FINAL REGISTRATION REPORT

Part B

Section 6

Mammalian Toxicology

Detailed summary of the risk assessment

Product code: GLOB2013F

Product name(s): Observer

Chemical active substance:

Zoxamide, 450 g/L

Central Zone

Zonal Rapporteur Member State: Poland

CORE ASSESSMENT

Applicant: Globachem NV

Submission date: January 2024

Update: July 2024 rev. 01

MS Finalisation date: 19/12/2024

Version history

When	What
January 2024	Initial dossier submission by applicant for approval of new product
April 2024	Dossier sent for evaluation
July 2024 Rev. 01	Applicant revision 01 to address zRMS initial comments With addition of study matching references
September 2024	zRMS finalised evaluation
December 2024	zRMS finalised evaluation after commenting period

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zRMS comments:
The text highlighted in grey was provided by the evaluator.

6 Mammalian Toxicology (KCP 7)

6.1 Summary

Table 6.1-1: Information on GLOB2013F *

Product name and code	GLOB2013F
Formulation type	Suspension concentrate [SC]
Active substance(s) (incl. content)	Zoxamide 450 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 GLOB2013F 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 GLOB2013F according to Regulation (EC) No 1272/2008

Hazard class(es), categories	Skin sensitisation Cat 1
Hazard pictograms or Code(s) for hazard pictogram(s)	GHS07
Signal word	Warning
Hazard statement(s)	H317 - May cause an allergic skin reaction.
Precautionary statement(s)	P261 - Avoid breathing dust/fume/ gas/mist/vapours/spray. P272 - Contaminated work clothing should not be allowed out of the workplace. P280 - Wear protective gloves/ protective clothing/eye protection/face protection. P302 + P352 - IF ON SKIN: Wash with plenty of water. P333 + P313 - If skin irritation or rash occurs: Get medical advice/attention. P321 - Specific treatment (see on this label). P362 + P364 - Take off contaminated clothing and wash it before reuse. P501 - Dispose of contents/ container in accordance with local regulation.
Additional labelling phrases	To avoid risks to man and the environment, comply with the instructions for use. [EUH401]
	Contains 1,2-Benzisothiazolin-3-one. ~~May produce an allergic reaction. [EUH 208]~~

Table 6.1-3: Summary of risk assessment for operators, workers, residents and bystanders for GLOB2013F

	Result	PPE / Risk mitigation measures
Operators	Acceptable	No PPE (work wear - arms , body and legs covered) Due to the product classification (Skin Sens. 1, H317), it is reccomended to use protective gloves at the M/L step.
Workers	Acceptable	No PPE (work wear - arms , body and legs covered)
Residents	Acceptable	None (potatoes) 5m of buffer zone (grapes)
Bystanders	Acceptable	None (potatoes) 5m of buffer zone (grapes)

No unacceptable risk for operators, workers, residents and bystanders was identified when the product is used as intended. No specific PPE is necessary.

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) a.s. 1 b) a.s. 2**	**Water L/ha min / max**			**Operator**	**Worker**	**Residents**	**Bystander**
1	Potato (BBCH 21-79)	F	Spraying, LCTM	a) 3 (7) b) 3 (7)	a) 0.135	150-300	7	Guidance on the assessment of exposure of operators, workers, residents and bystanders in risk assessment of plant protection products. EFSA Journal 2022;20(1):7032, 134 pp.	A	A	A	A
3	Grape (BBCH 53-83)	F	Spraying, LCTM	a) 2 (8) b) 2 (8)	a) 0.166	100-1000	28		A	A	A	A

* 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

Data gaps should be listed in the summary to give an overview (especially for cMS).

Noticed data gaps are:

6.2 Toxicological Information on Active Substance(s)

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 substance(s)

	Zoxamide
Common Name	Zoxamide

	Zoxamide
CAS-No.	156052-68-5
Classification and proposed labelling	
With regard to toxicological endpoints (according to the criteria in Reg. 1272/2008, as amended)	Hazard classes (s), categories: Skin Sens. 1, H317 Code(s) for hazard pictogram(s): GHS07 Signal word: Warning Hazard statement(s): H317 Precautionary statement(s): *Not applicable for a.s.*
Additional C&L proposal	-
Agreed EU endpoints	
AOEL systemic	0.3 mg/kg bw/d
Reference	EFSA Journal 2017; 15 (9):4980
Conditions to take into account/critical areas of concern with regard to toxicology	
According to Review Report/EFSA Conclusion for active substance	None*

*None but additional matching gentox studies were generated by Globachem to support the grape use. Indeed, the data matching package evaluated by Latvia supported only the representative use included in the review report of the Annex I renewal of Zoxamide ie potato (after the notifier withdraw its support for the grape use in the renewal process). However, for this application on grape, additional studies on the active/processing metabolite RH-150721 were generated to support the grape use and the following studies are provided and added to the reference list: xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx, STUGC23AA0970-2 matching those initially included in the RAR.

6.3 Toxicological Evaluation of Plant Protection Product

A summary of the toxicological evaluation for GLOB2013F 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 GLOB2013F

Type of test, species, model system (Guideline)	Result	Acceptability	Classification (acc. to the criteria in Reg. 1272/2008)	Reference
LD_{50} oral, rat	Study not necessary	Y	None	Theoretical Calculations (see Part C)
LD_{50} dermal, rat	Study not necessary	Y	None	Theoretical Calculations (see Part C)
LC_{50} inhalation, rat	Study not necessary	Y	None	Theoretical Calculations (see Part C)
Skin irritation	Study not necessary	Y	None	Theoretical Calculations (see Part C)

Eye irritation	Study not necessary	Y	None	Theoretical Calculations (see Part C)
Skin sensitisation	Sensitising (based on calculations)	Y	Skin sensitisation Cat 1 H317	Theoretical Calculations (see Part C)
Supplementary studies for combinations of plant protection products	No data – not required			

Table 6.3-2: Additional toxicological information relevant for classification/labelling of GLOB2013F

	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)	Zoxamide (38.44 - 42.49% (w/w))	Skin Sens. 1, H317	Reg. (EC) No 1272/2008 as amended	Skin Sens. 1, H317
Toxicological properties of non-active substance(s) (relevant for classification of product)	–	–	–	–
Further toxicological information	See Part C	–	–	~~EUH 208~~ Contains 1,2-Benzisothiazolin-3-one. ~~May produce an allergic reaction~~

6.4 Toxicological Evaluation of Groundwater Metabolites

The predicted Environmental Concentration in groundwater calculated for zoxamide metabolite RH-141455 is greater than the regulatory threshold of 0.1 µg/L in the proposed use.

The following data on metabolites with the potential to reach the groundwater in concentrations above 0.1 µg/L and requiring relevance assessment were submitted. Note that the relevance assessment of the metabolites is reported in Part B.10; the submitted toxicological studies are summarised in this document.

6.4.1 RH-141455

An overview of the results of the accepted toxicological studies for groundwater metabolite RH-141455 is given in the following table. ~~Full summaries of studies on the metabolite that have not previously been considered within an EU peer review process are described in detail in Appendix 2 (A 2.11 Other/Special Studies).~~

Table 6.4-1: Summary of the results of toxicity studies for RH-141455

Type of test, species (Guideline)	Result	Acceptability	Reference*
Ames Test (OECD 471)	Non mutagenic	Y	Sames, J.L. Ciaccia, P.J. (1998b)*
In vitro mouse lymphoma Assay	Non mutagenic	Y	Woods, I. (2014a)**
In vitro Micronucleus Assay	Non mutagenic	Y	Woods, I. (2014b)**

* indicates that a study was reviewed at EU level
** Matching studies have been submitted as part of a data matching package in order to compensate for access to these references

6.5 Dermal Absorption (KCP 7.3)

A summary of the dermal absorption rates for the active substances in GLOB2013F are presented in the following table.

Table 6.5-1: Dermal absorption rates for active substances in GLOB2013F

	Zoxamide	
	Value	**Reference**
Concentrate	0.22 %	Hassler, A., 2022 20220116
Dilution (dilution factor 1:3333)	10 %	Hassler, A., 2022 20220116

6.5.1 Justification for proposed values - zoxamide

Proposed dermal absorption rates for zoxamide are based on dermal absorption studies on GLOB2013F. The study results are summarised in the following table. Full summaries of studies on the dermal absorption of zoxamide/GLOB2013F that have not previously been evaluated within an EU peer review process are described in detail in Appendix 2.

Table 6.5-2: Summary of the results of submitted dermal absorption studies for zoxamide

Test	Concentrate	Spray dilution (1:3333)	Formulation in study	Acceptability of study	Justification provided on representativity of study formulation for current product	Acceptability of justification	Reference*
In vitro (human)	0.22 %	10 %	GLOB2013F	Y	Yes (see Appendix A 2.10)	Justification accepted. Endpoint can be used for current product	Hassler, S. (2022)

* indicates that a study was reviewed at EU level

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	GLOB2013F
Formulation type	SC
Category	Fungicide
Active substance(s) (incl. content)	**zoxamide** 450 g/L
AOEL systemic	0.3 mg/kg bw/d
Inhalation absorption	100%
Oral absorption	~~100%~~ 60% (based on EFSA Journal 2017;15(9):4980).
Dermal absorption	Concentrate: 0.22 % Dilution: 10 %

6.6.1 Selection of critical use(s) and justification

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

Justification

For potato, the exposure assessment was performed with intended use. For grape, the assessment was performed based at the use with the highest dose rate applicable (use No. 3).

6.6.2 Operator exposure (KCP 7.2.1)

zRMS's comment	Acceptable. The Applicant performed operator exposure calculations using the EFSA OPEX calculator version 1.0.2 (29/04/2024). The calculation results revealed that the use of GLOB2013F is safe for the operator wearing only a workwear, if the product is used as intended. However, taking into account the GLOB2013F classification (Skin Sens. 1, H317), the operator should use protective gloves during the mixing/loading step.

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 GLOB2013F according to the critical use(s) is presented in Table 6.6-2. The outcome of the estimation is presented in Table 6.6-3 (longer term exposure). Detailed calculations are in Appendix 3.

Table 6.6-2: Exposure models for intended uses

Critical use(s)	Potato (max. 0.3 L product/ha) Grape (max. 0.368 L product/ha)
Model(s)	Guidance on the assessment of exposure of operators, workers, residents and bystanders in risk assessment of plant protection products. EFSA Journal 2022;20(1):7032, 134 pp. calculator version: v 1.0.2 (29/04/2024)

Table 6.6-3: Estimated operator exposure (longer term exposure) using OPEX v 1.0.1

Model data	Level of PPE	Total absorbed dose [mg/kg bw per day]	% of systemic AOEL
Low vegetables/Outdoor/Downward spraying/Vehicle-mounted/Drift reduction: 0 %/75th percentile Crop density: Normal			
Number of applications and application rate: 3 x 0.135 kg a.s./ha Dermal absorption (concentrate): 0.22 % Dermal absorption (in-use dilution): 10 %			
Zoxamide	M/L: Workwear App: Workwear	0.003	1
Viticulture/Outdoor/Upward spraying/Vehicle-mounted/Drift reduction: 0 %/75th percentile Crop density: Normal			
Number of applications and application rate: 2 x 0.1656 kg a.s./ha Dermal absorption (concentrate): 0.22 % Dermal absorption (in-use dilution): 10 %			
Zoxamide	M/L: Workwear App: Workwear	0.01	4

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)

zRMS's comment	Acceptable. The Applicant performed worker exposure calculations using the EFSA OPEX calculator version 1.0.2 (29/04/2024). The calculation results revealed that the worker exposure to GLOB2013F is acceptable in both uses (potatoes and grapes) if worker is wearing the workwear. In the case of grapes, two options were taken into account in the OPEX model: *Hand harvesting* (8 hours/day) and *Inspection, irrigation* (2 hours/day). In the case of potatoes, only one option was taken into account in the OPEX model: *Inspection, irrigation* (2 hours/day) therefore zRMS supplemented the calculations with the option *Reaching, picking* (8 hours/day).

Level of PPE	Total absorbed dose [mg/kg bw per day]	% of systemic AOEL	Re-entry restriction [days]
Reaching, picking (all except Brassica) / Outdoor Work rate: 8 hours/day Interval: 7 days Body weight: 60 kg TC (potential): 5800 cm²/h TC (workwear (arms, body and legs covered)): 2500 cm²/h TC (workwear (arms, body and legs covered) and gloves): 580 cm²/h TC (gloves): NA cm²/h			
Zoxamid	Number of applications & application rate: 3 x 0.135 kg a.s./ha Dermal absorption: 10 % DFR: 3 µg/cm² foliage per kg a.s./ha DT50: 30 days		
Potential	0.08	26.8	0
Workwear	0.03	11.6	0
Workwear and gloves	0.008	2.7	0
Hands covered, no workwear			

This additional OPEX report for potatoes was included in the Appendix 3 (Exposure calculations).

6.6.3.1 Estimation of worker exposure

Table 6.6-4 shows the exposure model(s) used for estimation of worker exposure after entry into a previously treated area or handling a crop treated with GLOB2013F according to the critical uses. Outcome of the estimation is presented in Table 6.6-5 (longer term exposure). Detailed calculations are in Appendix 3.

Table 6.6-4: Exposure models for intended uses

Critical use(s)	Potato (max. 0.3 L product/ha) Grape (max. 0.368 L product/ha)
Model	Guidance on the assessment of exposure of operators, workers, residents and bystanders in risk assessment of plant protection products. EFSA Journal 2022;20(1):7032, 134 pp. calculator version: v 1.0.2 (29/04/2024)

Table 6.6-5: Estimated worker exposure (longer term exposure)

Level of PPE	Total absorbed dose [mg/kg bw per day]	% of systemic AOEL	Re-entry restriction [days]
Potato			Inspection, irrigation (All) / Outdoor Work rate: 2 hours/day Interval: 7 days Body weight: 60 kg TC (potential): 12500 cm²/h TC (workwear (arms, body and legs covered)): 1400 cm²/h TC (workwear (arms, body and legs covered) and gloves): 1250 cm²/h TC (gloves): NA cm²/h
Zoxamide			Number of applications & application rate: 3 x 0.135 kg a.s./ha Dermal absorption: 10 % DFR: 3 µg/cm² foliage per kg a.s./ha DT50: 30 days
Potential	0.04	14.5	0
Workwear	0.005	1.6	0
Workwear and gloves	0.004	1.4	0
Hands covered, no workwear	-	-	-
Grapes			Hand harvesting / Outdoor Work rate: 8 hours/day Interval: 8 days Body weight: 60 kg TC (potential): 30000 cm²/h TC (workwear (arms, body and legs covered)): 10100 cm²/h TC (workwear (arms, body and legs covered) and gloves): NA cm²/h TC (gloves): NA cm²/h
Zoxamide			Number of applications & application rate: 2 x 0.1656 kg a.s./ha Dermal absorption: 10 % DFR: 3 µg/cm² foliage per kg a.s./ha DT50: 30 days
Potential	0.4	121	9
Workwear	0.1	40.8	0
Workwear and gloves	-	-	-
Hands covered, no workwear	-	-	-

Level of PPE	Total absorbed dose [mg/kg bw per day]	% of systemic AOEL	Re-entry restriction [days]
Grapes			Inspection, irrigation / Outdoor Work rate: 2 hours/day Interval: 8 days Body weight: 60 kg TC (potential): 12500 cm²/h TC (workwear (arms, body and legs covered)): 1400 cm²/h TC (workwear (arms, body and legs covered) and gloves): 1250 cm²/h TC (gloves): NA cm²/h
Zoxamide			Number of applications & application rate: 2 x 0.1656 kg a.s./ha Dermal absorption: 10 % DFR: 3 µg/cm² foliage per kg a.s./ha DT50: 30 days
Potential	0.04	12.6	0
Workwear	0.004	1.4	0
Workwear and gloves	0.004	1.3	0
Hands covered, no workwear	-	-	-

6.6.3.2 Refinement of generic DFR value (KCP 7.2)

Not required.

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)

zRMS's comment	Acceptable. The Applicant performed resident exposure calculations using the EFSA OPEX calculator version 1.0.2 (29/04/2024). The calculation results revealed that resident exposure, both for child and adult, is acceptable (below the AOEL) considering all pathways of exposure – drift, vapour, deposit and re-entry, if a buffer zone of 2-3 meters for potatoes and 5 meter for grapes is used. The AAOEL values for zoxamide is not specified, therefore it is assumed that the bystander exposure estimation is covered by the calculated resident exposure.

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 6.6-6 shows the exposure model(s) used for estimation of resident and bystander exposure to zoxamide. The outcome of the estimation is presented in Table 6.6-7 (longer term resident exposure). Detailed calculations are in Appendix 3.

Table 6.6-6: Exposure models for intended uses

Critical use(s)	Potato (max. 0.3 L product/ha) Grape (max. 0.368 L product/ha)
Model	Guidance on the assessment of exposure of operators, workers, residents and bystanders in risk assessment of plant protection products. EFSA Journal 2022;20(1):7032, 134 pp. calculator version: v 1.0.2 (29/04/2024)

Table 6.6-7: Estimated resident exposure (longer term exposure)

Model data	Level of PPE	Total absorbed dose [mg/kg bw per day]	% of systemic AOEL
Potato			Season: Not relevant Buffer zone: 2-3 m Drift reduction technology: 0 % Interval between treatments: 7 days Minimum volume of water: 150 l
Zoxamide			Number of applications and application rate: 3 x 0.135 kg a.s./ha Dermal absorption: 10 % DFR: 3 µg/cm² foliage per kg a.s./ha DT50: 30 days
Resident child Body weight: 10 kg	Drift (75th perc.)	0.002	0.8
	Vapour (75th perc.)	0.0008	0.3
	Deposits (75th perc.)	0.0008	0.3
	Re-entry (75th perc.)	0.006	2
	Sum (mean)	0.007	2.5
Resident adult Body weight: 60 kg	Drift (75th perc.)	0.0006	0.2
	Vapour (75th perc.)	0.0003	0.09
	Deposits (75th perc.)	0.0002	0.08
	Re-entry (75th perc.)	0.003	1.1
	Sum (mean)	0.003	1.1

Model data	Level of PPE	Total absorbed dose [mg/kg bw per day]	% of systemic AOEL
Grapes			Season: Not relevant Buffer zone: 2-3 m Drift reduction technology: 0 % Interval between treatments: 8 days Minimum volume of water: 100 l
Zoxamide			Number of applications and application rate: 2 x 0.1656 kg a.s./ha Dermal absorption: 10 % DFR: 3 µg/cm² foliage per kg a.s./ha DT50: 30 days
Resident child Body weight: 10 kg	Drift (75th perc.)	*	*
	Vapour (75th perc.)	0.0008	0.3
	Deposits (75th perc.)	0.0008	0.3
	Re-entry (75th perc.)	0.005	1.7
	Sum (mean)	0.006	1.8
Resident adult Body weight: 60 kg	Drift (75th perc.)	*	*
	Vapour (75th perc.)	0.0003	0.09
	Deposits (75th perc.)	0.0003	0.08
	Re-entry (75th perc.)	0.003	0.9
	Sum (mean)	0.003	0.9
Grapes			Season: Not relevant Buffer zone: 5 m Drift reduction technology: 0 % Interval between treatments: 8 days Minimum volume of water: 100 l
Zoxamide			Number of applications and application rate: 2 x 0.1656 kg a.s./ha Dermal absorption: 10 % DFR: 3 µg/cm² foliage per kg a.s./ha DT50: 30 days
Resident child Body weight: 10 kg	Drift (75th perc.)	0.02	7.7
	Vapour (75th perc.)	0.0008	0.3
	Deposits (75th perc.)	0.0004	0.1
	Re-entry (75th perc.)	0.005	1.7
	Sum (mean)	0.02	6.8
Resident adult Body weight: 60 kg	Drift (75th perc.)	0.01	4.3
	Vapour (75th perc.)	0.0003	0.09
	Deposits (75th perc.)	0.0001	0.04
	Re-entry (75th perc.)	0.003	0.9
	Sum (mean)	0.01	3.7

*Due to limitations in current version of the EFSA model, for grapes a buffer zone different from 2-3m needs to be considered in order to consider drift. Nevertheless, assessment for 2-3m in the other categories is also presented here for the sake of completeness.

6.6.4.2 Measurement of resident and/or bystander exposure

Since the resident and/or bystander exposure estimations carried out indicated that the acceptable operator exposure level (AOEL) for zoxamide will not be exceeded under conditions of intended uses and considering above mentioned risk mitigation measures, a study to provide measurements of resident/bystander exposure was not necessary and was therefore not performed.

6.6.5 Combined exposure

Not relevant. The product contains only one active substance.

Appendix 1 Lists of data considered in support of the evaluation

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	Vertebrate study Y/N	Owner
KCP 7.3	Hassler, S.	2022	Zoxamide – In vitro percutaneous penetration of [^{14}C]Zoxamide formulated as GLOB2013F through Human Skin Membranes, Innovative Environmental Services, Report No.: 20220116, GLP, Unpublished	N	Globachem NV
KCA 5.4.1	Burns, K.	2023	Reverse Mutation Assay using Bacteria (Salmonella typhimurium and Escherichia coli) with Zoxamide metabolite RH-150721, Eurofins Biopharma Product Testing Munich Gmbh, Report No.: STUGC22AA1264-2, GLP, Unpublished	N	Globachem NV
KCA 5.4.1	Smith, K.	2023	RH-150721: Bacterial Reverse Mutation Assay, Labcorp Early Development Laboratories Ltd., Report No.: 8512200, GLP, Unpublished	N	Globachem NV
KCA 5.4.1	Gilby, B.	2023	RH-150721: In Vitro Human Lymphocyte Micronucleus Assay, Labcorp Early Development Laboratories Ltd., Report No.: 8512201, GLP, Unpublished	N	Globachem NV
KCA 5.4.2	xxxxxxxxxx	2024	In vivo Mammalian Alkaline Comet Assay of Liver and Glandular Stomach Cells in Rats with RH-150721 [CAS No.: 209809-78-9] xxxxxxxxxxxxxxxxxxxx, Report No.: STUGC23AA0970-2, GLP, Unpublished	Y	Globachem NV

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

*Studies in the table below were generated to data match the AIR protected studies from the main notifier. The data matching package has been evaluated by the RMS Latvia and a copy was already sent to all MS.

Data point	Author(s)	Year	Title Company Report No. Source (where different from company) GLP or GEP status Published or not	Vertebrate study Y/N	Owner
KCA 5.2.7	Brinkmann, C.	2022	In Vitro 3T3 NRU Phototoxicity Test with Zoxamide Tech, Eurofins Biopharma Product Testing Munich Gmbh, Report No.: STUGC22AA0666-2, GLP, Unpublished	N	Globachem NV
KCA 5.8.1	Schmidt, E.	2022	In vitro Mammalian Cell Gene Mutation Assay (Thymidine Kinase Locus/tk+/-) in L5178Y Mouse Lymphoma Cells with Zoxamide metabolite RH-141455, Eurofins Biopharma Product Testing Munich Gmbh, Report No.: STUGC22AA1264-3, GLP, Unpublished	N	Globachem NV
KCA 5.8.1	Graf, J.	2022	In vitro Mammalian Micronucleus Assay in Human Lymphocytes with Zoxamide metabolite RH-141455, Eurofins Biopharma Product Testing Munich Gmbh, Report No.: STUGC22AA1264-4, GLP, Unpublished	N	Globachem NV

Appendix 2 Detailed evaluation of the studies relied upon

zRMS's comment	The toxicological assessment of the GLOB2013F formulation was carried out by calculation method in accordance with the principles of Regulation 1272/2008. Details are included in Doc. C. According to the calculation results, GLOB2013F should be classified for human health as Skin Sens.1 with hazard statement H317 – *May cause an allergic skin reaction* and with the additional statement *Contains 1,2-benzisothiazolin-3-one*.

A 2.1 Statement on bridging possibilities

Not applicable.

A 2.2 Acute oral toxicity (KCP 7.1.1)

No study provided.

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

No study provided.

A 2.4 Acute inhalation toxicity (KCP 7.1.3)

No study provided.

A 2.5 Skin irritation (KCP 7.1.4)

No study provided.

A 2.6 Eye irritation (KCP 7.1.5)

No study provided.

A 2.7 Skin sensitisation (KCP 7.1.6)

No study provided.

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

No study provided.

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)

A 2.10.1 Study 1 – zoxamide in GLOB2013F

Comparative dermal absorption, in vitro using rat and human skin

Comments of zRMS:	Study acceptable. The study was performed according to the OECD 428 Test (Method B.45 in accordance with Council Regulation (EC) 440/2008) in compliance with GLP. One deviation was noted: *The applied formulation of the high dose level dried to a solid pellet which sticked to the skin membrane except for one cell. This pellet could not be suspended or removed by the skin membrane wash at 6 hours without damaging the skin membrane. In deviation to the study plan this pellet was removed by a pair of tweezers at the end of the experiment (24 hours) and was added to the skin membrane wash 24 hours.* Considering that during the exposure time of 6 hours, very low amounts of the applied radioactivity penetrated through the human skin membrane into the receptor fluid (0.02% of high dose), this deviation appears to be acceptable. The study results revealed that less than 75% of the absorption occurs within half the duration of the study ($t_{0.5}$ = 73% for dilution and $t_{0.5}$ = 66% for concentrate), therefore tape strips 3-10 were included in the skin absorption calculations (in accordance with the EFSA guidance on dermal absorption, 2017). To address variability between replicates, a multiple of the standard deviation was added to the mean dermal absorption value. For 11 duplicates, a multiplication factor k=0.67 was used. Total absorption = Absorption (including Tape strips 3-10) + 0.67SD Concentrate: 0.16 + 0.67 x 0.09 = 0.2203 Dilution: 7.34 = 0.67 x 4.29 = 10.2443 Taking into account the rounding rules recommended in the EFSA guidance, the final dermal absorption of zoxamide in GLOB2013F was accepted: Concentrate (450g/L) - 0.22%, dilution (0.135 g/L) – 10%.

Reference KCP 7.3

Report	Zoxamide – In vitro percutaneous penetration of [^{14}C]Zoxamide formulated as GLOB2013F through Human Skin Membranes, Hassler, S., 2022, Innovative Environmental Services, Report No.: 20220116
Guideline(s)	OECD 428
Deviations	No
GLP	Yes
Acceptability	Yes

Materials and methods

The percutaneous penetration of Zoxamide formulated as GLOB2013F, was investigated in vitro using split-thickness skin membranes from human skin.

The skin membranes were set up in flow-through diffusion cells and formulated [^{14}C]Zoxamide was applied onto the skin membranes at two nominal dose levels. The high dose level reflects the commercial formulation (450 g a.i./L). The low dose reflects the lowest concentration recommended for use, i.e. 0.3 L commercial product/ha diluted in 1000 L water.

The exposure of the test item was performed under non-occluded conditions over an exposure time of 6 hours. Thereafter, the remaining test item was removed by washing the skin membranes with a mild soap solution. Further penetration of the remaining test item after removal was measured for additionally 18 hours. At the end of the experiment, i.e. 24 hours after application, an additional skin membrane wash was performed. Test item remaining in/on the application site was removed by tape stripping of the application site until the epidermis was removed. During the experimental period, the receptor fluid (phosphate physiological buffered saline with the addition of 5 % (w/v) Volpo N20) was collected in hourly intervals between 0-6 hours and thereafter in 2 hours intervals until the end of the experiments.

Dose Level		Species	Conc. [mg/cm^3]	Appl. Dose [µg/cm^2]	Number of Replicates	Number of Donors	Collection period [h]
Low Dose	A1	Human	1.25	1.25	11*	5	0-24 h
High Dose	A2		446.2	4462	11	6	

* One cell was excluded from mean calculation

Results and discussions

Within the exposure period of 6 hours very low amounts of the applied radioactivity penetrated through the human skin membrane into the receptor fluid accounting for 0.59% and 0.02% of the low and high dose, respectively. Most of the measured values in the receptor fluid of the high dose level were close or below LOQ level, therefore the calculated cumulative values should be considered as worst case. The Flux within the first 6 hours was calculated to be 0.0018 and 0.3970µg·cm^{-2}·h^{-1} for the low and high dose level, respectively.

At the end of the exposure period, i.e. after 6 hours, a part of radioactivity could be removed from the application site by skin membrane wash, accounting for 43.13 % for the low dose and 11.90 % of the high dose. For the high dose level it was observed that the applied formulation dried to a solid pellet which sticked to the skin membrane. This pellet could not be suspended or removed by the skin membrane wash at 6 hours without damaging the skin membrane. Within 24 hours a total amount of 1.28 % (low dose) and 0.07 % (high dose) penetrated through the human skin membranes. An average of 73 % and 66 % of the total penetration was found in the receptor fluid after 12 hours for the low and high dose level, respectively.

However, due to the low amount of penetration at the high dose level the calculated Absorption $t_{0.5}$ values are considered as not meaningful.

An additional amount of 9.60 %, and 87.38 % could be removed by the second skin membrane wash at 24 hours, whereas the solid pellet of the high dose level was removed by a pair of tweezers and was added to the skin membrane wash 24 hours. In total, 52.80 % of the low dose and 99.37 % of the high dose could be recovered in skin membrane wash at 6 and 24 hours in donor cell wash.

After the washing procedure a remarkable part of the applied low dose was still present on the skin membrane. The major portion of this remaining test item could be removed from the surface of the skin membranes by applying the first two tape strips. After tape stripping only 0.13 % and 0.03 % of the dose remained in the skin membrane for the low and high dose level, respectively.

Formulation	A1		A2	
Dose applied [µg·cm^{-2}]	1.25		4462	
	Mean	SD	Mean	SD
Receptor Fluid				
0- 6 h	0.59	0.27	0.02	0.02
6-12 h	0.35	0.16	0.03	0.01
0-12 h	0.95	0.35	0.05	0.03
12-24 h	0.33	0.20	0.02	< 0.01
Receptor Cell Rinse	0.03	0.03	< 0.01	< 0.01
Subtotal	**1.31**	0.49	**0.07**	0.03
Skin Membrane	**0.13**	0.12	**0.03**	0.06
Absorption	**1.44**	0.59	**0.10**	0.07
(incl. Tape Strip 3-10)	(7.34)	(4.29)	(0.16)	(0.09)
Membrane Wash 6 h	43.13	18.17	11.90	28.61
Membrane Wash 24 h	9.60	3.34	87.38	29.05
Donor-Cell Wash	0.07	0.10	0.08	0.13
Dislodged Dose	**52.80**	17.00	**99.37**	1.39
Tape Strip 1	26.23	16.19	0.17	0.17
Tape Strip 2	15.36	17.15	0.02	0.02
Subtotal	**41.59**	20.71	**0.20**	0.18
Tape Strip 3	3.74	3.62	0.03	0.04
Tape Strip 4	1.11	1.45	< 0.01	0.01
Tape Strip 5	0.79	1.49	< 0.01	0.01
Tape Strip 6	0.14	0.19	< 0.01	< 0.01
Tape Strip 7	0.13	0.31	< 0.01	< 0.01
Tape Strip 8	< 0.01	< 0.01	< 0.01	0.01
Tape Strip 9	< 0.01	< 0.01	< 0.01	< 0.01
Tape Strip 10	< 0.01	< 0.01	< 0.01	< 0.01
Subtotal	**5.90**	4.50	**0.06**	0.04
Tape Strips	**47.49**	19.28	**0.25**	0.20
Absorption $t_{0.5}$	73 %	11 %	66 %	21 %
Recovery	**101.73**	10.63	**99.72**	1.34

For the performed experiments an average of 102 % and 100 % of total recovery was found for the low and high dose level, respectively.

Conclusion/endpoint:

EFSA derivation of dermal absorption based on the human in vitro study

Active Ingredient	**Concentrations tested in the study**	
Formulation (type) (code)	Concentrate	Spray Dilution
Dose Concentration (g/L)	450	0.135
Meets EFSA criteria for exclusion of all tape strips (% absorbed in first 12h)	Yes/No N	Yes/No N
Meets EFSA criteria for mass balance (Recovery (%) of applied dose)	Yes/No Y	Yes/No Y
Tape strips 3-20 (%)	0.06	5.9
Exposed Skin (%)	0.03	0.13
Receptor Fluid and Chamber wash (%)	0.07	1.31
Total (%)	0.16	7.34
Meets EFSA criteria for addition of Standard Deviation (SD) (SD (%) of mean)	Yes/No Y	Yes/No Y
SD	0.09	4.29
Mean + SD	0.36	14.26
Dermal Penetration (%)	0.216	10.426
	Concentrations recommended on the product label (g/L)	
	Concentrate	**Spray dilution**
Dermal Penetration (%) to be used in risk assessment (EFSA rounding, pro-rata correction if necessary)	**0.22**	**10**

A 2.11 Other/Special Studies

None.

Appendix 3 Exposure calculations