prevention) may be needed in some cases (WHO, 2018).

Table 16. Risk characterization for all populations and exposure scenarios.			
Population	**Operator exposure (dermal and inhalation) (µg/kg bw/day)**	**TSD (µg/kg bw/day)**	**Risk ratio**
Total operator exposure – TWA scenario			
Adult – guideline	**1.007**	**20**	**0.05**
Total operator exposure – maximal scenario			
Adult – guideline	**5.102**	**500**	**0.01**
Population	**Residential exposure (dermal and foodstuffs) (µg/kg bw/day)**	**TSD (µg/kg bw/day)**	**Risk ratio**
Total exposure – TWA scenario			
Adult	**0.481**	**20**	**0.02**
Children	**0.706**	**20**	**0.04**
Toddler	**1.683**	**20**	**0.08**
Infant	**3.775**	**20**	**0.19**
Total exposure – maximal scenario			
Adult	**1.145**	**500**	**0.002**
Children	**1.681**	**500**	**0.003**

Table 16. Risk characterization for all populations and exposure scenarios.			
Toddler	**4.006**	**500**	**0.008**
Infant	**8.987**	**500**	**0.018**
Total operator/residential exposure – TWA scenario			
Adult – guideline	**1.487**	**20**	**0.07**
Adult – maximal	**6.247**	**500**	**0.01**
TWA Total exposure – breast milk – residential			
Newborn	**0.062**	**20**	**0.003**

For operators (mixing/loading/applying/maintenance), the risk ratios are all below 1.

For adult resident scenario (dermal exposure through surfaces and ingestion of foodstuffs), the risk ratios are below 1 for all populations of concern.

For resident operators, the risk ratios are all below 1.

For the potential exposure via breast milk of mother as resident, the risk ratio is below 1.

2.4 Conclusions

The use of SOVRENTA 15WP formulated as wettable powder (containing 15% w/w isocycloseram) and used as IRS in the course of vector control does not present any unacceptable risk for operators, residents, residents working as operators, or to children, toddlers, infants, or newborns exposed through breastmilk. Therefore, it can be concluded that SOVRENTA 15WP can be used safely for its intended purpose. Assessment of the submitted information supports the prequalification of this product.

3 References

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4 Appendices

4.1 Appendix A. Toxicity profile: Isocycloseram technical

Table A.1 Acute toxicity of isocycloseram technical.

Route of exposure	Species	Toxicity	GHS category	Reference
Acute oral toxicity	Rat	LD_{50} = 4500 mg/kg	5	JMPR, 2023
Acute dermal toxicity	Rat	LD_{50} > 5000 mg/kg	Not classified	JMPR, 2023
Acute Inhalation (nose-only)	Rat	LC_{50} > 4.60 mg/L	4	JMPR, 2023
Dermal irritation	Rabbit	Non-irritant	-	JMPR, 2023
Eye irritation	Rabbit	Minimally to slightly irritating	2B	JMPR, 2023
Skin sensitization, LLNA	Mouse	Sensitizer		JMPR, 2023
Skin sensitization, Maximization Test (Buehler)	Guinea Pig	Non-sensitizer		JMPR, 2023

Table A.2 Summary of subchronic, chronic, and carcinogenicity studies with isocycloseram.

Study dose levels	Results (mg/kg bw/day)	Reference
28-day oral study, mice Doses: 0, 100, 300, 700, 1000 ppm equivalent to 0, 17.4, 55.9, 132, 172 mg/kg/day for males 0, 20.9, 60.5, 142, 176 mg/kg/day for females	NOAEL = 17.4 mg/kg/day LOAEL = 55.9 mg/kg/day based on histopathological findings in liver, spleen, and duodenum.	JMPR, 2023
28-day feeding study, rats Doses: Males: 0, 50, 200, 350, 500 ppm equivalent to 0, 4.3,16.3, 26.8, 37.0 mg/kg/day Females: 0, 50, 700 ppm Equivalent to 0, 4.5,50.1, mg/kg/day for females Doses above 50.1 mg/kg/day were not tolerated and animals were terminated prematurely on Day 11.	NOAEL = 4.3 mg/kg/day LOAEL = 16.3 mg/kg/day based on histopathological findings in the adrenals of males and on clinical signs, reductions in body weight gain and food consumption, and on microscopic findings in adrenals, liver, and kidneys in females.	JMPR, 2023
90-day dietary oral toxicity, mice Doses: 0 ppm, 50 ppm, 300 ppm, 700 ppm equivalent to 0, 8.0, 48.8, 117 mg/kg bw/day males and 0, 9.9, 51.6, 140 mg/kg/day females	NOAEL = 8 mg/kg/day LOAEL = 48.8 mg/kg bw/day in males and 41 mg/kg bw/day in females based on histopathological findings in adrenals and spleen (these findings are supported by alterations in clinical chemistry parameters)	JMPR, 2023
90-day dietary oral toxicity study, rats	NOAEL = 3.9 mg/kg bw/day LOAEL = 11.2 mg/kg/day in males based on higher kidney weight and histopathological	JMPR, 2023

Table A.2 Summary of subchronic, chronic, and carcinogenicity studies with isocycloseram.		
Study dose levels	**Results (mg/kg bw/day)**	**Reference**
Doses: 0 ppm, 50 ppm, 150 ppm, 300 ppm equivalent to 0, 3.9, 11.2, 22.0 mg/kg bw/day males and 0, 4.4, 13.4, 24.0 mg/kg/day females	findings in testis and epididymis.	
28-day oral (capsule) study, dogs Doses: 0, 10, 50, 150 (later reduced to 80) mg/kg bw/day (males) 0, 10, 35, and 70 mg/kg/day (females)	NOAEL = 10 mg/kg bw/day LOAEL= 35/50 mg/kg/day (m/f) based on body weight losses and reduced food intake	JMPR, 2023
90-day feeding study, dogs Doses: 0, 5, 15, 35 mg/kg/day The high dose was later reduced to 25 mg/kg/day due to marked body weight losses.	NOAEL = 15 mg/kg/day LOAEL = 35/25 mg/kg/day based on body weight losses and reduced food intake.	JMPR, 2023
18-month Carcinogenicity Study, mice Doses: 0, 15, 60, 200ppm Equivalent to: 0, 1.7, 6.7, 23.1 mg/kg/day (M) 0, 1.8, 7.1, 24.4 mg/kg/day (F)	Systemic NOAEL = 1.7 mg/kg bw/day Systemic LOAEL = 6.7 mg/kg bw/day based on increased plasma cell infiltration in the mesenteric lymph nodes Carcinogenicity NOAEL = 23.1 mg/kg bw/day Carcinogenicity LOAEL = Not determined No evidence of carcinogenicity.	JMPR, 2023
Combined Chronic toxicity and Carcinogenicity, rats Doses: 0, 20, 50, 150 ppm Equivalent to: 0, 0.9, 2.3, 7.0 mg/kg/day in males 0, 1.2, 3.0, 9.2 mg/kg/day in females	Systemic NOAEL = 2.3 mg/kg bw/day Systemic LOAEL = 7.0 mg/kg bw/day based on histopathological findins in the testes and epididymides of males Carcinogenicity NOAEL = 7.0 mg/kg bw/day Carcinogenicity LOAEL = Not determined No evidence of carcinogenicity.	JMPR, 2023
Summary of genotoxicity studies with isocycloseram		
Study dose levels	**Results**	**Reference**
Bacterial mutation assay (Ames) Both plate-incorporation and pre-incubation assays: 3, 10, 33, 100, 333, 1000, 2500, and 5000 µg/plate; ±S9-mix	Negative	JMPR, 2023
Mammalian cell mutation assay (Mouse lymphoma assay in L5178Y cells) Experiment I: 3.9, 7.8, 15.6, 31.3, 62.5 µg/mL (±S9-mix) Experiment II: 15.5, 31.0, 46.5, 62.0, 77.5 µg/mL (-S9); 7.8, 15.5, 31.0, 46.5, or 62.0 µg/mL (+S9) Experiment I: 15, 30, 45, 60 µg/mL (±S9) Experiment II: 12.5, 25, 55, and 60 µg/mL (+S9)	Non-mutagenic	JMPR, 2023
Chromosome aberration in vitro (Human lymphocytes) 4-hour exposure: 4.3, 13.2, 23.0 (-S9); 23.0, 40.3, 80.6 (+S9) 22-hour exposure (-S9): 6.4, 11.2, 19.6, 34.4 µg/mL	Non-clastogenic	JMPR, 2023

Table A.2 Summary of subchronic, chronic, and carcinogenicity studies with isocycloseram.		
Study dose levels	**Results (mg/kg bw/day)**	**Reference**
Micronucleus assay in rat bone marrow (oral administration) Range finding experiment: 2 x 2000 mg/kg bw/day with blood analysis Main study: 2 x 0, 500, 1000, and 2000 mg/kg bw/day	Neither clastogenic nor aneugenic	JMPR, 2023
Summary of developmental toxicity and reproductive studies with isocycloseram		
Study dose levels	**Results (mg/kg bw/day)**	**Reference**
Two Generation Reproduction Toxicity Study, rats. Diet at 0, 1.5, 4, and 12 mg/kg bw/day	Parental systemic NOAEL = 4 mg/kg bw/day Parental systemic LOAEL = 12 mg/kg bw/day based on organ weight changes (adrenals, kidney, and liver) and histopathological findings in intestines and testes in adult rats of both generations. Offspring NOAEL = 4 mg/kg bw/day Offspring LOAEL = 12 mg/kg bw/day based on organ weight changes (adrenals, kidney, and liver) and histopathological findings in intestines and testes in adult rats of both generations. Reproductive NOAEL = 4 mg/kg bw/day Reproductive LOAEL = 12 mg/kg bw/day based on a significant increased in post-implantation loss and impaired pup viability over the first four postnatal days (PNDs).	JMPR, 2023
Developmental Toxicity Study in rats Oral Administration (Gavage) Doses: 0, 3.5, 7.5, and 15 mg/kg/day	Maternal tox NOAEL = 15 mg/kg bw/day (HDT) Maternal tox LOAEL = not established Embryo/fetal tox NOAEL = 7.5 mg/kg bw/day Embryo/fetal tox LOAEL = 15 mg/kg/day rare anomaly of bifid sternebrae in two fetuses from two litters and slight overall increase in skeletal variations in fetuses. It is known that effects on sternal development have a relatively narrow critical sensitivity window in rodents.	JMPR, 2023
Developmental Toxicity Study, New Zealand White Rabbits Oral Administration (Gavage). Doses: 0, 3.5, 7.5, or 15 mg/kg/day	Maternal tox NOAEL = 7.5 mg/kg bw/day Maternal tox LOAEL = 15 mg/kg/day based on slightly reduced body weight gain in rabbits Embryo/fetal tox NOAEL = 15 mg/kg bw/day Embryo/fetal tox LOAEL = not established	JMPR, 2023
Summary of neurotoxicity studies with isocycloseram		
Study dose levels	**Results (mg/kg bw/day)**	**Reference**
Acute neurotoxicity study, rat Doses: 0, 50, 200 or 1000 mg/kg bw	Neurotoxic NOAEL = 1000 mg/kg bw/day (HDT) Systemic NOAEL = 50 mg/kg/day Systemic LOAEL = 200 mg/kg/day based on lower body weight gain, reduced food consumption and transiently depressed activity	JMPR, 2023

Table A.2 Summary of subchronic, chronic, and carcinogenicity studies with isocycloseram.		
Study dose levels	**Results (mg/kg bw/day)**	**Reference**
	at higher doses.	
Subchronic (90-day) neuro-toxicity study, rat Doses: 0, 50, 150, and 300 ppm Equivalent to 3.9, 13.2, 24.8 males 5.5, 15.6, 32.7 mg/kg/day females	NOAEL = 24.8 mg/kg bw/day LOAEL = not established	JMPR, 2023

4.2 Appendix B. Hazard assessment Isocycloseram

1 Introduction to Isocycloseram (CAS No. 2061933-85-3)

The use of vector control products (VCPs) is critical in the protection of global human health by combatting and preventing the transmission of major vector-borne diseases. Through the procedures of Prequalification Unit Vector Control Product Assessment Team (PQT/VCP), VCPs and public health pesticide active ingredients are assessed to determine that they can be used safely and effectively and are manufactured to a high-quality standard. The intent of the hazard assessment of each active ingredient (AI) is to consolidate the relevant toxicological information and authoritative evaluations from national and/or international organizations and characterize the chemical as it relates to uses of VCPs. PQT/VCP relies on these authoritative evaluations, focusing on the studies and endpoints applicable to the risk assessment of the use patterns of VCPs. As such, this hazard assessment is not exhaustive in its summary or assessment of publicly available information characterizing the hazard of the AI.

Chemically, isocycloseram (CAS No. 2061933-85-3) is a new insecticide in the isooxazoline chemical class developed by Syngenta Crop Protection AG (Switzerland). Isocycloseram produces an insecticidal effect by binding to the gamma aminobutyric acid (GABA) receptor, thereby inhibiting the neurotransmission followed by hyperexcitation in insects. Isocycloseram was evaluated by JMPR for the first time in 2023.

2 Hazard Characterization

Only studies relevant to the hazard evaluation are discussed, for a full description of all toxicology studies related to the active ingredient, the reader is referred to the references cited. There is sufficient information on the toxicity of the active ingredient, isocycloseram technical, to conduct a human health hazard assessment.

2.1 Acute Toxicity

Isocycloseram is of low toxicity following acute exposure. The acute oral has a median lethal dose (LD50) is greater than 4500 mg/kg bw in female rats and the dermal 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 (LC50) 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 (Appendix 5.1).

2.2 Subchronic Toxicity

Subchronic toxicity studies on isocycloseram were conducted in 28- and 90-day oral route toxicity studies in rats, mice, and dogs. There were no subchronic repeat dose dermal exposure or inhalation studies submitted. The target organs identified were the adrenals, testes, liver, and intestines. Subchronic dermal and subchronic inhalation studies on isocycloseram were not submitted.

Administration of isocycloseram to rats, mice, and dogs by the oral route resulted in increases in histopathological findings in the adrenals, liver, spleen, intestine, testes, and epididymis and general body weight and food consumption changes. The principal target organs were the adrenals, testes, liver and intestines with the rat being the most sensitive species.

2.2.1 Rodent Studies

In a 28-day oral study in mice, groups of 5 male and 5 female Crl:CD 1 mice were fed diets containing isocycloseram (purity, 98%) at 0, 100, 300, or 1000 ppm equivalent to 0, 17.4, 55.9, 132, and 172 mg/kg/day for males and 0, 20.9, 60.5, 142, and 176 mg/kg/day for females, respectively. A NOAEL was established at 17.4 mg/kg/day, based on histopathological findings identified in the liver, spleen, and duodenum at the LOAEL of 55.9 mg/kg/day.

In a 90-day oral toxicity study, isocycloseram (purity 98.4%) was administered to groups of 10 male and 10 female Crl:CD 1 mice (10/sex/dose) in the diet at dose levels of 0 ppm, 50 ppm, 300 ppm, and 700 ppm (equivalent to 0, 8.0, 48.8, and 117 mg/kg bw/day males and 0, 9.9, 51.6, and 140 mg/kg bw/day females). A NOAEL of 8 mg/kg/day was established based on histopathological findings in adrenals and spleen at 48.8 mg/kg/day (LOAEL). The adverse findings were supported by alterations in the clinical chemistry measurements for these mice.

In a 28-day feeding study in rats, the isocycloseram was administered via diet at concentrations of 0, 50, 200, 350 or 500 ppm (0, 4.3, 16.3, 26.8 and 37.0 mg/kg bw per day) to male animals. Females received

isocycloseram at dose levels of 0, 50 or 700 ppm (0, 4.5 and 50.1 mg/kg bw per day). Doses above 700 ppm were not tolerated, and animals were terminated prematurely on day 11 due to mortality and severe clinical signs, and not further examined. The NOAEL of 50 ppm (equal to 4.3 mg/kg bw per day) was based on histopathological findings in the adrenals of males at the LOAEL of 16.3 mg/kg bw per day and on clinical signs, reductions in body weight gain and food consumption, and on microscopic findings in adrenals, liver, and kidneys in females at the LOAEL of 50.1 mg/kg bw per day.

In a 90-day feeding study in rats, isocycloseram was fed via the diet at concentrations of 0, 50, 150 or 300 ppm (0, 3.9, 11.2 and 22.0 mg/kg bw per day for males, 0, 4.4, 13.4 and 24.0 mg/kg bw per day for females). The NOAEL was 3.9 mg/kg bw per day derived from the LOAEL of 11.2 mg/kg bw per day in males, based on higher kidney weight and histopathological findings in testis and epididymis.

2.2.2 Dog Studies

In a 28-day study using capsule administration, dogs received isocycloseram at doses of 0, 10, 50 or 150 mg/kg bw per day (later reduced to 80 mg/kg bw per day) in males, and 0, 10, 35 or 70 mg/kg bw per day in females. Due to excessive toxicity in both sexes at the highest dose the study was prematurely terminated. The NOAEL was 10 mg/kg bw per day, based on body weight losses at higher dose levels at the LOAEL of 50/35 mg/kg/day (males/females).

In a 90-day feeding study in dogs, the dose levels were 0, 5, 15, and 35 mg/kg bw per day. However, since the high dose caused marked body weight losses, it was reduced to 25 mg/kg bw per day. The NOAEL was 15 mg/kg bw per day, based on body weight losses and reduced food intake at the top dose of 35/25 mg/kg bw per day (LOAEL).

2.3 Chronic Toxicity and Carcinogenicity

2.3.1 Rat Studies

In a combined chronic toxicity and carcinogenicity study in rats, isocycloseram was administered for 24 months at concentrations of 0, 20, 50 or 150 ppm (0, 0.9, 2.3 and 7.0 mg/kg bw per day for males, 0, 1.2, 3.0 and 9.2 mg/kg bw per day for females) via the diet. The NOAEL of 2.3 mg/kg bw per day was based on histopathological findings in the testes and epididymides of males at 150 ppm. The respective LOAEL was 7.0 mg/kg bw per day. There was no evidence of carcinogenicity and so accordingly the carcinogenicity NOAEL in this study was 150 ppm (7.0 mg/kg bw per day), the highest dose tested.

2.3.2 Mouse Studies

In an 18-month carcinogenicity study in mice, isocycloseram was administered via diet at concentrations of 0, 15, 60 or 200 ppm (0 1.7, 6.7 and 23.1 mg/kg bw per day for males, 0, 1.8, 7.1 and 24.4 mg/kg bw per day for females). A NOAEL of 1.7 mg/kg bw per day was identified based on increased plasma cell infiltration in the mesenteric lymph nodes at the LOAEL of 6.7 mg/kg bw per day. No increase in neoplastic lesions was seen and, accordingly, the highest dietary concentration of 23.1 mg/kg bw per day was the NOAEL for carcinogenicity.

2.4 Developmental Toxicity

In a rat developmental study, isocycloseram (96.9% purity) was administered to 22 time-mated female Crl:WI(Han) rats per group via gavage at doses of 0, 3.5, 7.5, and 15 mg/kg bw/day on gestation days (GD) 6 through 19. The control group, consisting of 25 females, was dosed with the vehicle (0.5% carboxymethylcellulose with 0.1% Tween 80 in parallel. The maternal NOAEL was 15 mg/kg bw per day, the highest dose tested. The developmental toxicity NOAEL of 7.5 mg/kg bw per day was based on the occurrence of bifid sternebrae (a rare skeletal anomaly) in two fetuses from two separate litters. As slight increase in skeletal variations at 15 mg/kg bw per day was also reported and supported the LOAEL.

In a rabbit developmental study, 22/group time-mated New Zealand female rabbits were artificially inseminated and treated with isocycloseram at dose levels of 0, 3.5, 7.5, or 15 mg/kg bw/day by oral gavage from GD 6 to 27. The maternal NOAEL was 7.5 mg/kg bw per day based on a slightly lower mean body weight gain in the does at the LOAEL of 15 mg/kg bw per day. The NOAEL for developmental toxicity was 15 mg/kg bw per day, the highest dose tested.

2.5 Reproduction Toxicity

In a two-generation reproduction toxicity study, isocycloseram was administered to groups of 24 male and 24 female healthy young Crl:WI(Han) rats (F0 parental generation) in the diet at concentrations of 0, 1.5, 4, 12 mg/kg bw/day. The parental, offspring, and reproductive toxicity all had the same NOAEL value of 4 mg/kg/day established from the LOAEL of 12 mg/kg/day. The LOAEL for reproduction was based on increased post-implantation loss and impaired pup viability during the first 4 postnatal days. The LOAEL for the parental and offspring animals was qualitatively different than the reproduction LOAEL and was based on organ weight changes (adrenals, kidney, and liver) and histopathology in the intestine and test of the adult rats of both generations.

2.6 Genotoxicity

In summary, over a range of standard test batteries, isocycloseram did not show any indication of genotoxicity in vitro or in vivo.

Isocycloseram was tested with Salmonella typhimurium and Escherichia coli tester strains at concentrations up to 5,000 µg/plate did not produce an increased number of reversions with or without S-9 metabolic activation. Isocycloseram did not induce chromosome aberrations in an in vitro cytogenetic test using cultured human lymphocytes. An in vivo bone marrow micronucleus test was performed with isocycloseram using rat at dose levels up to and including the limit dose 2000 mg/kg bw. No increase in the mean frequency of micronucleated polychromatic erythrocytes was observed in the bone marrow of isocycloseram-treated animals.

2.7 Neurotoxicity

Acute and subchronic (90-day) neurotoxicity studies were conducted to assess the neurotoxicological potential of isocycloseram.

In an acute neurotoxicity study, doses of 0, 50, 200 or 1000 mg/kg bw isocycloseram (98.4% purity) were administered by oral gavage to groups of 10 Han Wistar rats per sex. The systemic NOAEL was 50 mg/kg bw per day based on lower body weight gain, reduced food consumption and transiently depressed activity at higher doses. The LOAEL for these effects was 200 mg/kg bw per day. The NOAEL for acute neurotoxicity was 1000 mg/kg bw, the highest dose tested as no evidence of specific neurotoxic potential was observed.

In a 90-day feeding study the neurotoxic potential of isocycloseram (96.9% purity) was investigated in 10 Han Wistar rats per sex in the diet at daily dietary concentrations of 0, 50, 150 or 300 ppm (3.9, 13.2 and 24.8 mg/kg bw per day for males, 5.5, 15.6 and 32.7 mg/kg bw per day for females). The NOAELs for both systemic effects and neurotoxicity were 24.8 mg/kg bw per day, the highest dose tested. A LOAEL was not established.

2.8 Absorption, Distribution, Metabolism, and Excretion (ADME)

Absorption, distribution, metabolism and elimination (ADME) studies on the product are not required by PQT/VCP, however ADME on the AI are considered and integrated into the hazard assessment.

2.8.1 Oral route studies

Following daily oral doses, isocycloseram was moderately rapidly absorbed (Tmax 6-8 hours). It was almost completely absorbed at the low dose of 1 mg/kg bw, and 80% absorbed at the high dose of 10 mg/kg bw. Isocycloseram was widely distributed with the highest residues in kidneys, spleen, liver, and adrenals but there was no evidence of bioaccumulation. Excretion was mainly via feces (90% total) but was not complete by 7-8 days following exposure, with 6-10% administered dose still in the carcass and organs. 46-50% was excreted within 72 hours via bile for the low dose and urinary excretion was low (≤ 4%). Exhalation was negligible. Half-lives in blood ranged from 34-79 hours based on multiple studies cited by JMPR (2023). Parent isocycloseram was extensively metabolized but most metabolites were at low levels. Major metabolites were SYN549436, its glucuronide, and SYN549543.

2.8.2 Dermal route studies

A guideline dermal penetration study was not available, but the Syngenta submitted their review of a "triple pack" dermal absorption study for a SYN547407 SC (A21377X), different formulation of isocycloseram, available in open literature (2x Blackstock and Dickson, 2019; Punlar, 2019). A "triple pack" looks at rat in vivo, and rat and human skin in vitro. A human dermal adjustment factor can be calculated by using the value from the highest ratio for adsorption from the in vitro human and in vitro rat values (3.43/6.42 = 0.53) and multiplying that value by the highest in vivo rat absorption value (0.53 x 19.9% = 11%). Given the relativity of this formulation to the technical, and its closeness in value to the GRAM default dermal absorption of 10% (WHO 2018), this risk assessment considered the 10% default dermal absorption value to estimate dermal risks to be the most appropriate.

2.8.3 Inhalation route studies

Absorption via the inhalation route is assumed to be 100% that via the oral route. Due to the lack of a long-term inhalation study, oral exposure is used for risk assessment purposes.

3 Points of Departure (POD), Reference Doses (RfD), and Cancer Classification

3.1 Points of Departure

Points of departure (PODs) (No Observed Adverse Effect Level [NOAEL]; Benchmark Dose [BMD]) are determined from the toxicological database based on the most sensitive endpoints. Once PODs are developed, safety factors (SF) and uncertainty factors (UF) are used in conjunction with the PODs to derive a safe exposure level, generally referred to as reference dose (RfD) or acceptable daily intake (ADI).

3.2 Reference Doses

3.2.1 Acute Reference Dose (aRfD)

JMPR selected a POD from the 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 (2023). This study is appropriate for the route of duration of exposure and for the population of concern. Therefore, PQT/VCP selected the POD of 50 mg/kg bw. An uncertainty factor of 100X (10X for interspecies extrapolation and 10X for intraspecies variation) is applied to establish the aRfD.

aRfD = 50 mg/kg bw ÷ 100 = 0.5 mg/kg bw

3.2.2 Chronic Reference Dose (cRfD)

The 18-month carcinogenicity study is mouse and the chronic/(24-month) carcinogenicity study in rat support establishing a POD of 2 mg/kg/day. 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.

These studies are appropriate 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 cRfD.

cRfD = 2 mg/kg bw/day ÷ 100 = 0.02 mg/kg bw/day

3.2.3 Acceptable Daily Intake (ADI)

JMPR (2023) has established an acceptable daily intake at 0 – 0.02 mg/kg bw/day from the two chronic carcinogenicity studies in mouse and rat and the safety factor of 100X (10X for interspecies extrapolation and 10X for intraspecies variation).

ADI = 0.02 mg/kg bw/day

3.3 Cancer Classification

JMPR (2023) concluded that isocycloseram was not carcinogenic in mice or rats and was unlikely to be genotoxic based on the chronic carcinogenicity and genotoxic studies.

4 References

Charles River Laboratories Hungary Kft. No. 22/043-001P, 2022. Isocycloseram WP (A23752B) – Acute Oral Toxicity Study in Rats (Up and Down Procedure). Final Report.

Charles River Laboratories Hungary Kft. No. 22/043-002P, 2022. Isocycloseram WP (A23752B) – Acute Dermal Toxicity Study in Rats. Final Report.

Charles River Laboratories Hungary Kft. No. 22/043-004P, 2022. Isocycloseram WP (A23752B) – Acute Inhalation Toxicity Study (Nose-Only) in Rats. Final Report.

Charles River Laboratories Hungary Kft. No. 22/043-005N, 2022. Isocycloseram WP (A23752B) – Acute Eye Irritation Study in Rabbits. Final Report.

Charles River Laboratories Hungary Kft. No. 22/043-006N, 2022. Isocycloseram WP (A23752B) – Primary Skin Irritation Study in Rabbits. Final Report.

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GHS, 2017. United Nations Globally Harmonized System of Classification and Labelling of Chemicals.

JMPR (Joint FAO/WHO Meeting on Pesticide Residues), Draft Summary Report of 2023 Annual JMPR, 2023.

WHO, 2018. “A Generic Risk Assessment Model for Indoor Residual Spraying of Insecticides, 2nd edition” (GRAM).

4.3 Appendix C. Exposure (guideline and lax scenarios) and risk characterization

In the guideline scenario, 0.1 is used for the personal protective equipment (PPE) coefficient. In the lax scenario, 1.0 is used for the PPE coefficient. The results for the lax scenario of the GRAM are provided for information only. WHO does not recommend any application of IRS without appropriate PPE.

Table C.1. Risk characterization for all populations and exposure scenarios

Population	Operator exposure (dermal and inhalation) (µg /kg bw/day)	TSD (µg /kg bw/day)	Risk ratio
Total operator exposure – guideline scenarios			
Adult – TWA	1.007	20	0.05
Adult – max	5.102	500	0.01
Total operator exposure – lax scenarios			
Adult – TWA	10.065	20	0.50
Adult – max	51.024	500	0.10
Population	**Residential exposure (dermal and foodstuffs) (µg /kg bw/day)**	**TSD (µg /kg bw/day)**	**Risk ratio**
Total resident exposure – TWA scenario			
Adult	0.481	20	0.02
Children	0.706	20	0.04
Toddler	1.683	20	0.08
Infant	3.775	20	0.19
Total resident exposure – maximal scenario			
Adult	1.145	500	0.002
Children	1.681	500	0.003
Toddler	4.006	500	0.008
Infant	8.987	500	0.018
Population	**Operator-resident (combined exposure) (µg /kg bw/day)**	**TSD (µg /kg bw/day)**	**Risk ratio**
Operator-resident exposure – guideline scenario			
Guideline – TWA	1.487	20	0.07
Guideline – max	6.247	500	0.01
Operator-resident exposure – Worst case scenario [(a)]			
Lax – TWA	10.546	20	0.53
Lax – max	52.169	500	0.10
Population	**Breast milk exposure residential (µg /kg bw/day)**	**TSD (µg /kg bw/day)**	**Risk ratio**
Guideline scenarios			
Newborn - TWA	0.062	20	0.003

(a): Worst Case Scenario = Operator (Lax scenario - max) + Resident (Guideline scenario) since Lax scenario applies only to operator

The values given in Table C.2 are only for risk illustration purposes of a worst-case scenario. This scenario assumes the operator is also a nursing/lactating resident. Even under this scenario, which is neither recognized nor accepted by WHO, the risk estimate is still acceptable (< 1).

Table C.2. Estimated systemic dose from exposure to breast milk
Worst case scenario [a] Operator is also a nursing/lactating resident [b]

Population	SolC	Exposed Dose (µg/kg bw)	$T_{1/2}$ (days)	IR (kg/day)	Abs-O (%)	BW (kg)	Systemic dose (µg/kg/day)
Worst case – TWA							
Newborns	**0.361**	**0.481**	**2.4**	**0.53**	**100**	**4.2**	**0.057**
Risk estimate – breast milk exposure – worst case scenario [a][b]							
Population		**Operator resident breast milk exposure dose (µg/kg/day)**			**TSD (µg/kg/day)**		**Risk ratio**
Newborn – TWA		**0.057**			**20**		**0.003**

Sol C = Solubility constant = 0.361 for water soluble
$T_{1/2}$= First order kinetics half-life of isocycloseram ranged from 1.4 days-3.3 days. Based on available information the estimated average of 2.4 days (57 hours) was used.
IR= (default value=0.53 kg/day for first month and 0.68 kg/day for first 12 months
Exposed dose = Operator (Lax dose maximal) + Residential (Guideline Max dose)
(a): Worst Case Scenario = Operator (Lax scenario - max) + Resident (Guideline scenario) since Lax scenario applies only to operator
(b): The scenario of nursing/lactating mother working as an operator is neither recognized nor accepted by WHO