DRAFT REGISTRATION REPORT

Part B

Section 6

Mammalian Toxicology

Detailed summary of the risk assessment

Product code: SHA 076127 A

Product name: PROSIM

Chemical active substances:

Propamocarb, 400 g/L

Cymoxanil, 50 g/L

Central Zone

Zonal Rapporteur Member State: POLAND

CORE ASSESSMENT

Applicant: SHARDA Cropchem España S.L.

Submission date: October 2020

Update date: August 2023; 12.2023; 01.2024; 02/2024

MS Finalisation date: November 2022; March 2023 ; 08/2023

Version history

When	What
November 2022	Assessment by expert
March 2023	Assessment after updated by Applicant
August 2023	Corrected by expert
August 2023	Applicant updated
December 2023	Applicant updated
January 2024	Applicant updated
February 2024	Assessment by expert

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6 Mammalian Toxicology (KCP 7)

6.1 Summary

Table 6.1-1: Information on SHA 076127 A / PROSIM *

Product name and code	PROSIM / SHA 076127 A
Formulation type	Suspension concentrate [Code : SC]
Active substance(s) (incl. content)	Propamocarb 400 g/L Cymoxanil 50 g/L
Function	Fungicide
Product already evaluated as the 'representative formulation' during the approval of the active substance(s)	No
Product previously evaluated in another MS according to Uniform Principles	No

* Information on the detailed composition of SHA 076127 A / PROSIM can be found in the confidential dRR Part C.

Justified proposals for classification and labelling

According to the criteria given in Regulation (EC) No 1272/2008 of the European Parliament and of the Council of 16 December 2008, the following classification and labelling with regard to toxicological data is proposed for the preparation:

Table 6.1-2: Justified proposals for classification and labelling for SHA 076127 A / PROSIM according to Regulation (EC) No 1272/2008

Hazard class(es), categories	Skin Sens. 1, Repr. 2
Hazard pictograms or Code(s) for hazard pictogram(s)	GHS07, GHS08
Signal word	Warning
Hazard statement(s)	H317, H361fd
Precautionary statement(s)	P201, P261, P280, P302+P352,P308+P313, P333+P313, P405, P501
Additional labelling phrases	To avoid risks to man and the environment, comply with the instructions for use. [EUH401]

Table 6.1-3: Summary of risk assessment for operators, workers, residents and bystanders for SHA 076127 A / PROSIM

	Result	PPE / Risk mitigation measures
Operators	Acceptable	OPEX: Work wear (arms, body and legs covered) M/L and A + gloves
Workers	Acceptable	OPEX: Work wear (arms, body and legs covered)
Residents & Bystanders	Acceptable	OPEX: 5 m buffer zone + drift reduction

No unacceptable risk for operators, workers, residents and bystanders was identified when the product is used as intended and provided that the PPE/risk mitigation measures stated in Table 6.1-3 are applied.

Accepted

A summary of the critical uses and the overall conclusion regarding exposure for operators, workers and residents/bystanders is presented in the following table.

Table 6.1-4 Critical uses and overall conclusion of exposure assessment

1	2	3	4	5	6	7	8	9	10			
Use-No.*	**Crops and situation (e.g. growth stage of crop)**	**F, Fn, Fpn G, Gn, Gpn or I ****	**Application**		**Application rate**		**PHI (d)**	**Remarks:** **(e.g. safener/synergist (L/ha))** **critical gap for operator, worker, resident or bystander exposure based on [Exposure model]**	**Acceptability of exposure assessment**			
			Method / Kind **(incl. application technique *****	**Max. number (min. interval between applications)** **a) per use** **b) per crop/ season**	**Max. application rate kg as/ha** **a) Propamocarb** **b) Cymoxanil**	**Water L/ha** **min / max**			**Operator**	**Worker**	**Residents**	**Bystander**
1	Potato (BBCH 21-95)	F	Spraying, LCTM	a) 6 (7) b) 6 (7)	a) 1.0 b) 0.125	200 - 400	7					

* Use number(s) in accordance with the list of all intended GAPs in Part B, Section 0 should be given in column 1

** F: professional field use, Fn: non-professional field use, Fpn: professional and non-professional field use, G: professional greenhouse use, Gn: non-professional greenhouse use, Gpn: professional and non-professional greenhouse use, I: indoor application

*** e.g. LC: low crops, HC: high crop, TM: tractor-mounted, HH: hand-held

Explanation for column 10 "Acceptability of exposure assessment"

A	Exposure acceptable without PPE / risk mitigation measures
R	Further refinement and/or risk mitigation measures required
N	Exposure not acceptable/ Evaluation not possible

Data gaps

N/A

Noticed data gaps are:

- data gap 1
- data gap 2
- data gap 3

6.2 Toxicological Information on Active Substances

Information regarding classification of the active substances and on EU endpoints and critical areas of concern identified during the EU review are given in Table 6.2-1.

Table 6.2-1: Information on active substances

	Propamocarb	**Cymoxanil**
Common Name	Propamocarb hydrochloride	Cymoxanil
CAS-No.	25606-41-1	57966-95-7
Classification and proposed labelling		
With regard to toxicological endpoints (according to the	**Hazard classe, categories:** Skin sens. 1 **Code for hazard pictogram:** GHS07	**Hazard classes, categories:** Acute tox. 4, Skin sens. 1, Repr. 2, STOT RE 2,

	Propamocarb	Cymoxanil
criteria in Reg. 1272/2008, as amended)	**Signal word:** Warning **Hazard statement:** H317	**Codes for hazard pictograms:** GHS07, GHS08 **Signal word:** Warning **Hazard statements:** H302, H317, H361fd, H373(blood,thymus)
Additional C&L proposal	-	-
Agreed EU endpoints		
AOEL systemic	0.29 mg/kg bw/d	0.01 mg/kg bw/d
Reference	EFSA Scientific Report (2006) 78, 1-80	**Committee for Risk Assessment RAC Adopted 16 September 2021** Harmonized of Classification – Annex VI of Regulation (EC) No 1272/20008 (CLP Regulation) ATP Inserted / Updated: CLP00/ATP06 This field indicates when an entry in Annex VI to CLP has been inserted and/or updated with an Adaptation to Technical Progress (ATP) to the CLP Regulation. CLP Classification (Table 3) EFSA Scientific Report (2008) 167, 1-116
Conditions to take into account/critical areas of concern with regard to toxicology		
According to EFSA Scientific Report for Propamocarb and Cymoxanil	The operator, worker and bystander risk assessment is inconclusive.	None

6.3 Toxicological Evaluation of Plant Protection Product

A summary of the toxicological evaluation for SHA 076127 A / PROSIM is given in the following tables. Full summaries of studies on the product that have not been previously considered within an EU peer review process are described in detail in Appendix 2.

Table 6.3-1: Summary of evaluation of the studies on acute toxicity including irritancy and skin sensitisation for PROSIM

Type of test, species, model system (Guideline)	Result	Acceptability	Classification (acc. to the criteria in Reg. 1272/2008)	Reference
LD_{50} oral, rat	> 2000 mg/kg bw	Yes	None	Calculated
LD_{50} dermal, rat	>2000 mg/kg bw	Yes	None	Calculated
LC_{50} inhalation, rat	>5 mg/L	Yes	None	Calculated
Skin irritation, rabbit	Non-irritant	Yes	None	Calculated
Eye irritation, rabbit	Non-irritant	Yes	None	Calculated
Skin sensitisation, guinea pig	Sensitising	Yes	H317	Calculated

Supplementary studies for combinations of plant protection products	No data – not required			

Table 6.3-2: Additional toxicological information relevant for classification/labelling of SHA 076127 A / PROSIM

	Substance (concentration in product, % w/w)	Classification of the substance (acc. to the criteria in Reg. 1272/2008)	Reference	Classification of product (acc. to the criteria in Reg. 1272/2008)
Toxicological properties of active substance(s) (relevant for classification of product)	Popamocarb (40% (w/w))	H317	Reg. 1272/2008	H317
	Cymoxanil (5% w/w)	H302, H317, H361fd, H373(blood,thymus)	Reg. 1272/2008	H317, H361fd
Toxicological properties of non-active substance(s) (relevant for classification of product)	Co-formulant 1 < 1% (w/w)*	H319	Reg. 1272/2008	None
	Co-formulant 2 < 1% (w/w)*	H319	Reg. 1272/2008	None
	Co-formulant 3 < 1% (w/w)*	H302, H314, H318, H317	Reg. 1272/2008	H317
	Co-formulant 4 1-10% (w/w)*	H319	Reg. 1272/2008	None
	Co-formulant 5 < 1% (w/w)*	H317	Reg. 1272/2008	H317
Further toxicological information	No data – not required			

* Please use concentration range or concentration limit (e.g. 1-10% or > 1%) as provided in MSDS.
** Material safety data sheet by the applicant

6.4 Toxicological Evaluation of Groundwater Metabolites

All metabolite concentrations are predicted to stay below 0.1 µg/L – no groundwater assessment is required.

6.5 Dermal Absorption (KCP 7.3)

A summary of the dermal absorption rates for the active substances in SHA 076127 A / PROSIM are presented in the following table.

Table 6.5-1: Dermal absorption rates for active substances in SHA 076127 A / PROSIM

	Propamocarb hydrochloride		Cymoxanil	
	Value	Reference		Reference
Concentrate	1.9%	New study reported in Appendix 2	1.5%	New study reported in Appendix 2
Dilution	11%		10%	

6.5.1 Justification for proposed values - Propamocarb

Proposed dermal absorption rates for Propamocarb hydrochloride are based on dermal absorption studies on a formulation Propamocarb hydrochloride 40% + Cymoxanil 5% SC. The study results are summarised in the following table. Full summaries of studies that have not previously been evaluated within an EU peer review process are described in detail in Appendix 2.

According to the "In vitro percutaneous dermal absorption study of Propamocarb Hydrochloride and Cymaxanil, formulated as Propamocarb Hydrochloride 40% + Cymoxanil 5% SC, through human skin", Nabita Sam., 2022, Study No.: G22097
ACCEPTED

Table 6.5-2: Default dermal absorption rates for Propamocarb hydrochloride

	Value	Justification for value	Acceptability of justification
Concentrate	1.9%	*In vitro* human skin	Yes
Dilution	11%		Yes

6.5.2 Justification for proposed values - Cymoxanil

Proposed dermal absorption rates for Cymoxanil are based on dermal absorption studies on a formulation Propamocarb hydrochloride 40% + Cymoxanil 5% SC. The study results are summarised in the following table. Full summaries of studies that have not previously been evaluated within an EU peer review process are described in detail in Appendix 2.

ACCEPTED

According to the "In vitro percutaneous dermal absorption study of Propamocarb Hydrochloride and Cymaxanil, formulated as Propamocarb Hydrochloride 40% + Cymoxanil 5% SC, through human skin", Nabita Sam., 2022, Study No.: G22097

Table 6.5-3: Default dermal absorption rates for Cymoxanil

	Value	Justification for value	Acceptability of justification
Concentrate	1.5%	*In vitro* human skin	Yes
Dilution	10%		Yes

6.6 Exposure Assessment of Plant Protection Product (KCP 7.2)

Table 6.6-1: Product information and toxicological reference values used for exposure assessment

Product name and code	PROSIM / SHA 076127 A	
Formulation type	SC (Suspension concentrate)	
Category	Fungicide	
Active substances (incl. content)	**Propamocarb** 400 g/L	**Cymoxanil** 50 g/L
AOEL systemic	0.29 mg/kg bw/d	0.01 mg/kg bw/d

Inhalation absorption	100%	100%
Oral absorption	100%	75%
Dermal absorption	Concentrate: 1.9% Dilution: 11%	Concentrate: 1.5% Dilution: 10%

ACCEPTED

6.6.1 Selection of critical use and justification

The critical GAP used for the exposure assessment of the plant protection product is shown in Table 6.1-4. A list of all intended uses within the zone is given in Part B, Section 0.

6.6.2 Operator exposure (KCP 7.2.1)

6.6.2.1 Estimation of operator exposure

A summary of the exposure models used for estimation of operator exposure to the active substances during application of SHA 076127 A / PROSIM according to the critical use(s) is presented in Table 6.6-2. The outcome of the estimation is presented in **Błąd! Nie można odnaleźć źródła odwołania.** (longer term exposure, OPEX). Detailed calculations are in Appendix 3.

Table 6.6-2: Exposure models for intended uses

Critical use	Potato (max. 6 x 2.5 L product/ha)
Model(s)	Guidance on the assessment of exposure of operators, workers, residents and bystanders in risk assessment for plant protection products; EFSA Journal 2014;12(10):3874 OPEX Calculator: 2022

Table 6.6-3: Estimated operator exposure (OPEX)

		Propamocarb hydrochloride		Cymoxanil	
Model data	**Level of PPE**	**Total absorbed dose (mg/kg/day)**	**% of systemic AOEL**	**Total absorbed dose (mg/kg/day)**	**% of systemic AOEL**
Tractor mounted boom spray application outdoors to low crops					
Application rate		6 x 1 kg a.s./ha		6 x 0.125 kg a.s./ha	
Spray application (AOEM; 75th percentile) Body weight: 60 kg	Potential exposure	-	**26**	-	128
	Work wear (arms, body and legs covered) M/L and A	0.05	**16**	0.008	**85**
	Work wear (arms, body and legs covered) M/L and A + gloves	-	**5**	-	**19**

Conclusion

According to the EFSA calculator, it can be concluded that the risk for operator is acceptable with the use work wear (arms, body and legs covered) M/L and A + gloves during M/L and A.

Implication for labelling: P280: Wear protective gloves/protective clothing

ACCEPTED

ACCEPTED

6.6.2.2 Measurement of operator exposure

Since the operator exposure estimations carried out indicated that the acceptable operator exposure level (AOEL) will not be exceeded under conditions of intended uses and consideration of the above mentioned personal protective equipment (PPE), a study to provide measurements of operator exposure was not necessary and was therefore not performed.

6.6.3 Worker exposure (KCP 7.2.3)

6.6.3.1 Estimation of worker exposure

Błąd! Nie można odnaleźć źródła odwołania. shows the exposure model(s) used for estimation of worker exposure after entry into a previously treated area or handling a crop treated with SHA 076127 A / PROSIM according to the critical use(s). Outcome of the estimation is presented in

		Propamocarb	**Cymoxanil**

Model data	Level of PPE	Total absorbed dose (mg/kg bw/day)	% of systemic AOEL	Total absorbed dose (mg/kg bw/day)	% of systemic AOEL
Root and tuber vegetables Inspection, irrigation Outdoor Work rate: 2 hours/day, DT_{50}: 30 days DFR: 3 µg/cm^2/kg a.s./ha Interval between treatments: 7 days					
Number of applications and application rate		6 x 1 kg a.s./ha		6 x 0.125 kg a.s./ha	
Body weight: 60 kg	Potential TC: 12500 cm^2/person/h	0.6	197	0.07	650
	Work wear (arms, body and legs covered) TC: 1400 cm^2/person/h	0.06	**22**	0.007	**73**
	Work wear (arms, body and legs covered) and gloves TC: 1250 cm^2/person/h	0.06	**20**	0.007	**65**

(longer term exposure, OPEX). Detailed calculations are in Appendix 3.

Table 6.6-3: Exposure models for intended uses

Critical use	Potato (max. 6 x 2.5 L product/ha)
Model	Guidance on the assessment of exposure of operators, workers, residents and bystanders in risk assessment for plant protection products; EFSA Journal 2014;12(10):3874 OPEX Calculator: 2022

Table 6.6-4: Estimated worker exposure (OPEX)

		Propamocarb		Cymoxanil	
Model data	**Level of PPE**	**Total absorbed dose (mg/kg bw/day)**	**% of systemic AOEL**	**Total absorbed dose (mg/kg bw/day)**	**% of systemic AOEL**
Root and tuber vegetables Inspection, irrigation Outdoor Work rate: 2 hours/day, DT_{50}: 30 days DFR: 3 µg/cm²/kg a.s./ha Interval between treatments: 7 days					
Number of applications and application rate		6 x 1 kg a.s./ha		6 x 0.125 kg a.s./ha	
Body weight: 60 kg	Potential TC: 12500 cm²/person/h	0.6	197	0.07	650
	Work wear (arms, body and legs covered) TC: 1400 cm²/person/h	0.06	**22**	0.007	**73**
	Work wear (arms, body and legs covered) and gloves TC: 1250 cm²/person/h	0.06	**20**	0.007	**65**

Conclusion:

According to the EFSA calculator, it can be concluded that the risk for workers re-entering to treated crop is acceptable with the use of work wear (arms, body and legs covered ~~and 2 days re-entry period after treatment.~~

Implication for labelling: P280: Wear protective work/ gloves

ACCEPTED

ACCEPTED

6.6.3.2 Refinement of generic DFR value (KCP 7.2)

If no DFR data for the specific compound are available, a conservative default value for the DFR may be taken as 3 µg/cm² (30 mg a.s./m²).

6.6.3.3 Measurement of worker exposure

Since the worker exposure estimations carried out indicated that the acceptable operator exposure level (AOEL) will not be exceeded under conditions of intended uses and considering above mention PPE, a study to provide measurements of worker exposure was not necessary and was therefore not performed.

6.6.4 Resident and bystander exposure (KCP 7.2.2)

6.6.4.1 Estimation of resident and bystander exposure

The acute exposure assessment for bystanders covers the exposure that a resident could reasonably be expected to incur in a single day. Therefore, there is no need for a separate acute risk assessment for residents.

No bystander risk assessment is required for PPPs that do not have significant acute toxicity or the potential to exert toxic effects after a single exposure. Exposure in this case will be determined by average exposure over a longer duration, and higher exposures on one day will tend to be offset by lower exposures on other days. Therefore, exposure assessment for residents also covers bystander exposure.

Table 6.6-56 shows the exposure model(s) used for estimation of resident and bystander exposure to Propamocarb and Cymoxanil. The outcome of the estimation is presented in Table 6.6-7 (longer term resident exposure, OPEX). Detailed calculations are in Appendix 3.

Table 6.6-5: Exposure models for intended uses

Critical use	Potato (max. 6 x 2.5 L product/ha)
Model	Guidance on the assessment of exposure of operators, workers, residents and bystanders in risk assessment for plant protection products; EFSA Journal 2014;12(10):3874 OPEX Calculator: 2022

Table 6.6-6: Estimated resident exposure (longer term exposure)

		Propamocarb		Cymoxanil	
Model data		**Total absorbed dose (mg/kg bw/day)**	**% of systemic AOEL**	**Total absorbed dose (mg/kg bw/day)**	**% of systemic AOEL**
Tractor mounted boom spray application outdoors to low crops **Buffer zone: 5 (m)** Drift reduction technology: yes DT_{50}: 30 days DFR: 3 µg/cm²/kg a.s./ha Interval between treatments: 7 days					
Application rate		6 x 0.8 kg a.s./ha		6 x 0.1 kg a.s./ha	
Resident child Body weight: 10 kg	Drift (75th perc.)	0.004	1.7	0.0005	5.7
	Vapour (75th perc.)	0.0008	0.3	0.0008	8
	Deposits (75th perc.)	0.001	0.7	0.0001	2.2
	Re-entry (75th perc.)	0.08	26.6	0.009	87.8

	Sum (mean)	0.07	**23**	0.008	**82.8**
Resident adult Body weight: 60 kg	Drift (75th perc.)	0.0008	0.3	< 0.001	1
	Vapour (75th perc.)	0.0003	0.09	0.0003	2.7
	Deposits (75th perc.)	0.0004	0.2	< 0.001	0.7
	Re-entry (75th perc.)	0.04	14.8	0.005	48.8
	Sum (mean)	0.04	**12.2**	0.004	**42.7**

Refinement for 1-3 years old child:

The applicant, in order to improve the exposure assessment of children, would like to propose the use of DT_{50} = ~~1~~ 2 day for Cymoxanil, in accordance with DAR ~~Volume 3 - B.9- Cymoxanil 50 g/L + Propamocarb hydrochloride 400 g/L SC.~~ Cymoxanil - Volume 3,. **Annex B, part 2, B.6 October 2007**

Tractor mounted boom spray application outdoors to low crops **Buffer zone: 5 (m)** Drift reduction technology: yes DT_{50}: 30 days for propamocarb~~,~~ ~~1~~ 2 days for cymoxanil DFR: 3 µg/cm²/kg a.s./ha Interval between treatments: 7 days					
Application rate		6 x 0.8 kg a.s./ha		6 x 0.1 kg a.s./ha	
Resident child Body weight: 10 kg	Drift (75th perc.)	0.004	1.7	0.0006	5.7
	Vapour (75th perc.)	0.0008	0.3	0.0008	8
	Deposits (75th perc.)	0.001	0.7	5e-05	~~0.5~~ 0.6
	Re-entry (75th perc.)	0.08	26.6	0.002	~~21.3~~ 23.2
	Sum (mean)	0.07	23	0.003	~~28.5~~ 30.1
Resident adult Body weight: 60 kg	Drift (75th perc.)	0.0008	0.3	0.0001	1
	Vapour (75th perc.)	0.0003	0.09	0.0003	2.7
	Deposits (75th perc.)	0.0004	0.2	2e-05	0.2
	Re-entry (75th perc.)	0.04	14.8	0.001	~~11.8~~ 12.9
	Sum (mean)	0.04	12.2	0.001	~~12.8~~ 13.6

Conclusion

According to the EFSA calculator, it can be concluded that the risk for long term exposure for child residents is unacceptable.

~~**Therefore, further refinements for children are necessary. Bufor zone 5 m**ACCEPTED~~

Conclusion

According to the EFSA calculator, when a 5m buffer zone is employed and drift reduction technology is incorporated, the risk for residents (adult and child) can be considered as acceptable. Bufor zone 5 m ~~**10 m.**~~ The combined exposure (sum of exposures) of child resident to these two active substance expressed as percentage of their AOELs (105,8%)

ACCEPTED

6. 6. 4. 2 Measurement of resident and/or bystander exposure

Since resident and/or bystander exposure estimations carried out indicated that the acceptable operator exposure level (AOEL) was exceeded under conditions of intended uses, a field study measuring the resident and/or bystander exposure has been provided. A summary of the study is presented below. For the detailed evaluation of new/additional studies please refer to 0. No detailed summaries are provided if the study was already assessed and accepted at EU level.

6.6.5 Combined exposure

The product is a mixture of two active substances.

From a scientific point of view, it is regarded necessary to take into account potential combination effects. However, the evaluation of cumulative or synergistic effects as requested by Art. 4 (3b) of Regulation (EC) No. 1107/2009 should only be performed when harmonised "scientific methods accepted by the Authority to assess such effects are available."

6.6.5.1 Exposure assessment of Propamocarb and Cymoxanil in SHA 076127 A / PROSIM

Note: The combined toxicological effect of these active substances has not been investigated with regard to repeated dose toxicity.

At the first tier, combined exposure is calculated as the sum of the component exposures without regard to the mode of action or mechanism/target of toxicity. Initially, the individual Hazard Quotients (HQ) are calculated for all active substances in the PPP by assessing the exposure according to appropriate models and dividing the individual exposure levels by the respective systemic AOEL. This is equivalent to the predicted exposure as % of systemic AOEL converted to decimal. The Hazard Index (HI) is the sum of the individual HQs.

Table 6.6-7: Risk assessment from combined exposure (longer term exposure)

Application scenario	Active ingredient	Estimated exposure / AOEL (HQ)
Operators – Work wear (arms, body and legs covered) M/L and A + gloves	**Cumulative risk operators (HI)**	**0.247**
Workers – work wear	**Cumulative risk workers (HI)**	**0.9**
Resident – child Buffer zone: 5 m Drift reduction technology: 50 % DT_{50}: 30 days for propamocarb, ± 2 days for cymoxanil	**Cumulative risk resident – child (HI)**	
	Drift	0.07
	Vapour	0.08
	Deposits	0.01
	Re-entry	0.5

Application scenario	Active ingredient	Estimated exposure / AOEL (HQ)
	Sum of all pathways	0.5
Resident – adult Buffer zone: 5 m Drift reduction technology: 50 % DT_{50}: 30 days for propamocarb, 1 days for cymoxanil	**Cumulative risk resident – adult (HI)**	
	Drift	0.01
	Vapour	0.03
	Deposits	0.004
	Re-entry	0.3
	Sum of all pathways	0.3

The Hazard Index in sum of all pathways is < 1. Thus, combined exposure to all active substances in SHA 076127 A / PROSIM is not expected to present a risk for operators, workers, residents and bystanders.

ACCEPTED

~~For child resident an exposure to Propamocarb, calculated with the EFSA AOEM, is equal 23% of respective AOEL and to Cymoxanil 82.8% of respective AOEL, therefore the combined exposure (sum of exposures) of child resident to these two active substance expressed as percentage of their AOELs (105,8%) is slightly above 100%, therefore the application of product SHA 076127 A / PROSIM might pose an unacceptable risk to the health of child residents. However, it is noted that over 75% of the estimated exposure of child residents is due to their entry into treated crops for 0.25 hours, as foreseen as default in the input parameters of EFSA AOEM, which may leads to overestimation of exposure since such events are not occurring frequently. In fact for child residents not entering for 0.25 hours a field treated with SHA 076127 A / PROSIM the sum of hazard indexes of both actives substances would be well below 1, thus the risk for child residents due to combined exposure is considered as acceptable. No bystander acute exposure estimation is required since no acute acceptable operator exposure value (AAOEL) has be set for any of these active substances: Propamocarb and Cymoxanil. Therefore, as indicated in the EU guidance (SANTE-10832-2015 rev. 1.7; 24 January 2017), no unacceptable risk is expected for bystanders due to short-term single exposure to Propamocarb and Cymoxanil as a result of application of SHA 076127 A / PROSIM with accordance with intended use within good agricultural practice.~~
The Hazard Index in sum of all pathways is < 1. Thus, combined exposure to all active substances in SHA 076127 A / PROSIM is not expected to present a risk for operators, workers, residents and bystanders.
ACCEPTED

Appendix 1 Lists of data considered in support of the evaluation

Tables considered not relevant can be deleted as appropriate.

MS to blacken authors of vertebrate studies in the version made available to third parties/public.

List of data submitted by the applicant and relied on

Data point	Author(s)	Year	Title Company Report No. Source (where different from company) GLP or GEP status Published or not	Verte-brate study Y/N	Owner
KCP 7.6.2	Nabita Sam	2022	"In vitro percutaneous dermal absorption study of Propamocarb Hydrochloride and Cymaxanil, formulated as Propamocarb Hydrochloride 40% + Cymoxanil 5% SC, through human skin", Study No.: G22097 GLP Unpublished	N	Sharda

List of data submitted or referred to by the applicant and relied on, but already evaluated at EU peer review

Data point	Author(s)	Year	Title Company Report No. Source (where different from company) GLP or GEP status Published or not	Verte-brate study Y/N	Owner

The following tables are to be completed by MS

List of data submitted by the applicant and not relied on

Data point	Author(s)	Year	Title Company Report No. Source (where different from company) GLP or GEP status Published or not	Verte-brate study Y/N	Owner

List of data relied on not submitted by the applicant but necessary for evaluation

Data point	Author(s)	Year	Title Company Report No. Source (where different from company) GLP or GEP status Published or not	Verte-brate study Y/N	Owner

Appendix 2 Detailed evaluation of the studies relied upon

A 2.1 Statement on bridging possibilities

Comments of zRMS:	N/A

A 2.2 Acute oral toxicity (KCP 7.1.1)

Comments of zRMS:	**The acute oral toxicity of SHA 076127 A / PROSIM was estimated to be > 5000 mg/kg.** **Therefore, according to the Regulation EC No. 1272/2008, SHA 076127 A / PROSIM is not classified**

Acute toxicity studies for SHA 076127 A / PROSIM were **not** evaluated as part of the EU review of Propamocarb and Cymoxanil. Therefore, all relevant data are provided here and are considered adequate. Details of the co-formulants and their classification and the calculation methodology that was used to assess the acute oral toxicity of SHA 076127 A / PROSIM can be found in an appendix to the confidential dossier of this submission (Registration Report, Part C).

The acute oral toxicity of SHA 076127 A / PROSIM was calculated as follow:

$$ATE_{mix} = \frac{100}{\sum_r \frac{C_i}{ATE_i}}$$

$$ATE_{mix} = \frac{100}{\frac{4.75}{1100} + \frac{xx\%}{1121}} > 5000\, mg/kg\ bw$$

The acute oral toxicity of SHA 076127 A / PROSIM was estimated to be > 2000 mg/kg. Therefore, according to the Regulation EC No. 1272/2008, SHA 076127 A / PROSIM is **not classified**. No signal word or hazard statement is required for this hazard.

A 2.3 Acute percutaneous (dermal) toxicity (KCP 7.1.2)

Comments of zRMS:	**The acute dermal toxicity of SHA 076127 A / PROSIM was estimated to be > 2000 mg/kg bw.** **Therefore, according to the Regulation EC No. 1272/2008, SHA 076127 A / PROSIM is not classified.**

None of the co-formulants are classified as dermal acute toxic. According to the applicant, the calculations are not necessary, however, on request of Authority we present them below.

The acute dermal toxicity of SHA 076127 A / PROSIM was calculated as follow:

$$ATE_{mix} = \frac{100}{\sum_r \frac{C_i}{ATE_i}}$$

$$ATE_{mix} = \frac{100}{\frac{38.76}{2000} + \frac{4.75}{2000} + \frac{xx\%}{2000} + \frac{xx\%}{2000} + \frac{xx\%}{2000} + \frac{xx\%}{2000} + \frac{xx\%}{2000} + \frac{xx\%}{2000} + \frac{xx\%}{2000} + \frac{xx\%}{2000}}$$

$$> 3851.34\, mg/kg\ bw$$

The acute dermal toxicity of SHA 076127 A / PROSIM was estimated to be > 2000 mg/kg. Therefore, according to the Regulation EC No. 1272/2008, SHA 076127 A / PROSIM is **not classified**. No signal word or hazard statement is required for this hazard.

A 2.4 Acute inhalation toxicity (KCP 7.1.3)

Comments of zRMS:	**The acute inhalation toxicity of SHA 076127 A / PROSIM was estimated to be > 5mg/l.** **Therefore, according to the Regulation EC No. 1272/2008, SHA 076127 A / PROSIM is not classified**

None of the co-formulants are classified as inhalation acute toxic. According to the applicant, the calculations are not necessary, however, on request of Authority we present them below.

The acute inhalation toxicity of SHA 076127 A / PROSIM was calculated as follow:

$$ATE_{mix} = \frac{100}{\sum_r \frac{C_i}{ATE_i}}$$

$$ATE_{mix} = \frac{100}{\frac{38.76}{5.01} + \frac{4.75}{5.6} + \frac{xx\%}{5.0} + \frac{xx\%}{5.0} + \frac{xx\%}{5.2} + \frac{xx\%}{317042} + \frac{xx\%}{21.0} + \frac{xx\%}{5.0} + \frac{xx\%}{5.0} + \frac{xx\%}{5.0}}$$

$$> 10.05 \text{ mg/l}$$

The acute inhalation toxicity of SHA 076127 A / PROSIM was estimated to be > 5 mg/l. Therefore, according to the Regulation EC No. 1272/2008, SHA 076127 A / PROSIM is **not classified**. No signal word or hazard statement is required for this hazard.

A 2.5 Skin irritation (KCP 7.1.4)

Comments of zRMS:	**The product contains ≤ 1% of co-formulants considered as skin corrosive Under the GHS classification system this component gets the additive trigger value of the classification according to Regulation (EC) no. 1272/2008** **According to the Regulation EC No. 1272/2008, SHA 076127 A / PROSIM is not classified**

Acute toxicity studies for SHA 076127 A / PROSIM were **not** evaluated as part of the EU review Propamocarb and Cymoxanil. Therefore, all relevant data are provided here and are considered adequate. Details of the co-formulants and their classification and the calculation methodology that was used to assess the acute oral toxicity of SHA 076127 A / PROSIM can be found in an appendix to the confidential dossier of this

submission (Registration Report, Part C).

The product contains ≤ 1% of co-formulants considered as skin corrosive (classified as: Skin Corr. 1; H314). Under the GHS classification system this component gets the additive trigger value of the classification according to Regulation (EC) no. 1272/2008

According to the Regulation EC No. 1272/2008, SHA 076127 A / PROSIM is **not classified**. No signal word or hazard statement is required for this hazard.

A 2.6 Eye irritation (KCP 7.1.5)

Comments of zRMS:	**The product contains < 10% of co-formulants considered as eye damage (classified as: Eye Irrit. 2; H319). Under the GHS classification system this component gets the additive trigger value of the classification according to Regulation (EC) no. 1272/2008** **According to the Regulation EU No. 1272/2008, SHA 076127 A / PROSIM is not classified**

Acute toxicity studies for SHA 076127 A / PROSIM were **not** evaluated as part of the EU review Propamocarb and Cymoxanil. Therefore, all relevant data are provided here and are considered adequate. Details of the co-formulants and their classification and the calculation methodology that was used to assess the acute oral toxicity of SHA 076127 A / PROSIM can be found in an appendix to the confidential dossier of this submission (Registration Report, Part C).

The product contains < 10% of co-formulants considered as eye damage (classified as: Eye Irrit. 2; H319). Under the GHS classification system this component gets the additive trigger value of the classification according to Regulation (EC) no. 1272/2008

According to the Regulation EU No. 1272/2008, SHA 076127 A / PROSIM is **not classified**. No signal word or hazard statement is required for this hazard.

A 2.7 Skin sensitisation (KCP 7.1.6)

Comments of zRMS:	**The product contains > 1% of co-formulants considered as skin sensitizer (classified as: Skin Sens. 1; H317). Under the GHS classification system this component gets the additive trigger value of the classification according to Regulation (EC) no. 1272/2008.** **According to the Regulation EC No. 1272/2008, SHA 076127 A / PROSIM is classified as skin sensitizer, therefore Skin Sens.1/ H317 with pictogram GHS07**

Acute toxicity studies for SHA 076127 A / PROSIM were **not** evaluated as part of the EU review of Propamocarb and Cymoxanil. Therefore, all relevant data are provided here and are considered adequate. Details of the co-formulants and their classification and the calculation methodology that was used to assess the skin sensitisation of SHA 076127 A / PROSIM can be found in an appendix to the confidential dossier of this submission (Registration Report, Part C).

The product contains > 1% of co-formulants considered as skin sensitizer (classified as: Skin Sens. 1; H317). Under the GHS classification system this component gets the additive trigger value of the classification according to Regulation (EC) no. 1272/2008.

According to the Regulation EC No. 1272/2008, SHA 076127 A / PROSIM is classified as skin sensitizer, therefore H317 with pictogram GHS07 and signal word "Warning" is proposed

A 2.8 Supplementary studies for combinations of plant protection products (KCP 7.1.7)

No supplementary studies available.

A 2.9 Data on co-formulants (KCP 7.4)

A 2.9.1 Material safety data sheet for each co-formulant

Information regarding material safety data sheets of the co-formulants can be found in the confidential dossier of this submission (Registration Report - Part C).

A 2.9.2 Available toxicological data for each co-formulant

Available toxicological data for each co-formulant can be found in the confidential dossier of this submission (Registration Report - Part C).

A 2.10 Studies on dermal absorption (KCP 7.3)

~~According to the new EFSA guidance on dermal absorption (EFSA Journal 2017;15(6):4873 adopted: 24 May 2017) a default dermal absorption value 10 % (concentrate) and 50% (diluted) of may be applied for products that are water-based/dispersed[(a)] or solid[(b)]:~~

~~[(a)] Formulation types: soluble concentrate (SL), suspension concentrate (SC), flowable concentrate for seed treatment (FS), flowable (FL) (=SC).~~

~~[(b)] Formulation types: wettable powder (WP), water-dispersible granules (WG/WDG), water-soluble granules (SG), water-soluble powder (SP), powder for dry seed treatment (DS).~~

Reference	KCP 7.6.2
Report	**"In vitro percutaneous dermal absorption study of Propamocarb Hydrochloride and Cymaxanil, formulated as Propamocarb Hydrochloride 40% + Cymoxanil 5% SC, through human skin", XXXXXX, Study No.: G22097**
Guideline(s)	**OECD Guideline 428 "Skin Absortion: in vitro Method" April 2004**
Deviations	**No**
GLP	Yes
Acceptability	Yes
Duplication (if vertebrate study)	No

Materials and methods

Test material	Name (Lot/Batch No.)	^{14}C- Propamocarb (XXVII/1/A/1)

	Test preparation	radioformulation
	Specific activity	10.903 MBq/mg
	Radiochemical purity	100 %
Product	Name (Lot/Batch No.)	Propamocarb Hydrochloride 40%+Cymoxanil 5% SC (SCL-33625)
	Company code	Propamocarb HCL
	Concentration a.s.	400 g/L
	Formulation type	Propamocarb Hydrochloride 40%+Cymoxanil 5% SC
Blank product	Name (Lot/Batch No.)	Propamocarb Hydrochloride 40%+Cymoxanil 5% SC blank formulation (SCL-73321)
	Concentration a.s.	0 g/kg

Test material	Name (Lot/Batch No.)	^{14}C- Cymoxanil (XXV/30/C/1)
	Test preparation	radioformulation
	Specific activity	9.614 MBq/mg
	Radiochemical purity	100 %
Product	Name (Lot/Batch No.)	Propamocarb Hydrochloride 40%+Cymoxanil 5% SC (SCL-33625)
	Company code	Cymoxanil
	Concentration a.s.	50 g/L
	Formulation type	Propamocarb Hydrochloride 40%+Cymoxanil 5% SC
Blank product	Name (Lot/Batch No.)	Propamocarb Hydrochloride 40%+Cymoxanil 5% SC blank formulation (SCL-73321)
	Concentration a.s.	0 g/kg

Test system		
Diffusion cell	Cell type	dynamic
	(if dynamic) Flow rate	1.8 mL/h
	Exposed skin area	0.64 cm^2
Membrane	Skin type	isolated epidermis
	Skin thickness range	0.2-0.4 mm
	Skin donors age	34, 51, 41, 44 years
	Skin donors sex	female
	Location	abdomen
	Source	post-mortem
	Integrity test	yes
Receptor	Receptor medium	Phosphate buffered saline (PBS) + 0.01% sodium azide +6% polyethylene glycol (PEG), pH *ca*. 7.2
	Solubility in receptor medium	Yes
Sample Time	Exposure time	8 h
	Observation time	16 h
Sampling	Sample intervals	At 0-1 h, 1-2 h, followed by 2-h intervals until 24 hours after application
Washing		At 8 h using water and a mild soap solution (3% Dove)
Final Procedure	Tape stripping	y
	TS1-2 analysed separately	y

Tested doses	Concentrate	Spray dilution
Target concentration	Propamocarb Hydrochloride- 400 $g \cdot L^{-1}$ Cymoxanil - 50 $g \cdot L^{-1}$	Propamocarb Hydrochloride- 2.5 $g \cdot L^{-1}$ Cymoxanil - 0.31$g \cdot L^{-1}$

Area dose	Propamocarb Hydrochloride – 4014.96 µg/cm² Cymoxanil - 502.63 µg/cm²	Propamocarb Hydrochloride – 24.98 µg/cm² Cymoxanil - 3.10 µg/cm²
Specific activity	PropamocarbHydrochloride –3.7059 MBq.mL^{-1} Cymoxanil - 3.7553 MBq.mL^{-1}	PropamocarbHydrochloride 27.2911MBq.mL^{-1} Cymoxanil - 2.9729 MBq.mL^{-1}
No. of donors	4	4
No of cells used/valid cells*	8/8	8/8

Results and discussions - Propamocarb Hydrochloride

Dose group	High dose (Formulation concentrate)		Low dose (Spray dilution 1:60)	
Target concentration	401.50 g·L^{-1}		2.5 g·L^{-1}	
Mean actual applied dose	4014.96 µg/cm²		24.98 µg/cm²	
Number of replicates (n)	8		8	
	Mean	S.D.	Mean	S.D.
Dislodgeable dose				
Skin wash	98.81	3.11	87.80	1.20
Donor chamber wash	0.20	0.14	1.03	0.47
Dose associated to skin				
Tape strips: 1st sample, strips 1 + 2	0.13	0.04	0.74	0.11
Tape strips: 2nd sample; strips 3 - n	0.57	0.07	3.17	0.16
Skin preparation	0.49	0.08	1.42	0.23
Absorbed dose				
Receptor fluid	0.69	0.12	5.95	0.54
Receptor chamber wash	0.02	0.01	0.07	0.11
Total recovery[1]	100.90	3.19	100.17	1.42
Absorption essentially complete at end of study (>75% absorption within half the study duration) [%Absorption at $t_{0.5}$]	No [61.34%]		No [57.08%]	
If no: Absorption estimates = absorbed dose + skin preparation + tape strips sample 2)[2]	1.76	0.12	10.61	0.44
If yes: Absorption estimates = absorbed dose + skin preparation	N/A	N/A	N/A	N/A
Absorption estimate normalised[3]	1.76 ± 0.84 × 0.12		10.61 ± 0.84 × 0.44	
Relevant absorption estimate	1.86		10.97	
Absorption estimates [4]	**1.9**		**11**	

[1] Values may not calculate exactly due to rounding of figures

[2] In accordance with the EFSA Guidance on Dermal Absorption (EFSA Journal 2017;15(6):4873) the radioactivity in the second tape-strip pool (3rd to nth tape strip) is considered potentially absorbable if less than 75% of the absorption occurred in the first half of the study (see Table 7.6.2-1) Finally, the skin preparation is also considered potentially absorbable.

[3] In accordance with the EFSA Guidance on Dermal Absorption (2017), dermal absorption should be calculated as follows: Absorption (mean value) + ks, where s is the sample standard deviation. The multiplication factor required depends on the number of replicates and is given in Table 1 of EFSA Guidance.

[4] Relevant absorption estimate was rounded to the required number of significant figures.

N/A: not applicable

Results and discussions – Cymoxanil

Dose group	High dose (Formulation concentrate)		Low dose (Spray dilution 1:60)	
Target concentration	50.26 g·L^{-1}		0.31 g·L^{-1}	
Mean actual applied dose	24.98 µg/cm²		3.10 µg/cm²	
Number of replicates (n)	8		8	
	Mean	S.D.	Mean	S.D. .
Dislodgeable dose				
Skin wash	98.19	1.26	85.20	1.88
Donor chamber wash	0.08	0.03	0.87	20.66
Dose associated to skin				
Tape strips: 1st sample, strips 1 + 2	0.03	0.02	0.91	0.13
Tape strips: 2nd sample; strips 3 - n	0.19	0.06	2.51	0.36
Skin preparation	0.02	0.01	1.82	0.17
Absorbed dose				
Receptor fluid	1.36	0.13	7.92	0.58
Receptor chamber wash	0.01	0.01	0.32	0.15
Total recovery[1]	99.88	1.26	99.55	2.26
Absorption essentially complete at end of study (>75% absorption within half the study duration) [%Absorption at $t_{0.5}$]	Yes [82.00%]		Yes [78.70%]	
If no: Absorption estimates = absorbed dose + skin preparation + tape strips sample 2)[2]	N/A	N/A	N/A	N/A
If yes: Absorption estimates = absorbed dose + skin preparation	1.39	0.13	10.06	0.48
Absorption estimate normalised[3]	1.36 ± 0.84 × 0.13		10.06 ± 0.84 × 0.48	
Relevant absorption estimate	1.47		10.46	
Absorption estimates [4]	**1.5**		**10**	

[1] Values may not calculate exactly due to rounding of figures

[2] In accordance with the EFSA Guidance on Dermal Absorption (EFSA Journal 2017;15(6):4873) the radioactivity in the second tape-strip pool (3rd to nth tape strip) is considered potentially absorbable if less than 75% of the absorption occurred in the first half of the study (see Table 7.6.2-1) Finally, the skin preparation is also considered potentially absorbable.

[3] In accordance with the EFSA Guidance on Dermal Absorption (2017), dermal absorption should be calculated as follows: Absorption (mean value) + ks, where s is the sample standard deviation. The multiplication factor required depends on the number of replicates and is given in Table 1 of EFSA Guidance.

[4] Relevant absorption estimate was rounded to the required number of significant figures.

N/A: not applicable

ACCEPTED

According to the In vitro percutaneous dermal absorption study for :Propamo-carb Hydrochloride		
Absorption estimate normalised[3]	**1.76 ± 0.84 × 0.12**	**10.61 ± 0.84 × 0.44**
Relevant absorption	**1.86**	**10.97**

estimate		
Absorption estimates [4]	**1.9**	**11**

Cymoxanil

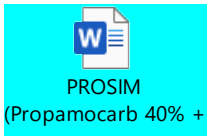
Absorption estimate normalised[3]	**1.36 ± 0.84 × 0.13**	**10.06 ± 0.84 × 0.48**
Relevant absorption estimate	**1.47**	**10.46**
Absorption estimates [4]	**1.5**	**10**

ACCEPTED

A 2.11 Other/SpecialStudies

A 2.12 No other or additional studies submitted.

Appendix 3 Exposure calculations



Please refer to KCP reports.

Appendix 4 Detailed evaluation of exposure and/or DFR studies relied upon (KCP 7.2, KCP 7.2.1.1, KCP 7.2.2.1, KCP 7.2.3.1)

Not relevant.