REGISTRATION REPORT

Part B

Section 6

Mammalian Toxicology

Detailed summary of the risk assessment

Product code: GLOB2111F

Product name(s): Starinta

Chemical active substance(s):

Bixafen, 125 g/L

Central Zone

Zonal Rapporteur Member State: Poland

CORE ASSESSMENT

(authorization)

Applicant: Globachem NV

Submission date: December 2023

zRMS Assessment : 09/08/2024

Version after commenting : 15/11/2024

Version history

When	What
August 2024	zRMS assesment
November 2024	zRMS: after first round of commenting

Table of Contents

6 Mammalian Toxicology (KCP 7)

6.1 Summary

Table 6.1-1: Information on GLOB2111F*

Product name and code	GLOB2111F
Formulation type	Emulsifiable concentrate [Code: EC]
Active substance(s) (incl. content)	bixafen; 125 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 GLOB2111F/Starinta 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 GLOB2111F according to Regulation (EC) No 1272/2008

Hazard class(es), categories	Skin Irrit. 2, Eye ~~Irrit.~~ Dam. 1.
Hazard pictograms or Code(s) for hazard pictogram(s)	GHS05~~, GHS07~~
Signal word	Danger
Hazard statement(s)	H315 - Causes skin irritation, H318 - Causes serious eye damage.
Precautionary statement(s)	P264 - Wash hands, forearms and face thoroughly after handling, P280 - Wear protective gloves, protective clothing, eye protection/face protection, P302 + P352 - IF ON SKIN: Wash with plenty of water/soap, P305 + P351 + P338 - IF IN EYES: Rinse cautiously with water for several minutes. Remove contact lenses, if present and easy to do. Continue rinsing, P310 - Immediately call a POISON CENTER or doctor, ~~P321,~~ P332 + P313 - If skin irritation occurs: Get medical advice/attention, P362 + P364 - Take off contaminated clothing and wash it before reuse.
Additional labelling phrases	To avoid risks to man and the environment, comply with the instructions for use. [EUH401]
	Contains: N-Octyl-2-pyrrolidone

Table 6.1-3: Summary of risk assessment for operators, workers, residents and bystanders for GLOB2111F

	Result	PPE / Risk mitigation measures
Operators	Acceptable	M&L and application: Work wear (arms, body and legs covered) (resulting from exposure assessment) M&L: work wear, protective gloves and eye protection or face protection due to the fact that the product is classified as Skin Irrit. 2 H315 and Eye Dam. 1 H318
Workers	Acceptable	~~Work wear (arms, body and legs covered)~~ None
Residents	Acceptable	None
Bystanders	Acceptable	None

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.

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	Cereals (winter and spring wheat, winter and spring barley, winter and spring rye, spelt, winter and spring oats and winter and spring triticale) (BBCH 30-69)	F	Normal downward spraying TM	a) 1 b) 1	a) 0.125 b) 0.125	100 - 300		Guidance on the assessment of exposure of operators, workers, residents and bystanders in risk assessment for plant protection products; EFSA Journal 2022;20(1):7032				

* 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:

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

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)

	Bixafen
Common Name	Bixafen
CAS-No.	581809-46-3

	Bixafen
Classification and proposed labelling	
With regard to toxicological endpoints (according to the criteria in Reg. 1272/2008, as amended)	Hazard classes (s), categories:/ Code(s) for hazard pictogram(s):/ Signal word:/ Hazard statement(s):/ Precautionary statement(s):/
Additional C&L proposal	/
Agreed EU endpoints	
AOEL systemic	0.13 mg/kg bw/d
Reference	EFSA Journal 2012; 10(11): 2917
Conditions to take into account/critical areas of concern with regard to toxicology	
According to Review Report/EFSA Conclusion for active substance	None

6.3 Toxicological Evaluation of Plant Protection Product

A summary of the toxicological evaluation for GLOB2111F 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 GLOB2111F

Type of test, species, model system (Guideline)	Result	Acceptability	Classification (acc. to the criteria in Reg. 1272/2008)	Reference
LD_{50} oral	Study not necessary	Yes ~~/ No / Supplementary~~	None	Calculation method (Part C)
LD_{50} dermal	Study not necessary	Yes ~~/ No / Supplementary~~	None	Calculation method (Part C)
LC_{50} inhalation	Study not necessary	Yes ~~/ No / Supplementary~~	None	Calculation method (Part C)
Skin irritation, EpiDermTM Standard Model (OECD 431)	Irritant	Yes ~~/ No / Supplementary~~	Skin Irrit. 2, H315	Calculation method (Part C) and [redacted] 2023
Eye irritation	Study not necessary	Yes ~~/ No / Supplementary~~	Eye Irrit. 1, H318	Calculation method (Part C)
Skin sensitisation	Study not necessary	Yes ~~/ No / Supplementary~~	None	Calculation method (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 GLOB2111F

	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)	Bixafen (13% (w/w))	Not relevant for toxicology	EFSA conclusion	None
Toxicological properties of non-active substance(s) (relevant for classification of product)	N-Octyl-2-pyrrolidone (> 3%)	Eye Dam. 1 H318	MSDS	Eye Dam. 1 H318
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

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 Metabolite M44

An overview of the results of the accepted toxicological studies for groundwater metabolite M44 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 metabolite M44

Type of test, species (Guideline)	Result	Acceptability	Reference*
bacterial reverse mutation test (OECD 471)	non-genotoxic	Yes / No / Supplementary	Schulz and Landsiedel, 2007
in vitro cytogenetic test (OECD 473)	non-genotoxic	Yes / No / Supplementary	Schulz and Landsiedel, 2008a
in vitro mammalian cell gene mutation test (OECD 476)	non-genotoxic	Yes / No / Supplementary	Schulz and Landsiedel 2008b
in vivo bone marrow micronucleus study	non-genotoxic	Yes / No / Supplementary	[redacted] 2009

Type of test, species (Guideline)	Result	Acceptability	Reference*
(OECD 474)			
rabbit developmental toxicity study (OECD 414)	NOEL for maternal toxicity : 300 mg/kg/d NOEL for developmental toxicity: 1000 mg/kg/d	Yes / No / Supplementary	[redacted]., 2009
rat oral 90-day toxicity study (OECD 408)	NOEL: 1000 mg/kg/d	Yes / No / Supplementary	[redacted]. 2009

* indicates that a study was reviewed at EU level

6.5 Dermal Absorption (KCP 7.3)

A summary of the dermal absorption rates for the active substances in GLOB2111F are presented in the following table.

Table 6.5-1: Dermal absorption rates for active substances in GLOB2111F

	Bixafen	
	Value	**Reference**
Concentrate	25 %	Default value EFSA Journal ~~2022;20(1):7032~~ 2017;15(6):4873
Dilution	70 %	

6.5.1 Justification for proposed values – bixafen

No data on dermal absorption for bixafen in GLOB2111F/Starinta are available. Justifications for default values according to Guidance on Dermal Absorption (EFSA Journal ~~2022;20(1):7032~~ 2017;15(6):4873) are presented in the following table.

Table 6.5-2: Default dermal absorption rates for bixafen

	Value	Justification for value	Acceptability of justification
Concentrate	25 %	Default value	accepted
Dilution	70 %	Default value	accepted

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	GLOB2111F
Formulation type	EC
Category	Fungicide

Container size(s), short description	0.25-0.5-1-2-3-5-10-15-20 L HDPE/PA, HDPE/F 42 mm (0 – 2 L), 63 mm (3 L, 10 L), 55 mm (5 L, 15 L, 20 L)
Active substance(s) (incl. content)	**Bixafen** 125 g/L
AOEL systemic	0.13 mg/kg bw/d
Inhalation absorption	100%
Oral absorption	100%
Dermal absorption	Concentrate: 25% (default) Dilution: 70% (default)

6.6.1 Selection of critical use(s) 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 central zone is given in Part B, Section 0.

Justification

All uses applied for are in cereals (winter and spring) a maximum number of 1 application. The only difference between some of the uses is the application timing.

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 GLOB2111F 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)	Cereals (max. 1x 1L 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 2022;20(1):7032 calculator version: opex v 1.0.1

Table 6.6-3: Estimated operator exposure (longer term exposure)

		Bixafen	
Model data	**Level of PPE**	**Total absorbed dose (mg/kg/day)**	**% of systemic AOEL**
Vehicle mounted downward spraying outdoors to field crops			
Application rate		0.125 kg a.s./ha	

Spray application (AOEM**;** 75th percentile) Body weight: 60 kg	Potential	0.2	144
	Work wear (arms, body and legs covered) M/L and A	0.1	94.7
	Work wear (arms, body and legs covered) M/L and A + Gloves while M/L	0.014	11.0

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.

Comments of zRMS study comment 6.6.2	The applicant presented calculations for the application of Starinta (GLOB2111F) on cereals: max. 1x 1L product/ha using the tractor-mounted on field. The exposure calculations were conducted by the applicant using the EFSA online calculator OPEX v 1.0.1.
agreed endpoints 6.6.2	According to EFSA OPEX calculations, it can be concluded that the risk of operator exposure during mixing & loading and application of Starinta (GLOB2111F) using the tractor-mounted on field is acceptable under conditions of intended use when work wear (arms, body and legs covered) is worn during mixing, loading and application. Due to the fact that the product is classified as Skin Irrit. 2 H315, workwear and protective gloves should be worn during mixing and loading. Due to the fact that the product is classified as Eye Dam. 1 H318, the operator should wear eye protection or face protection during mixing/loading.

6.6.3 Worker exposure (KCP 7.2.3)

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 GLOB2111F according to the critical use(s). Outcome of the estimation is presented in and 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)	Cereals (max. 1 x 1L product/ha)
Model	Guidance on the assessment of exposure of operators, workers, residents and bystanders in risk assessment for plant protection products; EFSA Journal 2022;20(1):7032 calculator version: opex v 1.0.1

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

		Bixafen	
Model data	**Level of PPE**	**Total absorbed dose (mg/kg bw/day)**	**% of systemic AOEL**
Inspection, irrigation Outdoor Work rate: 2 hours/day, DT_{50}: 30 days DFR: 3 µg/cm²/kg a.s./ha Interval between treatments: N/A			
Number of applications and application rate		1 x 0.125 kg a.s./ha	
Body weight: 60 kg	Potential TC: 12500 cm²/person/h	0.1	84.1
	Work wear (arms, body and legs covered) TC: 1400 cm²/person/h	0.01	9.4
	Work wear (arms, body and legs covered) and gloves TC: 1250 cm²/person/h	0.01	8.4

6.6.3.2 Refinement of generic DFR value (KCP 7.2)

Refinement of the generic Dislodgeable Foliar Residues (DFR) was not necessary since there is no risk for worker exposure.

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~~ without PPE, a study to provide measurements of worker exposure was not necessary and was therefore not performed.

Comments of zRMS study comment 6.6.3	The applicant presented calculations for worker exposure after entry into a previously treated area treated with Starinta (GLOB2111F) max. 1x 1L product/ha using the tractor-mounted.The exposure calculations were conducted using the EFSA online calculator OPEX v 1.0.1. The calculations provided by the applicant were done correctly.
agreed endpoints 6.6.3	According to EFSA OPEX calculations, it can be concluded that the risk of worker exposure during re-entry activities on area treated with Starinta (GLOB2111F) is acceptable under conditions of intended use without PPE, but the worker should wear an adequate workwear within good agricultural practice. As a standard rule, it should be mentioned on the label that treated crops should not be re-entered before spray deposits on leaf surfaces have completely dried.

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 6.6-6 shows the exposure model(s) used for estimation of resident and bystander exposure to bixafen. 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)	Cereals (max. 1 x 1 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 2022;20(1):7032 calculator version: opex v 1.0.1

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

		Bixafen	
Model data		**Total absorbed dose (mg/kg bw/day)**	**% of systemic AOEL**
Vehicle mounted downward spraying outdoors to field crops Buffer zone: 2-3 (m) Drift reduction technology: no DT_{50}: 30 days DFR: 3 µg/cm²/kg a.s./ha Interval between treatments: N/A			
Number of applications and application rate		1 x 0.125 kg a.s./ha	
Resident child Body weight: 10 kg	Drift (75th perc.)	0.01	9.1
	Vapour (75th perc.)	0.0008	0.6
	Deposits (75th perc.)	0.001	1.1
	Re-entry (75th perc.)	0.01	11.4
	Sum (mean)	**0.02**	**15.4**
Resident adult Body weight: 60 kg	Drift (75th perc.)	0.003	2.2
	Vapour (75th perc.)	0.0003	0.2
	Deposits (75th perc.)	0.0006	0.5
	Re-entry (75th perc.)	0.008	6.3
	Sum (mean)	**0.009**	**6.6**

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 bixafen will not be exceeded under conditions of intended uses ~~and considering above mentioned~~ without risk mitigation measures, a study to provide measurements of resident/bystander exposure was not necessary and was therefore not performed.

<table>
<tr><td>Comments of zRMS
study comment 6.6.4</td><td>The applicant presented calculations for resident exposure after application of Starinta (GLOB2111F) on cereals: max. 1x 1L product/ha using the tractor-mounted on field.
The exposure estimation of resident (adult and child) to active substances, applied on a field at dose of 1x1 L product/ha using tractor-mounted and min. water volume 200 l/ha calculated with the EFSA online calculator v 1.0.1. (OPEX) demonstrates that such an exposure for adult and child resident is 15.4% to 6.6% of respective AOEL for bixafen.
According to Table 6.1-4 Critical uses and overall conclusion of exposure assessment and appendix 3 Table A 5 minimal volume water for critical use is 100 l/ha (not 200 l/ha). The evaluator has revised the exposure calculations using min. water volume 100 l/ha and EFSA online calculator (OPEX v 1.0.2.).
According to revised calculations such an exposure for adult and child resident is 20.4% to 7.6% of respective AOEL for bixafen.
The revised calculations for resident exposure:
<table>
<tr><th>Model data</th><th>Level of PPE</th><th>Total absorbed dose [mg/kg bw per day]</th><th>% of systemic AOEL</th></tr>
<tr><td colspan="4">Season: Not relevant
Buffer zone: 2-3 m
Drift reduction technology: 0 %
Interval between treatments: NA
Minimum volume of water: 100 l</td></tr>
<tr><td>Bixafen</td><td colspan="3">Number of applications and application rate: 1 x 0.125 kg a.s./ha
Dermal absorption: 70 %
DFR: 3 µg/cm² foliage per kg a.s./ha
DT50: 30 days</td></tr>
<tr><td rowspan="5">Resident child
Body weight: 10 kg</td><td>Drift (75th perc.)</td><td>0.02</td><td>18.2</td></tr>
<tr><td>Vapour (75th perc.)</td><td>0.0008</td><td>0.6</td></tr>
<tr><td>Deposits (75th perc.)</td><td>0.001</td><td>1.1</td></tr>
<tr><td>Re-entry (75th perc.)</td><td>0.01</td><td>11.4</td></tr>
<tr><td>Sum (mean)</td><td>0.03</td><td>20.4</td></tr>
<tr><td rowspan="5">Resident adult
Body weight: 60 kg</td><td>Drift (75th perc.)</td><td>0.006</td><td>4.3</td></tr>
<tr><td>Vapour (75th perc.)</td><td>0.0003</td><td>0.2</td></tr>
<tr><td>Deposits (75th perc.)</td><td>0.0006</td><td>0.5</td></tr>
<tr><td>Re-entry (75th perc.)</td><td>0.008</td><td>6.3</td></tr>
<tr><td>Sum (mean)</td><td>0.01</td><td>7.6</td></tr>
</table>
</td></tr>
<tr><td>agreed endpoints 6.6.4</td><td>The exposure assessment for residents also covers bystander exposure. According to calculations, it can be concluded that there is no unacceptable risk to any resident (child and adult) and bystander after application of Starinta (GLOB2111F).</td></tr>
</table>

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

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	Vertebrate study Y/N	Owner
KCP 7.1.4	Ashwini, C.	2023	GLOB2020aF: in vitro skin corrosion: reconstructed human epidermis (RhE) test method AD-G1189 Adgyl Lifesciences Private Limited GLP Unpublished	N	Globachem NV

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	Vertebrate study Y/N	Owner
KCP 6.4	Schulz, M.; Landsiedel, R.	2007	Reg.No. 5435595 (metabolite of BAS 700 F) - *Salmonella typhimurium* / *Escherichia coli* reverse mutation assay (standard plate test and preincubation test). 2007/1051931 BASF AG GLP Unpublished	~~Y~~ N	BASF

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 6.4	Schulz, M.; Landsiedel, R.	2008a	Reg.No. 5435595 (metabolite of BAS 700 F) - In vitro chromosome aberration assay in V79 cells. 2008/1002741 BASF SE GLP Unpublished	~~Y~~ N	BASF
KCP 6.4	Schulz, M.; Landsiedel, R.	2008b	Reg.No. 5435595 (metabolite of BAS 700 F) - In vitro gene mutation test in CHO cells (HPRT locus assay). 2008/1014199 BASF SE GLP Unpublished	~~Y~~ N	BASF
KCP 6.4	[redacted]	2009	Reg.No. 5435595 (metabolite of BAS 700 F): Micronucleus test in bone marrow cells of the mouse. [redacted] GLP Unpublished	Y	BASF
KCP 6.4	[redacted]	2009	Reg.No. 5435595 (metabolite of BAS 700 F) - Prenatal developmental toxicity study in New Zealand white rabbits - Oral administration (gavage). [redacted] GLP Unpublished	Y	BASF
KCP 6.4	[redacted]	2009	Reg.No. 5069089 (metabolite of BAS 700 F) - Repeated dose 90-day oral toxicity study in Wistar rats - Administration in the diet [redacted] GLP Unpublished	Y	BASF

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	Vertebrate study Y/N	Owner
KCP XX	Author	YYYY	Title Company Report N Source GLP/non GLP/GEP/non GEP Published/Unpublished	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	Vertebrate study Y/N	Owner
KCP XX	Author	YYYY	Title Company Report N Source GLP/non GLP/GEP/non GEP Published/Unpublished	Y/N	Owner

Appendix 2 Detailed evaluation of the studies relied upon

Comments on zRMS:	For the acute toxicity including irritancy and skin sensitisation the assessments have been conducted by the applicant based on the calculation method according to the Regulation (EC) 1272/2008. Based on calculation method GLOB2111F should be classified as Skin Corr. 1 H31~~54~~ and Eye Dam. 1 H318. Proposed classification based on calculation method according to Regulation (EC) 1272/2008 is acceptable by the zRMS. As an hazardous constituent contributing to classification, the labelling should include: contains N-Octyl-2-pyrrolidone. In addition to the calculation method, the applicant submitted toxicology study (in vitro) conducted with the closely related formulation GLOB2020aF. Similarities on the composition of both products, as given in Part C, show that data generated with GLOB2020aF can be used for assessment of potential skin corrosion hazard of GLOB2111F. zRMS accepts skin corrosion in vitro study submitted by the applicant. The negative result of this study can also be used to exclude corrosive classification of GLOB2111F. Since no in vitro study was carried out to exclude classification as Skin Irrit. 2, according to Regulation EC 1272/2008 GLOB2111F should be classified as Skin Irrit. 2, H315.

A 2.1 Statement on bridging possibilities

The study of Ashwini J. (2023) conducted with the closely related formulation GLOB2020aF is used as surrogate for the evaluation of the skin irritation/corrosion capabilities of GLOB2111F below. Full details over the similarities on the composition of both products is given Part C.

Comments of zRMS:	Acceptable.

A 2.2 Acute oral toxicity (KCP 7.1.1)

No new study was submitted.
Classification – see Registration Report Part C.

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

No new study was submitted.
Classification – see Registration Report Part C.

A 2.4 Acute inhalation toxicity (KCP 7.1.3)

No new study was submitted.
Classification – see Registration Report Part C.

A 2.5 Skin irritation (KCP 7.1.4)

Comments of zRMS:	Study 1 was performed according to OECD 431 and was GLP compliant. The study is acceptable. Under the experimental conditions, GLOB2020aF is not cor-

	rosive to skin.

A 2.5.1 Study 1

Reference	KCP 7.1.4
Report	GLOB2020aF: *in vitro* skin corrosion: reconstructed human epidermis (RhE) test method, Ashwini C., 2023, AD-G1189, Adgyl Lifesciences Private Limited.
Guideline(s)	Yes, OECD Guideline No. 431
Deviations	No
GLP	Yes
Acceptability	Yes/~~No/Supplementary~~

Materials and methods

The test item GLOB2020aF was tested for its possible skin corrosion potential using a three-dimensional Reconstructed Human Epidermis model, EpiSkin, through topical application.

The test item is in liquid form and was applied directly on the top of the skin tissues at 50 µL /tissue and exposed for 3, 60 and 240 minutes.

Fifty microliters (50 µL) of sodium chloride (NaCl) 0.9% (w/v) was used as the negative control for each time of application (3 min, 60 min and 240 min). Similarly, 50 µL of glacial acetic acid was used as the positive control and was tested only at the 240 min exposure time.

After the respective post-incubation period, corrosion potential of the test item was determined by assessing the cytotoxic effect. Cytotoxicity is expressed as the reduction of mitochondrial dehydrogenase activity measured by formazan production from MTT at the end of the treatment.

Skin corrosion is expressed as the remaining cell viability after exposure to the test item. The relative mean tissue viability obtained after the respective treatment periods with the test item was compared to the negative control tissues.

Results and discussions

The mean OD values, true OD values and the individual viability percentage of individual epidermis units measured after treatment with the test item and controls are presented in Table 2, 3 and 4, respectively.

The results show the mean tissue viability obtained after the respective treatment duration with the test item compared to the negative control tissues.

Skin corrosion is expressed as the remaining cell viability after exposure to the test items. The relative mean tissue viability obtained after 3, 60 and 240 minutes treatment duration with the test item compared to the negative control tissues was 124.45, 100.91 and 123.51%, respectively. The positive control had a mean cell viability of 5.26% after 240 minutes exposure. The absolute mean OD570 of the negative control tissues was within the laboratory historical control data range.

The study indicated that the test item GLOB2020aF is predicted to be non-corrosive as the percent viability is 123.51% which is greater than the cut-off percentage cell viability value of 35 % after 240 min exposure, which distinguish corrosive from non-corrosive test chemicals in this *In Vitro* Skin Corrosion Test using Reconstructed Human Epidermis under the conditions of testing employed.

Table A 1: Mean OD Values of Individual Epidermis Units

3-minutes Exposure

	Absorption (OD_{570})	
	R1	**R2**
Negative control	0.956	0.977
Test Item	1.199	1.184

60-minutes Exposure

	Absorption (OD_{570})	
	R1	**R2**
Negative control	0.921	0.930
Test Item	0.942	0.925

240-minutes Exposure

	Absorption (OD_{570})	
	R1	**R2**
Negative control	0.888	0.889
Positive control	0.092	0.091
Test Item	1.104	1.068

OD: optical density
R1 & R2: duplicate exposures

Table A 2: True OD Values of Individual Epidermis Units

3-minutes Exposure

	Absorption (OD_{570})	
	R1	**R2**
Negative control	0.909	0.930
Test Item	1.151	1.137

60-minutes Exposure

	Absorption (OD_{570})	
	R1	**R2**
Negative control	0.874	0.882
Test Item	0.895	0.877

240-minutes Exposure

	Absorption (OD_{570})	
	R1	**R2**
Negative control	0.841	0.842
Positive control	0.045	0.044
Test Item	1.057	1.021

OD: optical density
R1 and R2: duplicate exposures
Blank OD Value (mean of 6 replicate values) = 0.047
True OD value = OD Raw – OD Blank

Table A 3: Individual Tissue Viability of Epidermis Units (Relative)

3-minutes Exposure

	% Individual Viability			
	R1	**R2**	**Mean Viability**	**Variability**
Test Item	125.24	123.66	124.45	1.26

Negative control mean: 0.919

60-minutes Exposure

	% Individual Viability			
	R1	**R2**	**Mean Viability**	**Variability**
Test Item	101.91	99.91	100.91	1.96

Negative control mean: 0.878

240-minutes Exposure

	% Individual Viability			
	R1	**R2**	**Mean Viability**	**Variability**
Positive control	5.35	5.17	5.26	3.36
Test Item	125.62	121.40	123.51	3.36

Negative control mean: 0.841

R1 & R2: duplicate exposures

Conclusion

Since the tissue viability was > 35% after the 240-minute exposure, the test item is predicted to be non-corrosive under the experimental conditions described in this report.

A 2.6 Eye irritation (KCP 7.1.5)

No new study was submitted.
Classification – see Registration Report Part C.

A 2.7 Skin sensitisation (KCP 7.1.6)

No new study was submitted.
Classification – see Registration Report Part C.

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

Not required.

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)

Not required.

A 2.11 Other/Special Studies

Not required.

Appendix 3 Exposure calculations

Table A 4: Information on product and active substance

Product name	GLOB2111F
Formulation type	Soluble concentrates, emulsifiable concentrate, etc.
Product category	Other
Name of active substance	Bixafen
Concentration of active substance [g a.s./l or kg]	125
AOEL [mg/kg bw/day]	0.13
AAOEL [mg/kg bw]	
Inhalation absorption [%]	100
Oral absorption [%]	100
Dermal absorption [%] (concentrate)	25

Table A 5: Assessed uses

Use	Crops	Max. application rate of the product [l or kg/ha]	Unit	Max. no. of applications	Interval between multiple applications [days]	Min. volume water [l/ha]	Max. volume water [l/ha]	Indoor/outdoor	Application method	Type of cultivation	Application technique	Buffer strip [m]	Drift reduction [%]
Use 1	Field crops	1	l/ha	1	NA	100	300	Outdoor	Downward spraying	Normal	Vehicle-mounted	2-3	0

A 3.1 Operator exposure calculations (KCP 7.2.1.1)

Table A 6: Calculations for bixafen according to EFSA guidance (including input parameters)

Mixing/loading	Application	Bixafen (% AOEL) Normal & ve-hicle-mounted
		144
		**94.7**

Model data		Level of PPE	Total ab-sorbed dose [mg/kg bw per day]	% of sys-temic AOEL
Field crops/Outdoor/Downward spraying/Vehicle-mounted/Drift reduction: 0 %/75th percentile Crop density: Normal				
Bixafen	Number of applications and application rate: 1 x 0.125 kg a.s./ha Dermal absorption (concentrate): 25 % Dermal absorption (in-use dilution): 70 %			
		M/L: Workwear App: Workwear	0.1	94.7

Bixafen , Input Data

Formulation type	Soluble concentrates, emulsifiable concentrate, etc.	**Name of active substance**	Bixafen
Concentration of active substance [g a.s./l or kg]	125	**Crops**	Field crops
Area treated [ha/day]	50	**Application method**	Downward spraying

Dermal absorption [%] (concentrate)	25	**Application technique**	Vehicle-mounted
Dermal absorption [%] (dilution)	70	**Indoor/outdoor**	Outdoor
Oral absorption [%]	100	**Drift reduction [%]**	0
Inhalation absorption [%]	100	**Type of cultivation**	Normal
Body weight (kg)	60		
AOEL [mg/kg bw/day]	0.13		
AAOEL [mg/kg bw]			

Bixafen , Per body part - Short term exposure

Activity	Systemic exposure per body part	With workwear	With workwear + PPE/RPE
Mixing and loading (µg/kg bw per day)	*Hand protection*	*None*	*None*
	Hands exposure	**109**	**109**
	Body protection	*Workwear*	*Workwear*
	Body exposure	**0.7**	**0.7**
	Head protection	*None*	*None*
	Head exposure	**1.6**	**1.6**
	Inhalation protection	*None*	*None*
	Inhalation exposure	**0.1**	**0.1**
Application (µg/kg bw per day)	*Hand protection*	*None*	*None*
	Hands exposure	**10.8**	**10.8**
	Body protection	*Workwear*	*Workwear*
	Body exposure	**0.2**	**0.2**
	Head protection	*None*	*None*
	Head exposure	**0.3**	**0.3**
	Inhalation protection	*None*	*None*
	Inhalation exposure	**0.04**	**0.04**

Activity	Systemic exposure per body part	With work-wear	With workwear + PPE/RPE
Total	Total systemic exposure [mg/kg bw per day]	0.1	0.1
	% of AOEL	94.7	94.7

A 3.2 Worker exposure calculations (KCP 7.2.3.1)

Table A 6: Calculations for bixafen according to EFSA guidance (including input parameters)

Level of PPE	Total absorbed dose [mg/kg bw per day]	% of systemic AOEL	Re-entry restriction [days]
			Inspection, irrigation / Outdoor Work rate: 2 hours/day Interval: NA 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
Bixafen			Number of applications & application rate: 1 x 0.125 kg a.s./ha Dermal absorption: 70 % DFR: 3 µg/cm² foliage per kg a.s./ha DT50: 30 days
Potential	0.1	84.1	0
Workwear	0.01	9.4	0
Workwear and gloves	0.01	8.4	0
Hands covered, no workwear			

Bixafen , Input Data

Indoor/outdoor	Outdoor	**AOEL [mg/kg bw/day]**	0.13
Re-entry activity	Inspection, irrigation	**Dermal transfer coefficient - Total potential exposure [cm²/h]**	12500

Crops	Field crops	**Dermal transfer coefficient - Arm, body and legs covered [cm²/h]**	1400
Application method	Downward spraying	**Dermal transfer coefficient - Hands, arm, body and legs covered [cm²/h]**	1250
Application technique	Vehicle-mounted	**Dermal transfer coefficient - Hands covered, no workwear [cm²/h]**	
Max. application rate of the product [l or kg/ha]	1	**DFR refined worker [µg/cm² foliage per kg a.s./ha]**	3
Max. no. of applications	1	**DT50 foliar worker [days]**	30
Interval between multiple applications [days]	NA		
Multiple application factor	1		
Body weight (kg)	60		
Name of active substance	Bixafen		
Dermal absorption [%] (dilution)	70		
Inhalation absorption [%]	100		
Time [hours per day]	2		

Bixafen , Per body part - Long term exposure

Exposure route	Description	Potential	Workwear	Workwear and gloves	Gloves
Dermal	Systemic dermal exposure [mg a.s. per day]	6.6	0.7	0.7	NA
Inhalation	Systemic inhalation exposure [mg a.s. per day]				NA
Total	Total systemic exposure [mg a.s. per day]	6.6	0.7	0.7	NA
	Total systemic exposure [mg/kg bw per day]	0.1	0.01	0.01	NA

Exposure route	Description	Potential	Workwear	Workwear and gloves	Gloves
	% of AOEL	84.1	9.4	8.4	NA

A 3.3 Resident and bystander exposure calculations (KCP 7.2.2.1)

A 3.3.1 Calculations for bixafen

Table A 7: Calculations for bixafen according to EFSA guidance (including input parameters)

Model data	Level of PPE	Total absorbed dose [mg/kg bw per day]	% of systemic AOEL
			Season: Not relevant Buffer zone: 2-3 m Drift reduction technology: 0 % Interval between treatments: NA Minimum volume of water: 200 l
Bixafen			Number of applications and application rate: 1 x 0.125 kg a.s./ha Dermal absorption: 70 % DFR: 3 µg/cm² foliage per kg a.s./ha DT50: 30 days
Resident child Body weight: 10 kg	Drift (75th perc.)	0.01	9.1
	Vapour (75th perc.)	0.0008	0.6
	Deposits (75th perc.)	0.001	1.1
	Re-entry (75th perc.)	0.01	11.4
	Sum (mean)	0.02	15.4
Resident adult Body weight: 60 kg	Drift (75th perc.)	0.003	2.2
	Vapour (75th perc.)	0.0003	0.2
	Deposits (75th perc.)	0.0006	0.5
	Re-entry (75th perc.)	0.008	6.3
	Sum (mean)	0.009	6.6

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)

No new studies submitted.