

FINAL REGISTRATION REPORT

Part B

Section 6

Mammalian Toxicology

Detailed summary of the risk assessment

Product code: SHA 4100 A

Product name: HIFEN

Chemical active substance:

Thifensulfuron-methyl, 750 g/kg

Central Zone

Zonal Rapporteur Member State: Poland

CORE ASSESSMENT

Applicant: SHARDA Cropchem Ltd.

Submission date: September 2023

MS Finalisation date: March 2024; February 2025; April 2025

February 2026

SHA 4100 A / HIFEN
Part B – Section 6 - Core Assessment
SHARDA Cropchem Ltd./ CEU version

Version history

When	What
March 2024	zRMS assessment
February 2025	The final Registration Report.
April 2025	Corrected of final Registration Report.
February 2026	Corrected nr. 2 of final Registration Report.

Table of Contents

6	Mammalian Toxicology (KCP 7).....	5
6.1	Summary	5
6.2	Toxicological Information on Active Substance	7
6.3	Toxicological Evaluation of Plant Protection Product.....	8
6.4	Toxicological Evaluation of Groundwater Metabolites.....	9
6.4.1	IN-L9225.....	9
6.4.2	IN-JZ789	10
6.4.3	IN-L9223.....	10
6.4.4	IN-A4098	12
6.4.5	IN-W8268	13
6.4.6	2-acid-3-triuret	13
6.5	Dermal Absorption (KCP 7.3)	14
6.5.1	Justification for proposed values – Thifensulfuron-methyl	14
6.6	Exposure Assessment of Plant Protection Product (KCP 7.2).....	14
6.6.1	Selection of critical use and justification	15
6.6.2	Operator exposure (KCP 7.2.1)	15
6.6.2.1	Estimation of operator exposure	15
6.6.2.2	Measurement of operator exposure.....	16
6.6.3	Worker exposure (KCP 7.2.3)	16
6.6.3.1	Estimation of worker exposure	17
6.6.3.2	Refinement of generic DFR value (KCP 7.2).....	18
6.6.3.3	Measurement of worker exposure.....	18
6.6.4	Resident and bystander exposure (KCP 7.2.2)	18
6.6.4.1	Estimation of resident and bystander exposure	19
6.6.4.2	Measurement of resident and/or bystander exposure.....	20
6.6.5	Combined exposure	20
Appendix 1	Lists of data considered in support of the evaluation	21
Appendix 2	Detailed evaluation of the studies relied upon.....	23
A 2.1	Statement on bridging possibilities.....	23
A 2.2	Acute oral toxicity (KCP 7.1.1)	23
A 2.3	Acute percutaneous (dermal) toxicity (KCP 7.1.2)	23
A 2.4	Acute inhalation toxicity (KCP 7.1.3)	23
A 2.5	Skin irritation (KCP 7.1.4).....	24
A 2.6	Eye irritation (KCP 7.1.5)	24
A 2.6.1	Study 1	25
A 2.7	Skin sensitisation (KCP 7.1.6).....	27
A 2.8	Supplementary studies for combinations of plant protection products (KCP 7.1.7)	27
A 2.9	Data on co-formulants (KCP 7.4)	27
A 2.9.1	Material safety data sheet for each co-formulant.....	27
A 2.9.2	Available toxicological data for each co-formulant.....	27

SHA 4100 A / HIFEN
Part B – Section 6 - Core Assessment
SHARDA Cropchem Ltd./ CEU version

A 2.10	Studies on dermal absorption (KCP 7.3)	27
A 2.11	Other/Special Studies.....	27
Appendix 3	Exposure calculations	28
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)	28

6 Mammalian Toxicology (KCP 7)

6.1 Summary

Table 6.1-1: Information on SHA 4100 A / HIFEN *

Product name and code	HIFEN / SHA 4100 A
Formulation type	Water dispersible in water [Code: WG]
Active substance(s) (incl. content)	Thifensulfuron-methyl; 750 g/kg
Function	Herbicide
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 4100 A / HIFEN 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:

SHA 4100 A / HIFEN
 Part B – Section 6 - Core Assessment
 SHARDA Cropchem Ltd./ CEU version

Table 6.1-2: Justified proposals for classification and labelling for SHA 4100 A / HIFEN according to Regulation (EC) No 1272/2008

Hazard class(es), categories	none
Hazard pictograms or Code(s) for hazard pictogram(s)	none
Signal word	none
Hazard statement(s)	none
Precautionary statement(s)	WARNING SECTION OF THE LABEL (first page): none Other section of the label: P270: Do not eat, drink or smoke when using this product. And P280 as follows: <i>„Stosować rękawice ochronne oraz odzież roboczą (kombinezon) w trakcie przygotowywania cieczy roboczej oraz odzież roboczą w trakcie wykonywania zabiegu”</i> “Wear protective gloves and work wear (coverall) during mixing/loading and work wear during application”. Storage: P102: Keep out of reach of children. Section First aid: P101: If medical advice is needed, have product container or label at hand.
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 4100 A / HIFEN

	Result	PPE / Risk mitigation measures
Operators	Acceptable	None
Workers	Acceptable	None
Residents & Bystanders	Acceptable	Buffer zone: 2-3 (m).

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.

SHA 4100 A / HIFEN
Part B – Section 6 - Core Assessment
SHARDA Cropchem Ltd./ CEU version

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 situ- ation (e.g. growth stage of crop)	F, Fn, Fpn G, Gn, Gpn or I **	Application		Application rate		PHI (d)	Remarks: (e.g. safener/syn- ergist (L/ha)) critical gap for operator, worker, resident or by- stander exposure based on [Expo- sure model]	Acceptability of exposure assess- ment				
			Method / Kind (incl. applica- tion technique ***)	Max. number (min. interval between ap- plications) a) per use b) per crop/ season	Max. applica- tion rate kg as/ha	Water L/ha min / max			Operator	Worker	Residents	Bystander	
1	Winter cereals (wheat, barley, rye, oats, triti- cale) (BBCH 13-39) (Spring)	F	Spraying, LCTM	1 ; 1	0.03	200 - 400							

* 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

6.2 Toxicological Information on Active Substance

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

	Thifensulfuron-methyl
Common Name	Thifensulfuron-methyl
CAS-No.	79277-27-3
Classification and proposed labelling	
With regard to toxicological endpoints (according to the criteria in Reg. 1272/2008, as amended)	Hazard classes, categories: None Code for hazard pictogram: None Signal word: None Hazard statement: None Precautionary statement: None

SHA 4100 A / HIFEN
 Part B – Section 6 - Core Assessment
 SHARDA Cropchem Ltd./ CEU version

	Thifensulfuron-methyl
Additional C&L proposal	-
Agreed EU endpoints	
AOEL systemic	0.07 mg/kg bw/d
Reference	EFSA Journal 2015;13(7):4201
Conditions to take into account/critical areas of concern with regard to toxicology	
According to EFSA Journal 2015;13(7):4201 for Thifensulfuron-methyl	None.

6.3 Toxicological Evaluation of Plant Protection Product

A summary of the toxicological evaluation for SHA 4100 A / HIFEN 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 SHA 4100 A / HIFEN

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 (additivity formula)
LD ₅₀ dermal, rat	> 2000 mg/kg bw	Yes	None	Calculated (additivity formula)
LC ₅₀ inhalation, rat	> 5 mg/L air	Yes	None	Calculated (additivity formula)
Skin irritation, rabbit	Non-irritant	Yes	None	Calculated (additivity formula)
Eye irritation, rabbit (OECD 405)	Non-irritant	Yes	None	Shreyas S. Patel, 2016
Skin sensitisation, guinea pig	Non-sensitising	Yes	None	Calculated (additivity formula)
Supplementary studies for combinations of plant protection products	No data – not required			

SHA 4100 A / HIFEN
Part B – Section 6 - Core Assessment
SHARDA Cropchem Ltd./ CEU version

Table 6.3-2: Additional toxicological information relevant for classification/labelling of SHA 4100 A / HIFEN

	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)	Thifensulfuron- methyl (75% (w/w))	None	Reg. 1272/2008	None
Toxicological properties of non- active substance(s) (relevant for classification of product)	Co-formulant 1 (3%) Co-formulant 2 (≥10% (w/w))* Co-formulant 3 (≥10% (w/w))	Acute Tox. 4 (Oral); H302 Acute Tox. 4 (Inh.) H332 Eye Dam. 1; H318 STOT SE 3; H335 Eye Dam. 1, H318 H302, H332, H318, H335 Eye Irrit 2, H319	Reg. 1272/2008	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 IN-L9225

Comments of ZRM:	Taking into account the toxicological data, the metabolite IN-L9225 is considered toxicologically non-relevant. The use of SHA 4100 A (HIFEN) according to the list of intended uses presented in GAP Table, causes no risk for health of the adults, toddlers and infants. For details see dRR part 10.
---------------------	--

An overview of the results of the accepted toxicological studies for groundwater metabolite IN-L9225 is given in the following table.

Table 6.4-1: Summary of the results of toxicity studies for IN-L9225

Type of test, species (Guideline)	Result	Acceptability	Reference*
<i>In vitro</i> mammalian chromosome aberration test in human peripheral blood lymphocytes (OECD 473)	Negative	Yes / No / Supplementary	Glover, 2011b

SHA 4100 A / HIFEN
 Part B – Section 6 - Core Assessment
 SHARDA Cropchem Ltd./ CEU version

Type of test, species (Guideline)	Result	Acceptability	Reference*
<i>In vitro</i> mammalian cell gene mutation test (CHO/HGPRT assay) (OECD 476)	Non-mutagenic	Yes / No / Supplementary	Clarke, 2011c
Bacterial reverse mutation test (OECD 471)	Non-mutagenic	Yes / No / Supplementary	Myhre, 2011a
Bacterial reverse mutation assay using <i>Salmonella typhimurium</i> and <i>Escherichia coli</i> (OECD 471)	Non-mutagenic	Yes / No / Supplementary	Donath, 2011b
<i>In vitro</i> micronucleus test in human lymphocytes (OECD 487)	Negative	Yes / No / Supplementary	May, 2012a
Acute oral toxicity (OECD 420)	LD ₅₀ > 2000 mg/kg bw	Yes / No / Supplementary	2011 (EU reviewed)

* indicates that a study was reviewed at EU level

6.4.2 IN-JZ789

Comments of ZRMs:	Taking into account the toxicological data, the metabolite IN-JZ789 is considered toxicologically non-relevant. The results of consumer risk calculations indicate that the use of SHA 4100 A (HIFEN) according to the list of intended uses presented in GAP Table, causes no risk for health of the adults, toddlers and infants. For details see dRR part 10.
-------------------	---

An overview of the results of the accepted toxicological studies for groundwater metabolite IN-JZ789 is given in the following table.

Table 6.4-2: Summary of the results of toxicity studies for IN-JZ789

Type of test, species (Guideline)	Result	Acceptability	Reference*
Bacterial reverse mutation test (OECD 471)	Non-genotoxic	Yes / No / Supplementary	May, 2012b
<i>In vitro</i> micronucleus test in human lymphocytes (OECD 487)	Negative	Yes / No / Supplementary	May, 2012c

* indicates that a study was reviewed at EU level

6.4.3 IN-L9223

Comments of ZRMs:	According to the available toxicological data, the metabolite IN-L9223 is considered not genotoxic and without pesticidal activity. However, the toxicological profile of this metabolite is incomplete for full consumer risk assessment and does not allow to establish the reference dose (data gap). The results generated with OECD QSAR toolbox indicate that IN-L9223 might be more toxic than the parent substance (predicted oral LD₅₀ value) (RAR, Thifensulfuron-methyl - Volume 3, Annex B.6 : Toxicology and Metabolism).
-------------------	--

SHA 4100 A / HIFEN
 Part B – Section 6 - Core Assessment
 SHARDA Cropchem Ltd./ CEU version

	The parent substance is not classified in regards to mammalian toxicology. The maximum PEC_{gw} of IN-L9223 (acc. to the application rate presented in the GAP table) amounts to 3.174 µg/L. Since the predicted max. PEC_{gw} value (3.174 µg/L) is above the upper limit for metabolites (≥0.75 µg/L), the consumer risk calculation for this metabolite is required. The max. consumer exposure resulting from drinking water to IN-L9223 amounts to 4.8 % of ADI for parent substance and 24.4 % of maximum allowable concentration (MAC). Conclusions: Taking into account all the data presented above, the level of exposure to the metabolite IN-L9223 is acceptable for consumers, when product SHA 4100 A (HIFEN) is used in accordance with the list of intended uses presented in the GAP Table. For details see dRR part 10.
--	---

An overview of the results of the accepted toxicological studies for groundwater metabolite IN-L9223 is given in the following table.

Table 6.4-3: Summary of the results of toxicity studies for IN-L9223

Type of test, species (Guideline)	Result	Acceptability	Reference*
Bacterial reverse mutation test (OECD 471)	Non mutagenic	Yes / No / Supplementary	Myhre, 2011b
<i>In vitro</i> Mammalian Chromosome Aberration Test in human peripheral blood lymphocytes (OECD 473)	Negative	Yes / No / Supplementary	Glover, 2011a
<i>In vitro</i> mammalian cell gene mutation test (CHO/HGPRT assay) (OECD 476)	Non-genotoxic	Yes / No / Supplementary	Clarke, 2011a
Reverse mutation assay using bacteria (<i>Salmonella typhimurium</i> and <i>Escherichia coli</i>) (OECD 471)	Non mutagenic	Yes / No / Supplementary	Donath, 2011c
<i>In vitro</i> Mammalian Chromosome Aberration Test in human peripheral blood lymphocytes (OECD 473)	Negative	Yes / No / Supplementary	Lloyd, 2011a
<i>In vitro</i> mammalian cell gene mutation test in mouse lymphoma L5178Y cells (OECD 476)	Non mutagenic	Yes / No / Supplementary	Lloyd, 2011b

* indicates that a study was reviewed at EU level

6.4.4 IN-A4098

Comments of ZRMs:	Acc. to EFSA Journal 2015;13(7):4201, the metabolite IN-A4098 has moderate acute toxicity: Acute Tox 4., oral LD₅₀ = 1000 mg/kg bw, rat (noteworthy, higher than the parent substance). According to EFSA supporting publication 2020:EN-1627. 86 pp. doi:10.2903/sp.efsa.2020.EN-N1627, metabolite IN-A4098 is not toxicologically relevant The maximum PEC_{gw} IN-A4098 amounts to 0.279 µg/L and is below the upper limit for metabolites (<0.75 µg/L). ~~The available data indicate that the genotoxic potential of the IN-A4098 cannot be ruled out (data gap). It might be of concern for consumer exposure because the results exceed the limit for the relevant metabolites, i.e. 0.01 µg/L (the maximum PEC_{gw} amounts to 0.279 µg/L).~~ ~~Further genotoxicity studies and toxicological data is needed to finalize consumer risk assessment.~~
-------------------	---

An overview of the results of the accepted toxicological studies for groundwater metabolite IN-A4098 is given in the following table.

Table 6.4-4: Summary of the results of toxicity studies for IN-A4098

Type of test, species (Guideline)	Result	Acceptability	Reference*
Ames test (OECD 471)	Negative	Yes / No / Supplementary	Wagner, V.O., VanDyke, M.R. (2009)
<i>In vitro</i> mammalian cell gene mutation test (CHO/HGPRT assay) (OECD 476)	Non-genotoxic	Yes / No / Supplementary	Clarke, 2009
<i>In vitro</i> L5178Y gene mutation assay at the <i>tk</i> locus OECD 476 and OECD 490	Negative	Yes / No / Supplementary	Lloyd, 2016a
<i>In Vitro</i> Mammalian Chromosome Aberration Test (OECD 473)	Negative	Yes / No / Supplementary	Gudi & Rao, 2009, amended report by Roy and Rao, 2016
<i>In Vitro</i> Mammalian Chromosome Aberration Test in Human Lymphocytes (OECD 473)	Negative	Yes / No / Supplementary	Woods, 2011a
Chromosome studies on somatic cells of Chinese hamster (OECD 475)	No clastogenicity	Yes / No / Supplementary	1988 (EU reviewed)
Acute oral toxicity to rat (OECD 401)	LD ₅₀ = 1000 mg/kg bw	Yes / No / Supplementary	1991 (EU reviewed)
Reverse mutation assay using bacteria (<i>Salmonella typhimurium</i> and <i>Escherichia coli</i>)	Negative	Yes / No / Supplementary	Donath, 2011a
Bacterial reverse mutation assay (OECD 471)	Negative	Yes / No / Supplementary	May, 2011

SHA 4100 A / HIFEN
Part B – Section 6 - Core Assessment
SHARDA Cropchem Ltd./ CEU version

Type of test, species (Guideline)	Result	Acceptability	Reference*
<i>In vitro</i> mutation test using mouse lymphoma L5178Y cells (OECD 476)	Not mutagenic	Yes / No / Supplementary	Woods, 2011b

* indicates that a study was reviewed at EU level

6.4.5 IN-W8268

Comments of ZRMs:	Acc. to EFSA Journal 2015;13(7):4201, the metabolite IN-W8268 has no pesticidal activity. The available data indicate that the genotoxic potential of metabolite IN-W8268 cannot be ruled out (data gap). It might be of concern for consumer exposure because the results exceed the limit for the relevant metabolites, i.e. 0.01 µg/L (the maximum PEC _{gw} amounts to 0.343 µg/L).
-------------------	--

An overview of the results of the accepted toxicological studies for groundwater metabolite IN-W8268 is given in the following table.

Table 6.4-5: Summary of the results of toxicity studies for IN-W8268

Type of test, species (Guideline)	Result	Acceptability	Reference*
Bacterial reverse mutation assay (OECD 471)	Negative	Yes / No / Supplementary	Wagner & Nguyen, 2002
<i>In vitro</i> mammalian chromosome aberration (OECD 473)	Clastogenic	Yes / No / Supplementary	Gudi & Brown, 2002
<i>In vitro</i> mammalian cell gene mutation test (OECD 476)	Negative	Yes / No / Supplementary	San & Clarke, 2002
<i>In vitro</i> L5178Y gene mutation assay at the tk locus (OECD 476 and 490)	Non-genotoxic	Yes / No / Supplementary	Lloyd, 2017d
HPRT study in mouse lymphoma cells (OECD 476)	Negative	Yes / No / Supplementary	Lloyd, 2017c
<i>In vitro</i> micronucleus assay (OECD 474)	Negative	Yes / No / Supplementary	2002 (EU reviewed)
Acute oral toxicity in rat (OECD 420)	LD ₅₀ > 2000 mg/kg bw	Yes / No / Supplementary	2002 (EU reviewed)

* indicates that a study was reviewed at EU level

6.4.6 2-acid-3-triuret

The genotoxicity studies of 2-acid-3-triuret are not available yet. Results of *in vitro* bacterial assay for gene mutation and *in vitro* mammalian cell micronucleus assay in human peripheral blood lymphocytes will be available for the submission of the zonal re-authorisations.

SHA 4100 A / HIFEN
 Part B – Section 6 - Core Assessment
 SHARDA Cropchem Ltd./ CEU version

Comments of ZRMs:	Acc. to EFSA Journal 2015;13(7):4201, the toxicological data on the metabolite 2-acid-3-triuret is not available. The maximum PEC_{gw} of 2-acid-3-triuret (acc. to the application rate presented in the GAP table) amounts to 0.283 µg/L and is below the upper limit for metabolites (<0.75 µg/L).
-------------------	--

6.5 Dermal Absorption (KCP 7.3)

A summary of the dermal absorption rates for the active substances in SHA 4100 A / HIFEN are presented in the following table.

Table 6.5-1: Dermal absorption rates for active substances in SHA 4100 A / HIFEN

	Thifensulfuron-methyl	
	Value	Reference
Concentrate	10%	Default value (EFSA Journal 2017;15(6):4873)
Dilution	50%	Default value (EFSA Journal 2017;15(6):4873)

6.5.1 Justification for proposed values – Thifensulfuron-methyl

No data on dermal absorption for Thifensulfuron-methyl in SHA 4100 A / HIFEN is available. Justifications for default values according to Guidance on Dermal Absorption (EFSA Journal 2017; 10(4):2665) are presented in the following table.

Table 6.5-2: Default dermal absorption rates for Thifensulfuron-methyl

	Value	Justification for value	Acceptability of justification
Concentrate	10%	Default values for WG formulation (water dispersible granules)	accepted
Dilution	50%		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	SHA 4100 A / HIFEN
Formulation type	WG (water dispersible granules)
Category	Herbicide
Active substance (incl. content)	Thifensulfuron-methyl 750 g/kg
AOEL systemic	0.07 mg/kg bw/d
Inhalation absorption	100%

SHA 4100 A / HIFEN
 Part B – Section 6 - Core Assessment
 SHARDA Cropchem Ltd./ CEU version

Oral absorption	100%
Dermal absorption	Concentrate: 10% Dilution: 50% (Default values)

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)

Comments of zRMS:	The estimations of the operator exposure to the active substance contained in SHA 4100 A /HIFEN (based on AOEM) performed by the Applicant are correct. <u>Conclusions:</u> According to the estimation based on AOEM (calculator version: 1.0.1), the use of SHA 4100 A / HIFEN containing Thifensulfuron-methyl (750 g/kg) causes acceptable health risk for unprotected operator. The potential exposure to the active substance amounts to the value significantly lower than the AOEL for Thifensulfuron-methyl. Taking into account the hygienic rules governing the handling of pesticides, protective gloves and work wear during M&L and work wear during product application is recommended. Thus, the following sentence regarding the use of PPE is recommended by the evaluator to be placed in the label: <i>„Stosować rękawice ochronne oraz odzież roboczą (kombinezon) w trakcie przygotowywania cieczy roboczej oraz odzież roboczą w trakcie wykonywania zabiegu”</i> “Wear protective gloves and work wear (coverall) during mixing/loading and work wear during application”.
-------------------	---

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 4100 A / HIFEN 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	Winter cereals (max. 0.04 kg 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: 1.0.1

SHA 4100 A / HIFEN
 Part B – Section 6 - Core Assessment
 SHARDA Cropchem Ltd./ CEU version

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

		Thifensulfuron-methyl	
Model data	Level of PPE	Total absorbed dose (mg/kg/day)	% of systemic AOEL
Tractor mounted boom spray application outdoors to low crops			
Application rate		1 x 0.03 kg a.s./ha	
Spray application (AOEM; 75 th percentile) Body weight: 60 kg	Potential exposure	0.011	14.4
	Work wear (arms, body and legs covered) M/L and A	0.007	9.4

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)

Comments of zRMS:	The estimations of worker exposure to the active substance contained in SHA 4100 A /HIFEN (based on AOEM, calculator version 1.0.1) performed by the Applicant are correct. According to current requirements of Polish Authorities, it is recommended to apply EUROPOEM II for the estimation of worker exposure in case of single use of PPP. However, the difference in the results of worker exposure estimation based on EUROPOEM II are only slightly different from those gained from AOEM-based estimation. The results of estimations are presented below:
-------------------	---

SHA 4100 A / HIFEN
 Part B – Section 6 - Core Assessment
 SHARDA Cropchem Ltd./ CEU version

WORKER EXPOSURE		EUROPOEM II MODEL	
form		Re-entry in the field	
a.s.			
Parameter	Value	Unit	References, comments
Re-entry activities in the field			
AR Application rate	0.03	kg a.s./ha	summary of intended uses
Worker			
Duration			
T	2	hours / day	default: 6 h (Europoem II)
Inhalation Exposure			
no model available	-		without PPE
Dermal Exposure			
DFR Dislodgeable foliar residue	30	mg a.s./m ² /kg a.s./ha	default (Europoem II)
TC Transfer coefficient	0.14	m ² / hour	vegetable (field): 0.25; ornamentals: 0.5; small fruit: 0.3; large fruit: 0.45 (Europoem II)
Dermal Exposure	0.252	mg a.s./ day	DE = DFR x AR x TC x T
Internal exposure			
DA Dermal Absorption	50	%	
PPE-factor dermal	5		gloves*
AOEL	4.2	mg a.s./ day	based on 70 kg bw
		Without PPE	With PPE
		[mg a.s./ day]	[mg a.s./ day]
Internal exposure			
Inhalation		-	-
Dermal		0.126	0.025
Total		0.126	0.025
			sum
% AOEL			
Inhalation		-	-
Dermal		3	1
Total		3	1
			sum

Conclusions:
 According to the estimations, the use of SHA 4100 A /HIFEN containing Thifensulfuron-methyl (750 g/kg) **does not cause unacceptable health risk for unprotected worker** (inspection, 2h) because the exposure level to the active substances is below the AOEL value. Nevertheless, it is forbidden to re-enter area treated with SHA 4100 A /HIFEN until spray deposit on plant surfaces has dried.
 Bearing in minds the hygienic rules, the use of work wear and protective gloves is recommended by the evaluator during inspection of the treated area.

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 4100 A / HIFEN according to the critical use(s). 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	Winter cereals (max. 0.04 kg 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: 1.0.1

SHA 4100 A / HIFEN
Part B – Section 6 - Core Assessment
SHARDA Cropchem Ltd./ CEU version

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

		Thifensulfuron-methyl	
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/cm ² /kg a.s./ha Interval between treatments: 365 days			
Number of applications and application rate		1 x 0.03 kg a.s./ha	
Body weight: 60 kg	Potential TC: 12500 cm ² /person/h	0.02	26.8
	Work wear (arms, body and legs covered) TC: 1400 cm ² /person/h	0.00	3
	Work wear (arms, body and legs covered) and gloves TC: 1250 cm ² /person/h	0.002	2.7

6.6.3.2 Refinement of generic DFR value (KCP 7.2)

Not relevant.

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)

Comments of zRMS:	The results of bystander and resident exposure estimations to the active substance contained in the formulation SHA 4100 A /HIFEN presented by the applicant are accepted. The reference values acutely toxic active substance (RVAAS) for Thifensulfuron-methyl is not allocated. Consequently, it is assumed that the estimation of bystander exposure is covered by the calculation of resident exposure towards this substance. According to the estimation based on AOEM, the use of SHA 4100 A /HIFEN does not cause unacceptable health risk for bystander and resident; the exposure value is below the AOEL for this active substance. Summary and conclusions: The incidental short-time exposure of bystander and resident (children and adult) to Thifensulfuron-methyl contained in the formulation SHA 4100 A /HIFEN causes no risk to human health if the product is used in accordance to the intended uses listed in the GAP Table.
-------------------	--

SHA 4100 A / HIFEN
 Part B – Section 6 - Core Assessment
 SHARDA Cropchem Ltd./ CEU version

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 used for estimation of resident and bystander exposure to Thifensulfuron-methyl. The outcome of the estimation is presented in Table 6.6-7 (long term exposure). Detailed calculations are in Appendix 3.

Table 6.6-6: Exposure models for intended uses

Critical use	Winter cereals (max. 0.04 kg 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: 1.0.1

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

		Thifensulfuron-methyl	
Model data		Total absorbed dose (mg/kg bw/day)	% of systemic AOEL
Tractor mounted boom spray application outdoors to low crops Buffer zone: 2-3(m) Drift reduction technology: no DT ₅₀ : 30 days DFR: 3 µg/cm ² /kg a.s./ha Interval between treatments: 365 days			
Number of applications and application rate		1 x 0.03 kg a.s./ha	
Resident child Body weight: 10 kg	Drift (75 th perc.)	0.002	2.9
	Vapour (75 th perc.)	0.0008	1.1
	Deposits (75 th perc.)	0.0002	0.3
	Re-entry (75 th perc.)	0.003	3.6
	Sum (mean)	0.004	5.9
Resident adult Body weight: 60 kg	Drift (75 th perc.)	0.0005	0.7
	Vapour (75 th perc.)	0.0003	0.4
	Deposits (75 th perc.)	0.0001	0.1
	Re-entry (75 th perc.)	0.001	2
	Sum (mean)	0.002	2.4

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 Thifensulfuron-methyl 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

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 7.1.1	Shreyas S. Patel	2016	Acute Eye Irritation Study of Thifensulfuron Methyl 75% WDG in Rabbits (OECD guideline No. 405) JAI Reaserch Foundation, Report No. 407-1-01-12771 GLP, Unpublished	Y	Sharda Cropchem Limited

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

SHA 4100 A / HIFEN
 Part B – Section 6 - Core Assessment
 SHARDA Cropchem Ltd./ CEU version

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

A 2.1 Statement on bridging possibilities

Comments of zRMS:	The classification of the formulation SHA 4100 A/HIFEN is based on toxicological data of individual ingredients of the mixture and <i>in vivo</i> data as supplementary data (Eye irritation test).
-------------------	---

A 2.2 Acute oral toxicity (KCP 7.1.1)

Comments of zRMS:	Taking into account the ATE_{mix} value, the product SHA 4100 A (HIFEN) does not require classification in regards to oral toxicity.
-------------------	---

Acute toxicity studies for SHA 4100 A / HIFEN were **not** evaluated as part of the EU review of thifensulfuron. 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 4100 A / HIFEN can be found in an appendix to the confidential dossier of this submission (Registration Report, Part C).

The acute oral toxicity of SHA 4100 A / HIFEN was calculated as follow:

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

$$ATE_{mix} = \frac{100}{\frac{xx\%}{600}} = 20000 \text{ mg/kg bw}$$

The acute oral toxicity of SHA 4100 A / HIFEN was estimated to be over 2000 mg/kg.

According to the Regulation EC No. 1272/2008, SHA 4100 A / HIFEN 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 product SHA 4100 A (HIFEN) does not contain ingredients classified in regards to acute dermal toxicity. Taking into account the composition, the product SHA 4100 A (HIFEN) does not require classification in regards to dermal toxicity.
-------------------	--

There is no co-formulant in the SHA 4100 A / HIFEN recipe classified as danger through dermal contact.

According to the Regulation EC No. 1272/2008, SHA 4100 A / HIFEN 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:	Taking into account the ATE_{mix} value, the product SHA 4100 A (HIFEN) does not require classification with regard to inhalation acute toxicity.
-------------------	--

SHA 4100 A / HIFEN
 Part B – Section 6 - Core Assessment
 SHARDA Cropchem Ltd./ CEU version

Acute toxicity studies for SHA 4100 A / HIFEN were **not** evaluated as part of the EU review of thifensulfuron. 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 inhalation toxicity of SHA 4100 A / HIFEN can be found in an appendix to the confidential dossier of this submission (Registration Report, Part C).

The acute inhalation toxicity of SHA 4100 A / HIFEN was calculated as follow:

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

$$ATE_{mix} = \frac{100}{\frac{xx\%}{1.09}} = 36.33 \text{ mg/l}$$

The acute inhalation toxicity of SHA 4100 A / HIFEN was estimated to be > 5 mg/l.

Therefore, according to the Regulation EC No. 1272/2008, SHA 4100 A / HIFEN 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 SHA 4100 A (HIFEN) does not contain ingredients classified in regards to skin irritation/corrosion. Taking into account the composition, the product SHA 4100 A (HIFEN) does not require classification in regards to skin irritation.
-------------------	--

There is no co-formulant in the SHA 4100 A / HIFEN recipe classified as skin irritant.

According to the Regulation EC No. 1272/2008, SHA 4100 A / HIFEN 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:	Taking into account the sum of concentrations of the ingredients classified as Eye Dam.1 and the generic concentration limit that triggers classification of the mixture ($\geq 3\%$), the product SHA 4100 A (HIFEN) requires classification in regards to eye damage. Acc. to Polish Authorities, the results of classification obtained using calculation method presented above justify the use of the experimental data for the purpose of product classification if such data has been generated and the results are available. Therefore, the study presented by the applicant (Shreyas S. Patel, 2016) is accepted and considered relevant for the classification of SHA 4100 A (HIFEN). The results of the study are not consistent with the results of calculation: the product SHA 4100 A (HIFEN) has no irritation/corrosion potential to the eyes. The results of experimental data are decisive for the product classification. <u>Conclusions:</u> All in all, it is concluded that the formulation SHA 4100 A (HIFEN) does not require classification in respect to eye irritation/corrosion.
-------------------	--

Based on the composition and in accordance with the provisions of the Regulation EC 1272/2008, the formulation SHA 4100 A / HIFEN requires classification in regards to eye irritation as Eye Dam. 1 (H318).

However, since the results of eye irritation study on rabbits were available the applicant decided to compare

SHA 4100 A / HIFEN
 Part B – Section 6 - Core Assessment
 SHARDA Cropchem Ltd./ CEU version

the findings of in vivo testing with calculated result. According to acute eye irritation study (Shreyas S. Patel, 2016) which was carried out in compliance with OECD Guideline No 405, SHA 4100 A / HIFEN does not possess skin irritation potency.

In the opinion of applicant despite the lack of in vitro studies (multi-level approach), if the results of in vivo tests are contrary to the results obtained from calculation method, data generated from animal study should be considered superior.

A 2.6.1 Study 1

Reference	KCP 7.1.1
Report	Acute Eye Irritation Study of Thifensulfuron Methyl 75% WDG in Rabbits, Shreyas S. Patel, 2016, Report No. 407-1-01-12771
Guideline(s)	Yes: OECD guideline No. 405
Deviations	No
GLP	Yes
Acceptability	YES
Duplication (if vertebrate study)	No

Materials and methods

Test material (Lot/Batch No.)	Thifensulfuron Methyl 75% WDG (Batch No. SWEPL-13205)
Species	New Zealand White Rabbit (<i>Oryctolagus cuniculus</i>)
No. of animals (group size)	3 females
Initial test using one animal	Yes
Exposure	0.1 mL (single instillation in conjunctival sac)
Irrigation (time point)	No
Vehicle/Dilution	None
Post exposure observation period	21 days
Remarks	None

Results and discussions

Table A 1: Eye irritation of SHA 4100 A / HIFEN

Animal No.		Scores after treatment *				Mean scores (24-72 h)	Reversible (day)
		1 h	24 h	48 h	72 h		
1	Corneal opacity	0.00	0.00	0.00	0.00	0.00	3 days
	Iritis	0.00	0.00	0.00	0.00	0.00	
	Redness conjunctivae	1.00	1.00	1.00	0.00	0.67	
	Chemosis conjunctivae	1.00	0.00	0.00	0.00	0.00	
2	Corneal opacity	0.00	0.00	0.00	0.00	0.00	3 days
	Iritis	0.00	0.00	0.00	0.00	0.00	
	Redness conjunctivae	1.00	1.00	1.00	0.00	0.67	
	Chemosis conjunctivae	1.00	0.00	0.00	0.00	0.00	

SHA 4100 A / HIFEN
 Part B – Section 6 - Core Assessment
 SHARDA Cropchem Ltd./ CEU version

3	Corneal opacity	0.00	0.00	0.00	0.00	0.00	3 days
	Iritis	0.00	0.00	0.00	0.00	0.00	
	Redness conjunctivae	1.00	1.00	1.00	0.00	0.67	
	Chemosis conjunctivae	1.00	0.00	0.00	0.00	0.00	

* scores in the range of 0 to 4 for cornea opacity and chemosis, 0 to 3 for redness of conjunctivae and 0 to 2 for iritis

Clinical signs:	No signs of systemic toxicity were observed.
------------------------	--

Conclusion

Under the experimental conditions, Thifensulfuron Methyl 75% WDG is not an eye irritant. Thus, no classification is required according to Regulation (EC) No. 1272/2008.

SHA 4100 A / HIFEN
Part B – Section 6 - Core Assessment
SHARDA Cropchem Ltd./ CEU version

A 2.7 Skin sensitisation (KCP 7.1.6)

Comments of zRMS:	The product SHA 4100 A (HIFEN) does not contain ingredients classified in regards to skin sensitization. Taking into account the composition, the product SHA 4100 A (HIFEN) does not require classification in regards to skin sensitization.
-------------------	--

There is no co-formulant in the SHA 4100 A / HIFEN recipe classified as skin sensitizer.

According to the Regulation EC No. 1272/2008, SHA 4100 A / HIFEN is **not classified**. No signal word or hazard statement is required for this hazard.

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

No supplementary 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)

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^(c) or solid^(d):

^(c): Formulation types: soluble concentrate (SL), suspension concentrate (SC), flowable concentrate for seed treatment (FS), flowable (FL) (=SC).

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

A 2.11 Other/Special Studies

No other study provided.

Appendix 3 Exposure calculations

Please refer to KCP reports.



Thifensulfuron 75%
WG_20230904.docx

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.