FINAL REGISTRATION REPORT

Part B

Section 6

Mammalian Toxicology

Detailed summary of the risk assessment

Product code: BAS 768 00 F

Product name(s): Revytur

Chemical active substance(s):

Mefentrifluconazole, 25 g/L
Sulfur, 600 g/L

Central Zone

Zonal Rapporteur Member State: Poland

CORE ASSESSMENT

(authorization)

Applicant: BASF

Submission date: March 2023

MS Finalisation date: 11/12/2023

Version history

When	What
03/2023	Initial dRR – BASF DocID 2023/2003362
04/2023	Dossier sent for evaluation
08/2023	zRMS evaluation of dRR
11/2023	Update dRR (Table 6.1-2) – BASF DocID 2023/2052239
12/2023	Final version prepared by zRMS after Commenting period

Table of Contents

Evaluator 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 BAS 768 00 F

Product name and code	BAS 768 00 F
Formulation type	SC
Active substance(s) (incl. content)	25 g/L mefentrifluconazole 600 g/L sulfur
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 BAS 768 00 F 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 BAS 768 00 F according to Regulation (EC) No 1272/2008

Hazard class(es), categories:	Skin Corr./Irrit. 2 Eye Dam./Irrit. 2 Skin Sens. 1
Hazard pictograms or Code(s) for hazard pictogram(s):	 GHS07
Signal word:	Warning
Hazard statement(s):	H315: Causes skin irritation H319: Causes serious eye irritation H317: May cause an allergic skin reaction
Precautionary statement(s):	
- General:	P101: If medical advice is needed, have product container or label at hand P102: Keep out of reach of children. P103: Read carefully and follow all instructions.
- Prevention:	P280: Wear protective gloves and eye protection or face protection. P261: Avoid breathing mist or vapour or spray. P272: Contaminated work clothing should not be allowed out of the workplace. P264: Wash contaminated body parts thoroughly after handling.
- Response:	P302+P352: IF ON SKIN: Wash with plenty of soap and water.

	P305+P351+P338: IF IN EYES: Rinse cautiously with water for several minutes. Remove contact lenses, if present and easy to do. Continue rinsing. P337+P313: If eye irritation persists: Get medical attention. P333+P313: If skin irritation or rash occurs: Get medical attention. P362+P364: Take off contaminated clothing and wash it before reuse.
- Storage	–
- Disposal	P501: Dispose of contents and container to hazardous or special waste collection point.
Additional labelling phrases:	To avoid risks to human health and the environment, comply with the instructions for use. [EUH401]
	~~May produce an allergic reaction.~~ Contains: 1,2-benzisothiazol-3(2H)-one, reaction mass of: 5-chloro-2- methyl-4-isothiazolin-3-one [EC no. 247-500-7] and 2-methyl-2H -isothiazol-3- one [EC no. 220-239-6] (3 :1)
Ingredients of unknown toxicity	9 % of the mixture consists of ingredient(s) of unknown acute inhalation toxicity

Table 6.1-3: Summary of risk assessment for operators, workers, bystanders and residents for BAS 768 00 F

	Result	PPE / Risk mitigation measures
Operators	Acceptable	Gloves and workwear during mixing/loading, workwear during application
Workers	Acceptable	None (workwear)
Bystanders	Acceptable	None
Residents	Acceptable	None

No unacceptable risk for operators, workers, bystanders and residents 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 bystanders/residents 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, bystander or resident 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**	**Bystander**	**Residents**
#1-6	Cereals (wheat, barley, triticale) (BBCH 30-59)	F	Spraying, LCTM	a) 2 b) 2 Min. interval between applications - 14 days	a) 0.100 b) 2.400	100 - 300	F §	Critical GAP for operator, worker, bystander or resident exposure based on EFSA guidance 2022	R	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
§ Defined by latest application timing. Fixed by professional use.
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

Noticed data gaps are:

- None

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)

	~~BAS 750 F~~	~~BAS 175 F~~
Common Name	Mefentrifluconazole	Sulfur
CAS-No.	1417782-03-6	7704-34-9
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	Skin Irrit 2
Code(s) for hazard pictogram(s):	 GHS07	 GHS07
Signal word:	Warning	Warning
Hazard statement(s):	H317: May cause an allergic skin reaction.	H315: Causes skin irritation.
Precautionary statement(s):	P261: Avoid breathing dust or fume. P272: Contaminated work clothing should not be allowed out of the workplace. ~~P273 Avoid release to the environment.~~ P280: Wear protective gloves. P302 + P352: IF ON SKIN: Wash with plenty of soap and water. P333 + P313: If skin irritation or rash occurs: Get medical attention. P362 + P364: Take off contaminated clothing and wash it before reuse. ~~P391 Collect spillage.~~ P501: Dispose of contents and container to hazardous or special waste collection point.	P264: Wash contaminated body parts thoroughly after handling. P280: Wear protective gloves/protective clothing/eye protection/face protection. P302 + P352: IF ON SKIN: Wash with plenty of soap and water. P332 + P313: If skin irritation persists: Get medical advice/attention. P362+P364: Take off contaminated clothing and wash it before reuse.
Reference:	Com. Del. Reg.(EU) 2020/1182	Comm. Regulation (EC) No 790/2009 RAC Opinion (adopted 18 March 2022) EFSA Conclusion on sulfur (EFSA Journal 2023;21(3):7805)
Additional C&L proposal	None.	None.
Agreed EU endpoints		
AOEL systemic	0.035 mg/kg bw/d (no correction for oral absorption required)	Not necessary (Exposure assessed against the average sulfur background level (24 mg/kg bw/day)
AAOEL	0.15 mg/kg bw/d	Not allocated
Reference	EFSA Journal 2018; 16(7):5379 Review Report mefentrifluconazole, SANTE/11612/2018 Rev.3, 26 Jan 2021	EFSA Draft LoEP (10 January 2023) EFSA Scientific Report (2008), 221, 37-70
Conditions to take into account/critical areas of concern with regard to toxicology		
Review Report/EFSA Conclusion for active	None related to toxicology	None related to toxicology

	~~BAS 750 F~~	~~BAS 175 F~~
Common Name	Mefentrifluconazole	Sulfur
CAS-No.	1417782-03-6	7704-34-9
substance		

6.3 Toxicological Evaluation of Plant Protection Product

A summary of the toxicological evaluation for BAS 768 00 F 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 BAS 768 00 F

Type of test, species, model system (Guideline)	**Result**	**Acceptability**	**Classification (acc. to the criteria in Reg. 1272/2008)**	**Reference** (BASF DocID)
Acute oral toxicity, predicted from composition [97%]	LD_{50} > 2000 mg/kg bw	Yes	None	CLP 1272/2008 Appendix 2
Acute dermal toxicity, predicted from composition [89%] and supported by oral toxicity non-classification.	LD_{50} > 2000 mg/kg bw	Yes	None	CLP 1272/2008 Appendix 2
Acute inhalation toxicity, predicted from composition [91%]	LC_{50} > 5 mg/L	Yes	None	CLP 1272/2008 Appendix 2
Skin corrosion / irritation, predicted from composition [99%]	Skin irritant [C/L ratio: 49.5 > 10]	Yes	**Skin Irrit. 2; H315** (Weight-of-evidence)	CLP 1272/2008 Appendix 2
In vitro Skin corrosion / irritation, EpiDerm tests (OECD 431/439)	Non irritant (1+24h viability: 57%)	Yes		(2021/2045077) Appendix 2
Eye corrosion / irritation, predicted from composition [99%]	~~Non~~ Irritant [C/L ratio: ~~6.1 <~~ >10]	Yes	**Eye Irrit 2; H319** (Weight-of-evidence)	CLP 1272/2008 Appendix 2
In vitro Eye irritation, EpiOcular (OECD 492)	Eye irritation potential (viability: 20.7%)	Yes		~~(2022/2045076)~~ (2021/2045076) Appendix 2
Skin sensitisation predicted from composition [97%]	Skin sensitiser	Yes	**Skin Sens 1; H317**	CLP 1272/2008 Appendix 2
Supplementary studies for combinations of plant protection products	No data – not required		–	–

BAS 768 00 F is assessed to be of low acute toxicity, when applied by oral, dermal and inhalation routes not warranting classification for these endpoints. BAS 768 00 F is a skin and eye irritant, as predicted by weight-of-evidence from composition and from results of *in vitro* studies performed with the product. BAS 768 00 F is classified as a skin sensitizer based on the product composition.

Table 6.3-2: Additional toxicological information relevant for classification/labelling of BAS 768 00 F

	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)	Mefentrifluconazole (1.84 % (w/w))	Skin Sens 1; H317 (≥ 1 %)	Comm Del. Reg. 2020/1182 (ATP to CLP 1272/2008)	Skin Sens 1; H317
	Sulfur (44.12 % (w/w))	Skin Irrit 2; H315 (≥ 10 %)	Comm. Regulation (EC) No 790/2009 RAC Opinion (2022) EFSA Conclusion on sulfur (EFSA Journal 2023;21(3):7805)	Skin Irrit 2; H315
Toxicological properties of non-active substance(s) (relevant for classification of product)	Alcohol, C12-C18, ethoxylated (4EO), propoxylated (13 PO) (<3 % (w/w))	Skin Irrit 2; H315 (≥ 10 %)	MSDS**	Skin Irrit 2; H315
	Sodium alkyl-naphthalenesulfonate, formaldehyde condensate (< 3 %)*	Skin Irrit 2; H315 (≥ 10 %) ~~Eye Irrit 2; H319 (≥ 10 %)~~ Eye Dam. 1; H318 (≥ 3 %)	MSDS**	Skin Irrit 2; H315 Eye Irrit 2; H319
	Sodium salts of alkylnaphthalene sulfonic acids (< 5%)*	Acute Tox. 4; H332 (ATEi 1.57 mg/L) Eye Irrit 2; H319 (≥ 10 %)	MSDS**	Eye Irrit 2; H319
	Oxirane, 2-methyl-, polymer with oxirane, mono(2-propylheptyl) ether (<3 %)*	Eye Irrit 2; H319 (≥ 10 %)	MSDS**	Eye Irrit 2; H319
	1,2-benzlisothiazol-3(2H)-one (< 0.035%)*	~~Acute Tox 3; H301~~ ~~Acute Tox 2; H330~~ ~~Skin Cor 1B; H314~~ Acute Tox. 4, H302 Skin Irrit. 2, H315 Eye Dam. 1, H318 Skin Sens 1; H317 (criteria C ≥ 0.05%)	MSDS**	--- (to be mentioned on the label, without EUH208)
	Reaction mass of 5-chloro-2-methyl-4-isothiazolin-3-one and 2-methylisothiazol-3(2H)-one (C < 0.0015%)*	~~Acute Tox 4; H302~~ Acute Tox 3; H301 Acute Tox 2; H310 Acute Tox 2; H330 ~~Skin Irrit 2; H315~~ Skin Corr. 1C, H314 Eye Dam. 1, H318	MSDS**	--- (to be mentioned on the label, without EUH208)

	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)
		Skin Sens 1; H317 (criteria C ≥ 0.0015%)		
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

zRMS comment	Acceptable. See also dRR B10.

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

With regards to sulfur and metabolites, it was concluded in the last EU-wide peer review that sulfur is not of concern for the contamination of groundwater, but there is potential for groundwater contamination for sulfates, which needs to be addressed (see EFSA Conclusion [EFSA Scientific Report (2008) 221, 17-70]. According to information provided in section 6.6.2 of the EFSA Conclusion (2008), both sulfur and sulfates are of no toxicological relevance; it was concluded that the potential for groundwater contamination by sulfates (the main oxidation product of sulfur in soil) above a toxicologically based concentration limit of 250 mg/L (set in the Drinking Water Directive 98/83/EC), was assessed as low.

For estimations of sulfate concentration in groundwater from product use in cereals, see Section 8.8 of this dossier.

6.5 Dermal Absorption (KCP 7.3)

Dermal absorption studies performed with BAS 768 00 F are not available. Following the Guidance on Dermal absorption (EFSA Journal 2017; 15(6):4873), default values for water-based formulation types will be used, in the absence of experimental data, for model estimations of non-dietary exposure to the active ingredients contained in the product. The default values to be used for the active ingredient sulfur are 10% for the undiluted concentrate and 50% for spray-strength dilutions. For mefentrifluconazole, the concentration in the product is 1.854%, thus below or equal 5%. Therefore, in line with the EU guidance (SANTE/2018/10591 rev.1 of 24 October 2018) the default dermal absorption estimate of 50% for diluted SC-type plant protection products according to EFSA Guidance applies in the case of mefentrifluconazole also for the concentrate.

A summary of the dermal absorption rates for the active substances in BAS 768 00 F is presented in the following table.

Table 6.5-1: Dermal absorption rates for active substances in BAS 768 00 F

	Mefentrifluconazole		Sulfur	
	Value	**Reference**	**Value**	**Reference**
Concentrate	50 % (default)	EFSA Journal 2017; 15(6):4873 Table 2 (p. 19); SANTE/2018/10591 rev.1 of 24 October 2018	10 % (default)	EFSA Journal 2017; 15(6):4873 Table 2 (p. 19)
Dilution (all dilutions)	50 % (default)	EFSA Journal 2017; 15(6):4873 Table 2 (p. 19)	50 % (default)	EFSA Journal 2017; 15(6):4873 Table 2 (p. 19)

6.5.1 Justification for proposed values - mefentrifluconazole

No data on dermal absorption for mefentrifluconazole in BAS 768 00 F is available. Justifications for default values according to Guidance on Dermal Absorption (EFSA Journal 2017; 15(6):4873, Table 2 [p.19) are presented in the following table.

Table 6.5-2: Default dermal absorption rates for mefentrifluconazole

	Value	Justification for value	Acceptability of justification
Concentrate	50 %	BAS 768 00 F is a suspension concentrate (SC) type formulation. Therefore, the default value for water-based formulation types was selected for mefentrifluconazole according to EFSA Guidance, but applying the estimate for dilutions, to correct for low concentration of active substance. In line with the EU guidance (SANTE/2018/10591 rev.1 of 24 October 2018), such correction is triggered when the active substance is present in the plant protection product at a concentration ≤ 50 g/L (or 50 g/kg or 5%).	Yes
Dilution	50 %	See justification above	Yes

6.5.2 Justification for proposed values - sulfur

No data on dermal absorption for sulfur in BAS 768 00 F is available. Justifications for default values according to Guidance on Dermal Absorption (EFSA Journal 2017; 15(6):4873, Table 2 [p.19) are presented in the following table.

Table 6.5-3: Default dermal absorption rates for sulfur

	Value	Justification for value	Acceptability of justification
Concentrate	10 %	BAS 768 00 F is a suspension concentrate (SC) type formulation and the active substance is contained in the product at a concentration above 50 g/L (or 50 g/kg or 5%). Therefore, the default value for water-based formulation types was selected according to EFSA Guidance without modification, in line with EU Guidance (SANTE/2018/10591 rev.1 of 24 October 2018).	Yes
Dilution	50 %	See justification above	Yes

6.6 Exposure Assessment of Plant Protection Product (KCP 7.2)

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

Product name and code	BAS 768 00 F
Formulation type	SC

Category	Fungicide	
Container size(s), short description	0.15 – 1000 L HDPE or f-HDPE container, wide-opening ≥ 42 mm inner diameter. For details please refer to section B 4.1	
Active substance(s) (incl. content)	**Mefentrifluconazole** 25 g/L	**Sulfur** 600 g/L
AOEL systemic	0.035 mg/kg bw/d	Not applied: Exposure estimates assessed against the average sulfur background level of 24 mg/kg bw/d
AAOEL	0.15 mg/kg bw/d	Not allocated
Inhalation absorption	100 %	100 %
Oral absorption	100 %	100 %
Dermal absorption	Concentrate 25 g/L: 50 % Dilution 0.33 g/L: 50 % (Dilution rate: 1:75) (Default)	Concentrate: 600 g/L 10% Dilution: 8 g/L: 50 % (Dilution rate: 1:75) (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 zone/ EU is given in Part B, Section 0.

Justification

As the intended use is for cereals only the GAP with the highest application rate and highest number of applications defines the critical GAP. According to the EFSA guidance 2022 the selected use is field crop with vehicle-mounted application and scouting/irrigation is the only relevant re-entry activity.

6.6.1.1 Operator exposure (KCP 7.2.1)

Comments of zRMS:	Acceptable. Operator exposure calculations performed using the OPEX model, version 1.0.0, showed that short-term operator exposure to both mefentrifluconazole and sulfur is acceptable (32.5% of AOEL for mefentrifluconazole and 0.7% of AOEL for sulfur), if the product is used as intended (vehicle mounted, normal cultivation) and the operator is wearing a workwear and additionally protective gloves during the mixing/loading step. The AAOEL was only determined for mefentrifluconazole, therefore the acute operator exposure included exposure to mefentrifluconazole only. Acute exposure is also acceptable if the operator is wearing a workwear and additionally protective gloves during the mixing/loading step (76.3% of AAOEL for mefentrifluconazole). Conclusion: Operator exposure (both short-term and acute) is acceptable if the operator is wearing a workwear and additionally protective gloves during the mixing/loading step.

6.6.1.2 Estimation of operator exposure

A summary of the exposure models used for estimation of operator exposure to the active substances during

application of BAS 768 00 F according to the critical use(s) is presented in Table 6.6-2. Outcome of the estimation is presented in Table 6.6-3. Detailed calculations are in Appendix 3.

Table 6.6-2: Exposure models for intended uses

Critical use(s)	#1-6 Cereals (4 L product/ha)
Model(s)	EFSA guidance AOEM (LCTM) [European Food Safety Authority (2022) 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 doi: 10.2903/j.efsa.2022.7032.]

Table 6.6-3: Estimated operator exposure: Use field crop vehicle-mounted spraying

		Mefentrifluconazole ~~(BAS 750 F)~~		**Sulfur ~~(BAS 175 F)~~**	
Scenario 1: Field crop/Downward spraying / Vehicle-mounted / Drift reduction: 0 % Crop density: Normal		**Dermal absorption: Concentrate: 50% In-use dilution: 50%**		**Dermal absorption: Concentrate: 10% In-use dilution: 50%**	
Application rate: 2 x 4 L product/ha		**0.1~~5~~ kg/ha**		**2.4 kg/ha**	
Short-term exposure					
Model data	Model data	Total absorbed dose (mg/kg/day)	% of RVNAS (AOEL)	Total absorbed dose (mg/kg/day)	% of RVNAS (AOEL)
EFSA AOEM 75th percentile Body weight: 60 kg	*M/L and Appl.: Work wear – arms, body & legs covered*		572	0.5	1.9
	M/L: Workwear + Protected hands App: Workwear	0.01	32.5	~~0.5~~	~~1.9~~ 0.7
Acute exposure					
Model data	Model data	Total absorbed dose (mg/kg/day)	% of AAOEL	Total absorbed dose (mg/kg/day)	% of AAOEL
EFSA AOEM 95th percentile Body weight: 60 kg	*M/L and Appl.: Work wear – arms, body & legs covered*	~~0.1~~	~~76.3~~ 534	Not applicable	
	M/L: Workwear + Protected hands App: Workwear	0.1	76.3		

When applying BAS 768 00 F in cereals a safe use is demonstrated for operators wearing gloves and long-sleeved workwear during mixing/loading and wearing workwear during application.

6.6.1.3 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 considering above mentioned personal protective equipment (PPE), a study to provide measurements of operator exposure was not necessary and was therefore not performed.

6.6.2 Worker exposure (KCP 7.2.3)

Comments of zRMS:	Acceptable. Worker exposure calculations performed using the OPEX model, version 1.0.0, showed that worker exposure to both mefentrifluconazole and sulfur is acceptable (34.4% of AOEL for mefentrifluconazole and 1.2% of AOEL for sulfur) during inspection/irrigation if worker is wearing only a workwear.

6.6.2.1 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 BAS 768 00 F according to the critical use(s). Outcome of the estimation is presented in Table 6.6-5. Detailed calculations are in Appendix 3.

Table 6.6-4: Exposure models for intended uses

Critical use(s)	#1-6 Cereals
Model	EFSA Guidance [European Food Safety Authority (2022) 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 doi: 10.2903/j.efsa.2022.7032.]

Table 6.6-5: Estimated worker exposure

		Mefentrifluconazole			**Sulfur**		
Model data	Level of PPE	Total absorbed dose (mg/kg/day)	% of systemic AOEL	Re-entry interval	Total absorbed dose (mg/kg/day)	% of systemic AOEL	Re-entry interval
Number of applications & application rate: 2 x 4 L product/ha; Minimum spray interval: 14 days Scenario: Inspection / Irrigation Outdoor; Work rate: 2 hours/day; Body weight: 60 kg,		No. applications & application rate: 2 x 0.1 kg a.s./ha Dermal absorption: 50% DFR: 3 µg/cm² foliage per kg a.s./ha DT50: 30 days			No. applications & application rate: 2 x 2.4 kg a.s./ha Dermal absorption: 50% DFR: 3 µg/cm² foliage per kg a.s./ha DT50: 30 days		
TC (potential): 12500 cm²/h	Potential	0.1	307	49	2.6	10.8	0
TC (workwear (arms, body and legs covered)): 1400 cm²/h	Workwear	0.01	34.4	0	0.3	1.2	0
TC (workwear (arms, body and legs covered) and gloves): 1250 cm²/h	Workwear and gloves	0.01	30.7	0	0.3	1.1	0

A safe use is demonstrated for a worker conducting re-entry activities like scouting and irrigation in cereals when wearing workwear.

6.6.2.2 Refinement of generic DFR value (KCP 7.2)

Since the worker exposure estimations carried out indicated that the acceptable operator exposure levels (AOEL) will not be exceeded under conditions of intended uses and considering above PPE, refinement of generic DFR values was not necessary and was therefore not performed.

6.6.2.3 Measurement of worker exposure

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

6.6.3 Bystander and resident exposure (KCP 7.2.2)

Comments of zRMS:	Acceptable. Resident exposure calculations performed using the OPEX model, version 1.0.0, showed that exposure of both child and adult to mefentrifluconazole and sulfur is acceptable (below AOEL) considering all pathways of exposure – drift, vapour, deposit and re-entry. The AAOEL was only determined for mefentrifluconazole, therefore bystander exposure was calculated for mefentrifluconazole only. The calculation results showed that bystander exposure (both child and adult) is below the AAOEL for mefentrifluconazole, considering all pathways of exposure – drift, vapour, deposit and re-entry. The AAOEL for sulfur is not specified, therefore the exposure of a bystander to sulfur is assumed to be covered by the calculated resident exposure to that substance.

6.6.3.1 Estimation of bystander and resident exposure

Table 6.6-6 shows the exposure model(s) used for estimation of bystander and resident exposure to mefentrifluconazole and sulfur. Outcome of the estimation is presented in Table 6.6-7. Detailed calculations are in Appendix 3.

Table 6.6-6: Exposure models for intended uses

Critical use(s)	Use # 1-6: Vehicle mounted downward spraying in cereals (4 L product/ha)
Model	EFSA Guidance [European Food Safety Authority (2022) 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 doi: 10.2903/j.efsa.2022.7032.]

Table 6.6-7: Estimated bystander and resident exposure

Field crop, outdoor	**Mefentrifluconazole ~~(BAS 750 F)~~**	**Sulfur ~~(BAS 175 F)~~**
Application rate: 2 x 4 L product/ha	2 x 0.1 kg mefentrifluconazole/ha Dermal absorption: 50% DFR: 3 µg/cm² foliage per kg a.s./ha	2 x 2.4 kg sulfur/ha Dermal absorption: 50% DFR: 3 µg/cm² foliage per kg a.s./ha

		DT_{50}: 30 days		DT_{50}: 30 days	
Model data: Buffer zone: 2-3 m Drift reduction technology: 0 % Interval between treatments: 14 days Minimum volume of water: 100 l		**Total absorbed dose (mg/kg bw/d)**	**% of RVAAS (Acute AOEL)**	**Total absorbed dose (mg/kg bw/d)**	**% of RVAAS (Acute AOEL)**
Bystander child Body weight: 10 kg	Drift (95th perc.)	0.03	20.3	Not applicable	
	Vapour (95th perc.)	0.0008	0.5		
	Deposits (95th perc.)	0.004	2.8		
	Re-entry (95th perc.)	0.01	9.7		
Bystander adult Body weight: 60 kg	Drift (95th perc.)	0.008	5.5		
	Vapour (95th perc.)	0.0003	0.2		
	Deposits (95th perc.)	0.002	1.2		
	Re-entry (95th perc.)	0.008	5.4		
		Total absorbed dose (mg/kg bw/d)	**% of RVAS (AOEL)**	**Total absorbed dose (mg/kg bw/d)**	**% of RVAS (AOEL)**
Resident child Body weight: 10 kg	Drift (75th perc.)	0.01	38.7	0.3	1.4
	Vapour (75th perc.)	0.0008	2.3	0.0008	0.003
	Deposits (75th perc.)	0.001	4	0.03	0.1
	Re-entry (75th perc.)	0.01	41.5	0.3	1.5
	Sum (mean)	0.02	59.4	0.5	2
Residents (adults) Body weight: 60 kg	Drift (75th perc.)	0.003	9.2	0.08	0.3
	Vapour (75th perc.)	0.0003	0.8	0.0003	0.001
	Deposits (75th perc.)	0.0006	1.7	0.01	0.06
	Re-entry (75th perc.)	0.008	23	0.2	0.8
	Sum (mean)	0.009	24.7	0.2	0.8

6.6.3.2 Measurement of bystander and/or resident exposure

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

6.6.4 Combined exposure

The product is a mixture of two active substances. Currently no EU-harmonized guidance is available on the risk assessment of combined exposure to multiple active substances. Most assessment approaches employed up to now make use of the Hazard Index (HI) concept which was therefore used as a first tier assessment.

6.6.4.1 Exposure Assessment of mefentrifluconazole and sulfur in BAS 768 00 F

Comments of zRMS:	Acceptable. The Hazard Index calculated using the OPEX model, version 1.0.0, is < 1, therefore the combined exposure to both active substances mefentrifluconazole and sulfur in BAS 768 00 F is not expected to pose a risk for operators, workers, bystanders and residents.

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

At the first tier, combined exposure is calculated as the sum of the component exposures without regard to the mode of action or mechanism/target of toxicity. Initially, the individual Hazard Quotients (HQ) are calculated for all active substances in the PPP by assessing the exposure according to appropriate models and dividing the individual exposure levels by the respective systemic AOEL. This is equivalent to the predicted exposure as % of systemic AOEL from Table 6.6-3 converted to decimal. The Hazard Index (HI) is the sum of the individual HQs.

Table 6.6-8: Acute risk assessment from combined exposure

Application scenario		Estimated exposure / Hazard index
Operators – LCTM – short-term exposure	M/L: Workwear + Protected hands App: Workwear	0.3
Workers – Inspection/Irrigation	Workwear	0.4
Resident – ~~Adult~~ Child	Drift (75th perc.)	0.4
	Vapour (75th perc.)	0.02
	Deposits (75th perc.)	0.04
	Re-entry (75th perc.)	0.4
	Sum (mean)	0.6
Resident – ~~Child~~ Adult	Drift (75th perc.)	0.1
	Vapour (75th perc.)	0.008
	Deposits (75th perc.)	0.02
	Re-entry (75th perc.)	0.2
	Sum (mean)	0.3

Since sulfur is a naturally occurring compound of low toxicity concern no AAOEL is established and therefore a combined exposure assessment for acute operator exposure or bystander exposure is not indicated.

The Hazard Index is < 1. Thus, combined exposure to all active substances in BAS 768 00 F is not expected to present a risk for operators, workers, bystanders and residents. No further refinement of the assessment is required.

Appendix 1 Lists of data considered for national authorization

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 7.1.4/1	Remmele, M.	2022	BAS 768 00 F -In Vitro Skin Irritation and Corrosion Turnkey Testing Strategy 2021/2045077 BASF SE, Ludwigshafen/Rhein, Germany Fed.Rep. yes Unpublished	No	BASF
KCP 7.1.5/1	Remmele, M.	2022	BAS 768 00 F - In Vitro Eye Irritation Test (EIT) in Reconstructed Human Cornea 2021/2045076 BASF SE, Ludwigshafen/Rhein, Germany Fed.Rep. yes Unpublished	No	BASF
KCP 7.2/1	Wiemann, C.	2023	BAS 768 00 F Core C EFSA Calculator Report: Exposure assessment for operator, worker, resident and bystander, OPEX version 1.0.0 2023/2003363 BASF no Unpublished	No	BASF

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

BAS 768 00 F is a new product, no already evaluated product studies are available

Appendix 2 Detailed evaluation of the studies relied upon

BAS 768 00 F is an SC (suspension concentrate) type formulation containing the active substances mefentrifluconazole (25 g/L) and sulfur (600 g/L).

For toxicological evaluation of this product, alternatives to vertebrate animal testing were taken into consideration as far as could be scientifically justified. A weight-of-evidence approach was pursued to provide a sufficiently reliable assessment of the product's acute toxicity by oral, dermal and inhalation routes of exposure, and of its potential to cause skin irritation, eye irritation and skin sensitization:

a) Prediction of toxicity, based on toxicity data from active ingredient and co-formulants, as far as available and
b) results of *in vitro* studies for assessment of skin and eye irritation
c) in the absence of available similar SC-type products containing both active substances, limited (acute oral and inhalation toxicity) testing of the product in vertebrate animals to verify if the additivity assumption applies for predicting the health hazards from the product's composition according to CLP Regulation 1272/2008 (GHS calculating approaches) – and as prerequisite for waiving the acute dermal toxicity study.

Availability of acute toxicity data of BAS 768 00 F components

A consolidated overview of the available safety data sheet information on acute toxicity classification of the individual components contained in BAS 768 00 F is given in the following table, listing, where applicable and scientifically justified, those co-formulant alternatives deemed "worst-case" on account of classification or (lack of) toxicological information provided in respective safety data sheet chapter 11.

Details on the selection of the worst-case / representative co-formulants with justification are provided in Confidential Document Part C, Appendix 2. For confidentiality reasons, the co-formulants, in Table A 1 below, are coded; in Confidential Document Part C, Appendix 2, see corresponding Table A 2-2 disclosing the co-formulant identity.

Table A 1: Overview of BAS 768 00 F ingredient SDS information concerning acute toxicity C&L (CLP) considering "worst-case" co-formulant alternatives

Ingredient	Conc [% w/w] (rounded)	Acute tox. C&L (MSDS)	Acute oral toxicity	Acute dermal toxicity	Acute inhalation toxicity	Skin Corr / Irrit	Eye Dam / Irrit	Skin Sens
Mefentri-fluconazole	1.84 #	Skin Sens. 1, H317	No	No	No	No	No	H317
Sulfur	44.12 #	Skin Irrit. 2, H315	No	No	No	H315	No	No
#3-3	1.84	Acute Tox 4 (INH), H332; Eye Irrit 2, H319	No	No data	H332 (LC_{50} 1.57 mg/L)	No	H319	No
#4	4.41	–	No	No	No	No	No	No
#5	2.94	Eye Irrit 2, H319	No	No data	No data	No	H319	No
#6	2.94	Skin Irrit. 2, H315	No	No data	No data	H315	No	No
#7-3	2.21	Skin Irrit. 2, H315; ~~H319~~ Eye Dam. 1, H318	No data	No data	No data	H315	~~H319~~ H318	No data
#8	0.74	–	No data	No data	No data	No data	No data	No data
#9	0.29	–	No	No data	No	No	No	No
#10	0.15	EUH208	No	No	No data	No	No	EUH208
#11*	0.15	Skin Corr, H314(1B); Skin Sens 1, H317	No	No	No data	H314	(H318)	H317
#12**	0.074	Skin Corr., H314 (1C); Skin Sens 1A, H317	No	No	No data	H314	(H318)	H317

Water	38.30	–	No	No	No	No	No	No
% of product with acute toxicity data			97	89	91	99	99	97

Hazardous ingredients in co-formulant mixtures
#11: 3% NaOH (← H314, pH 11-12.5) and 20% 1,2-benzisothiazolin-3-one [BIT, CAS-No. 2634-33-5]*
#12: 1.48% CIT/MIT 3:1 [CAS-No. 55965-84-9] (← H314, H317)**/***
* SCL (H317) ≥ 0.05%; ** SCL (H314, H318): ≥0.6%, (H315, H319): ≥0.06%; *** SCL (H317) ≥ 0.0015%

A 2.1 Statement on bridging possibilities

No BASF products with sufficiently similar composition are available for read-across to BAS 768 00 F.

Comments of zRMS:	Acceptable

A 2.2 Acute oral toxicity (KCP 7.1.1)

Comments of zRMS:	Acceptable. The toxicological assessment of BAS 768 00 F is based on the composition of the formulation and takes into account the classification of each component of the mixture. None of the components is classified as acute oral toxic, therefore the whole formulation does not need to be classified in this hazard class.

Data for assessment of acute oral toxicity are available for 97% of the product's composition (Table A 1). No data is available for an alternative of co-formulant #7-3 (2.21% in BAS 768 00 F) and for co-formulant #8 (0.74%).

None of the active ingredients or co-formulants are classified for acute oral toxicity.

Hence, a classification for acute oral toxicity is not indicated for BAS 768 00 F on the basis of its composition and concentration of hazardous ingredients present at relevant concentrations.

It is concluded that the acute oral toxicity of BAS 768 00 F is low.
The predicted rat acute oral LD_{50} is > 2000 mg/kg bw.

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

Comments of zRMS:	Acceptable. The toxicological assessment of BAS 768 00 F is based on the composition of the formulation and takes into account the classification of each component of the mixture. None of the components is classified as acute dermal toxic. Although acute dermal toxicity data are available for only 89% of the product composition, based on the weight of evidence, the whole formulation does not need to be classified in this hazard class.

Acute dermal toxicity data are available for 89% of the product's composition (Table A 1). No data is reported in safety data sheets available for co-formulants #5 and #6 (2.94% each in BAS 768 00 F), #7-3 (2.21%) and #3-3 (1.84%). Furthermore, co-formulants #8 (0.74%), and #9 (0.29%) are without acute dermal toxicity data but each contained below the 1% relevance cut-off concentration and therefore not relevant for product classification according to the CLP Regulation.

None of the active ingredients or co-formulants are classified for acute dermal toxicity.

Since acute oral toxicity is low for all co-formulants, it can be safely concluded that none of the ingredients in BAS 768 00 F give rise to concern for acute dermal toxicity.

Thus, based on weight-of-evidence (composition and oral-to-dermal extrapolation), it is concluded BAS 768 00 F does not require classification for acute dermal toxicity.

A 2.4 Acute inhalation toxicity (KCP 7.1.3)

Comments of zRMS:	Acceptable. The toxicological assessment of BAS 768 00 F is based on the composition of the formulation and takes into account the classification of each component of the mixture. Given that acute inhalation data are available for more than 90% of the product and only one component (1.84% in the formulation) is classified as acute inhalation toxic (Cat. 4, H332), the whole formulation does not need to be classified in this hazard class based on the results of the calculation method used in accordance with the CLP principles.

Data for assessment of acute inhalation toxicity of BAS 768 00 F is available for 6 of 13 ingredients comprising approx. 91% of the total composition (see Table A 1).

No data is reported in safety data sheets available for co-formulants #5 and #6 (2.94% each in BAS 768 00 F) and #7-3 (2.21%). Furthermore, co-formulants #8 (0.74%), #10, #11 (each 0.15%) and #12 (0.074%) are without acute inhalation data but each contained in BAS 768 00 F below the 1% relevance cut-off concentration and therefore not relevant for product classification, according to the CLP Regulation.

One alternative co-formulant #3-3 (~~6.13%~~ 1.84% w/w) is classified as harmful by inhalation (Cat. 4; H332 with an ATE of 1.57 mg/L). None of the other ingredients with data indicate a concern for acute inhalation toxicity.

A calculation approach using the standard GHS algorithm for mixtures containing <10% relevant ingredients with unknown acute inhalation toxicity …

$$\frac{100}{ATE_{mix}} = \sum_{n} \frac{C_i}{ATE_i} = \frac{\text{~~6.13~~ 1.84}}{1.57}$$

$$ATE_{mix} = 100 \times \frac{1.57}{\text{~~6.13~~1.84}} = \text{~~26.6~~ 85.3 mg/L}$$

… predicts the product BAS 768 00 F to be of low acute toxicity by the inhalation route, with no need for acute toxicity classification (because LC_{50} > 5 mg/L).

Based on the lack of ingredients with relevant volatility or vapor pressure, the likelihood of relevant exposure to the product by the inhalation route is considered to be negligible. In view of low concern for an acute inhalation toxicity hazard, an acute inhalation toxicity study with BAS 768 00 F is therefore not considered to be required.

It is concluded that the acute inhalation toxicity of BAS 768 00 F is expected to be low on account of its composition. The predicted rat acute inhalation LC_{50} is > 5 mg/L.

A 2.5 Skin irritation (KCP 7.1.4)

Comments of zRMS:	Acceptable. The toxicological assessment of BAS 768 00 F is based on the composition of the formulation and takes into account the classification of each component of the mixture. According to the calculation result, the formulation should be classified as Skin Irrit. 2 with the hazard statement H315. The corrosive/irritant properties of the BAS 768 00 F formulation were also tested *in vitro* in accordance with OECD tests 431 and 439. The study results showed that BAS 768 00 F was not corrosive to the skin under *in vitro* study conditions (tissue viability was 96.7% after 3 min. of exposure and 99.0% after 1-hour exposure). The skin irritation test (SIT) did also not show the skin irritation potential of the BAS 768 00 F formulation, however, it is worth noting that the mean relative viability of tissues treated with BAS 768 00 F determined after a 1-hour exposure with an approximately 42-hour post-incubation period (56.9%) was just above the limit range (50%). Conclusion: Considering the above results of both the calculation method and *in vitro* study, it is acceptable to classify the BAS 768 00 F formulation as Skin Irrit. 2 with the hazard statement H315.

Data for assessment of skin irritation is available for 99% of the composition (see Table A 1).

For one ingredient (#8, 0.74% in BAS 768 00 F) that has no hazard classification, information on skin irritation is not provided in the respective safety data sheet.

The active ingredient sulfur has a harmonized classification as skin irritant (Skin Irrit 2; H315) and is contained at about **44.12%** in the product. According to data summarized in the RAC Opinion (2022), technical sulfur mixed with vaseline was identified as skin irritant in rabbits, whereas sulfur dust applied as a paste with deionized water was not skin irritating in rabbits. Data from acute dermal toxicity studies in rats indicated mild skin irritation after 24h exposure to technical sulfur in corn oil, while no skin irritation was observed in rats after exposure to sulfur using deionized water as vehicle. Available human data was considered by RAC to provide "robust and consistent evidence of the skin irritation potential of sulfur".

Beside of sulfur, BAS 768 00 F contains two skin irritating co-formulants #6 (**2.94%**) and #7-3 (**2.21%**), both relevant because above the generic 1% relevance cut-off concentration trigger.

Co-formulant #11 (0.15%) is a mixture classified as skin corrosive (Skin Cor 1B; H314) on account of its pH value of 11.0-12.5, resulting from its sodium hydroxide content (up to 3%). Undiluted BAS 768 00 F has a pH of 7.7-8.0 (see KCP 2.4., DocID 2022/2014755) indicating no concern for skin corrosivity. Thus, co-formulant #11 is not relevant for predicting the product's skin corrosion/irritation potential.

Co-formulant #12 (0.074% in BAS 768 00 F) contains 1.48% of the hazardous ingredient "reaction mass of 5-chloro-2-methylisothiazol-3-one and 2-methylisothiazol-3-one" (CIT/MIT), which is classified as Skin Corr. 1C; H314 and has been assigned respective SCLs (see footnote of Table A 1). The resulting CIT/MIT concentration in BAS 768 00 F (0.0011%) is >50x lower than the 0.06% SCL cut-off for considering CIT/MIT-containing mixtures as skin or eye irritants. Therefore, regarding skin corrosivity/irritation, co-formulant #~~11~~12 is not relevant for deriving the classification of BAS 768 00 F.

Based on skin corrosion/irritation data available for the components, product classification as skin irritant is triggered for BAS 768 00 F according to GHS/CLP criteria, because the total product concentration of skin irritating ingredients (>49%) is clearly above the 10% trigger for classification.

When the product was tested *in vitro* in the EpiDerm™ test (OECD 431 and OECD 439), BAS 768 00 F did not show evidence for a relevant skin irritation potential (viability ca. 57%, thus >50% after 1-h exposure followed by 42-h incubation period, compared to the negative control). However, based on published literature, a false-negative rate of 56% was identified for agrochemical formulations in this *in vitro* skin irritation test (Kolle et al. (Regul. Toxicol. Pharmacol. 89, 125-130, 2017). Therefore, some doubt

remains regarding the reliability of the study result.

In absence of bridging opportunities for read-across to similar products, for reasons of precaution, and to avoid vertebrate testing, it is proposed to classify BAS 768 00 F as skin irritant based on the composition information.

A 2.5.1 *In vitro* skin corrosion and skin irritation study with BAS 768 00 F

Reference:	CP 7.1.4/1
Report	BAS 768 00 F - In vitro skin irritation and corrosion turnkey testing strategy Remmele M., 2022a Report No 69V0026/21B088 BASF DocID 2021/2045077
Guideline(s):	OECD 431, OECD 439, Commission Regulation (EC) No 440/2008 - Part B No. B.40 bis, Commission Regulation EU No. 640/2012 of 06 July 2012 - B.46
Deviations:	No
GLP:	Yes (certified by Landesamt fuer Umwelt, Wasserwirtschaft und Gewerbeaufsicht, Mainz, Germany)
Acceptability:	Yes
Duplication (if vertebrate study)	No

Materials and methods

Test material (Lot/Batch No.)	BAS 768 00 F Batch No. FD-210120-1029 Purity/Content: - Mefentrifluconazole (BAS 750 F): 26.3 g/L - Sulfur (BAS 175 F): 614.9 g/L pH value: ca. 6 (undiluted, determined in test facility)	
Test system	Reconstructed in vitro human skin model, EpiDerm™	
Principle of the method	Induced cytotoxicity (loss of viability) is expressed as the reduction of mitochondrial dehydrogenase activity measured by reduction of MTT conversion to blue-colored formazan, in comparison to a negative control. The test substance's ability of direct MTT reduction was negligible as demonstrated in a pre-test with 3-h incubation of the test substance in MTT solution in the dark at 37 °C.	
	Skin Corrosivity test (SCT) OECD 431	***Skin Irritation test (SIT) OECD 439***
No. of tissues per exposure and group	2	3
Exposure	50 µL (3 min), 50 µL (1 h)	30 µL (1 h)
Vehicle / dilution	Tested undiluted	Tested undiluted

Post-exposure incubation period	Not applicable	42 h
Positive control	8 N potassium hydroxide	5% (w/v) sodium dodecyl sulfate (SDS)
Negative control	De-ionized water	Phosphate-buffered saline (PBS)
Assessment	***Mean tissue viability (% of negative control)***	
Corrosive (optional subcategory 1A) [a]	3 min: < 50	–
Corrosive (opt. subcategory 1B and 1C) [a]	3 min: ≥ 50 and 1 hour: < 15	–
Non-corrosive	3 min: ≥ 50 and 1 hour: ≥ 15	–
Irritant	–	1 +42 hours: ≤ 50
Non-Irritant	–	1 +42 hours: > 50

[a] According to the current OECD Guideline 431 a sub-categorization is possible based on the results. However, the sub-categorization into 1A is highly over-predictive as stated in the guideline and differentiation into sub-category 1B or 1C is not possible. If the test substance is identified to be corrosive by SCT and a transport classification is needed, the Corrositex® test (OECD 435) should be performed, if applicable, to confirm classification as 1A or to differentiate between 1B and 1C.

Results and discussions

Results of the skin corrosion and skin irritation tests are summarized in the table below.

Table A 2: *In vitro* skin corrosion / irritation of BAS 768 00 F

Parameter	Negative control (NC)	Test item	Positive control
	viable tissue	viable tissue	viable tissue
Skin corrosivity test (SCT) – Exposure: 3 min			
OD_{570} tissue I	1.824	1.806	0.290
OD_{570} tissue II	1.987	1.878	0.273
mean OD_{570}	1.905	1.842	0.282
Viability (% of NC)	**100.0 ± 6.0**	**96.7 ± 2.7**	**14.8 ± 0.6**
Skin corrosivity test (SCT) – Exposure: 1 h			
OD_{570} tissue I	1.892	1.999	0.096
OD_{570} tissue II	1.784	1.642	0.093
mean OD_{570}	1.838	1.820	0.094
Viability (% of NC)	**100.0 ± 4.1**	**99.0 ± 13.7**	**5.1 ± 0.1**
Skin irritation test (SIT) – Exposure:1 h + post-exposure incubation: 42 h			
OD_{570} tissue I	2.090	1.013	0.044
OD_{570} tissue II	1.918	1.262	0.039
OD_{570} tissue III	1.989	1.134	0.039
mean OD_{570}	1.999	1.136	0.041
Viability (% of NC)	**100.0 ± 4.3**	**56.9 ± 6.2**	**2.0 ± 0.2**

NC = negative control (deionised water), PC = positive control (8 N KOH); OD_{570} = optical density by λ = 570 nm

BAS 768 00 F was not corrosive to skin under the *in vitro* study conditions. The mean relative viability of the tissues treated with the test substance determined after an exposure period of 3 minutes was 96.7%, and it was 99.0% after a 1-hour exposure period.

In the skin irritation test (SIT), the mean relative viability of the tissues treated with BAS 768 00 F determined after an exposure period of 1 hour with an about 42-hour post-incubation period was about 56.9%. This viability value is above the 50% classification trigger for a substance with skin irritation potential.

Conclusion
Based on the results obtained, it is concluded that BAS 768 00 F does not show a skin irritation potential in the EpiDerm™ *in vitro* skin irritation and corrosion test strategy under the test conditions chosen.

A 2.6 Eye irritation (KCP 7.1.5)

Comments of zRMS:	Acceptable. The toxicological assessment of BAS 768 00 F is based on the composition of the formulation and takes into account the classification of each component of the mixture. According to the calculation result, the formulation should be classified as Eye Irrit. 2 with the hazard statement H319. The eye irritating properties of the BAS 768 00 F formulation were also tested *in vitro* in accordance with OECD 492 test. The study results showed that BAS 768 00 F was irritating to the eyes under *in vitro* study conditions (relative mean viability of tissues treated with the test substance was 20.7%, i.e. above a limit range of 60%). Conclusion: Considering the above results of both the calculation method and *in vitro* study, it is acceptable to classify the BAS 768 00 F formulation as Eye Irrit. 2 with the hazard statement H319.

Data for assessment of eye irritation is available for ca. 99% of the composition (see Table A 1).

For one ingredient (#8, 0.74% in BAS 768 00 F) that has no hazard classification, information on eye irritation is not provided in the respective safety data sheet.

BAS 768 00 F contains ~~3~~ 2 co-formulants with Eye Irrit 2; H319 classification: #3-3 (**1.84%**), #5 (**2.94%**) and #7-3 with Eye Dam. 1; H318 classification (**2.21%**), all relevant because above the generic 1% relevance cut-off concentration trigger.

Co-formulant #11 (0.15%) is classified as corrosive due to pH (see chapter A 2.5 for more details). In view of a pH of 7.7-8.0 obtained for undiluted product (see KCP 2.4., DocID 2022/2014755), which does not indicate concern for corrosivity, co-formulant #11 is considered not relevant for predicting the eye corrosion or irritation potential of BAS 768 00 F.

Co-formulant #12 (0.07**4**% in BAS 768 00 F) has a Skin Corr 1C / Eye Dam. 1 classification, because it contains 1.48% of the hazardous ingredient "reaction mass of 5-chloro-2-methylisothiazol-3-one and 2-methylisothiazol-3-one" (CIT/MIT). SCLs apply for CIT/MIT containing mixtures (see footnote of Table A 1). The resulting CIT/MIT concentration in BAS 768 00 F (0.0011%) is >50x lower than the 0.06% SCL cut-off for considering CIT/MIT-containing mixtures as skin or eye irritants. Therefore, regarding eye corrosivity/irritation, co-formulant #~~11~~12 is considered not relevant for classification of BAS 768 00 F.

Based on eye irritation data available for the components, product classification is ~~not~~ triggered for BAS 768 00 F according to GHS/CLP criteria, because the product contains ~~no~~ one eye damaging ingredient~~s~~ at relevant concentration~~s~~ (2.21%), and the total product concentration of ~~three~~ eye irritating and damaging ingredients (ca. 1.84+2.94+**10x**2.21= ~~**6.99%**~~ **26.88%**) is ~~below~~ above the 10% trigger for classification as eye irritant.

When BAS 768 00 F was investigated *in vitro*, the EpiOcular™ test (OECD 492) gave evidence for an eye irritating potential. A positive test result in the assay is not sufficient for a classification decision.

Based on the overall weight-of-evidence from product composition, pH data and *in vitro* study results, the available data indicates that classification of BAS 768 00 F with Eye Irrit 2; H319 is required according to Regulation (EC) No. 1272/2008.

A 2.6.1 *In vitro* eye irritation test (OECD 492) with BAS 768 00 F

Reference:	CP 7.1.5/1
Report	BAS 768 00 F – In Vitro Eye Irritation Test (EIT) in Reconstructed Human Cornea Remmele M., 2022b Report No: 62V0026/21B087 BASF DocID 2021/2045076
Guideline(s):	OECD 492 (2018) IATA for serious eye damage and eye irritation, Series on Testing and Assessment No. 263, 25 July 2019
Deviations:	No
GLP:	Yes (certified by Landesamt fuer Umwelt, Wasserwirtschaft und Gewerbeaufsicht, Mainz, Germany)
Acceptability:	Yes
Duplication (if vertebrate study)	No

Materials and methods

Test material (Lot/Batch No.)	BAS 768 00 F Batch No. FD-210120-1029 Purity/Content: - Mefentrifluconazole (BAS 750 F): 26.3 g/L - Sulfur (BAS 175 F): 614.9 g/L pH value: ca. 6 (undiluted, determined in test facility)

EpiOcular™ Test

Test system	Reconstructed in vitro human ocular model, EpiOcular™
Principle of the method	The test substance is administered to the surface of the EpiOcular™ tissue. Induced cytotoxicity (loss of viability) is expressed as the reduction of mitochondrial dehydrogenase activity measured by reduction of MTT conversion to blue-colored formazan, in comparison to a negative control.
No. of tissues per test group	2
Pretest for detection of direct (= non-enzymatic) MTT reduction	In a pre-test, the test substance is incubated with the substrate MTT and checked for formazan formation, indicating "direct" MTT reduction. In this event, two additional "freeze-killed" tissues each for the test substance group and the negative control group are added to the standard test protocol. Based on the result of the pretest, it was judged that application of killed control tissues is not necessary.
Exposure	50 µL: 30 min

Vehicle / dilution	Tested undiluted
Post-exposure wash solution	Phosphate-buffered saline (PBS)
Post-exposure incubation period	2 hours
Positive control	Methyl acetate
Negative control	De-ionized water
Assessment	***Mean tissue viability*** *(% of negative control)*
Irritant	≤ 60
Non-irritant	> 60

Results and discussions

Table A 3: *In vitro* eye corrosion / irritation of BAS 768 00 F (EpiOcular™ Assay)

Test substance		Tissue 1	Tissue 2	**Mean**	Inter-tissue variability [%]
Neg. control (NC)	mean OD_{570}	1.927	2.102	2.014	
	Viability [% of NC]	95.7	104.3	**100.0**	8.7
BAS 768 00 F	mean OD_{570}	0.377	0.459	0.418	
	Viability [% of NC]	18.7	22.8	**20.7**	4.1
Positive control (PC)	mean OD_{570}	0.664	0.727	0.696	
	Viability [% of NC]	33.0	36.1	**34.5**	3.1

NC = negative control (de-ionized water), PC = positive control (methyl acetate); OD_{570} = optical density by λ = 570 nm

~~The relative mean viability of reconstructed corneal tissues following exposure to BAS 768 00 F was 92.1% of the negative control value (thus higher than 60%), indicating no eye irritating properties of the test substance.~~

Conclusion

BAS 768 00 F showed an eye irritation potential in the *in vitro* eye irritation test (EpiOcular™, OECD 492), based on a relative viability score of 20.7% compared to the negative control incubation.

A 2.7 Skin sensitisation (KCP 7.1.6)

Comments of zRMS:	Acceptable. The toxicological assessment of BAS 768 00 F is based on the composition of the formulation and takes into account the classification of each component of the mixture. According to the calculation results, the formulation should be classified as Skin Sens. 1 with the hazard statement H317. The components CIT/MIT and BIT that may cause an allergic reaction should also be listed on the label.

No skin sensitisation test was performed for the product BAS 768 00 F.

Data for skin sensitization assessment is available for ca. 97% of the product's composition (Table A 1).

Skin sensitization information is missing for 2 co-formulants: #7-3 (2.21%) and #8 (0.74%).

The active ingredient mefentrifluconazole (1.84% in BAS 768 00 F) was identified as skin sensitizer in an animal test. On this basis, classification of BAS 768 00 F as skin sensitizer (Skin Sens 1; H317) is required.

Low concentrations of the skin sensitizing isothiazolinones CIT/MIT (CAS-No. 55965-84-9, ca. 0.0011%)) and BIT (2634-33-5, ca. 0.03%),) in BAS 768 00 F are due to their content in co-formulants #12 and #11, respectively. Co-formulant #10 (0.15% in BAS 768 00 F) requires labelling with EUH208 also due to minute contents of CIT/MIT and BIT. However, the contribution of CIT/MIT and BIT from coformulant #10 to the respective total contents in BAS 768 00 F is negligible. The overall isothiazolinone contents in BAS 768 00 F are below the respective specific concentration limits for CIT/MIT (0.0015%) and BIT (0.05%) as stipulated in the current ATP of CLP Regulation 1172/2008, and therefore do not trigger classification of BAS 768 00 F as skin sensitizer. However, listing on the label is required to indicate these ingredients are present in BAS 768 00 F and may cause an allergic reaction.

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

None available.

A 2.9 Data on co-formulants (KCP 7.4)

A 2.9.1 Material safety data sheet for each co- formulant

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

A 2.9.2 Available toxicological data for each co-formulant

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

A 2.10 Studies on dermal absorption (KCP 7.3)

zRMS comments	Acceptable. The default values for dermal absorption were used for risk assessment in accordance with the EFSA Guidance on Dermal Absorption (2017).

No dermal absorption studies are available for active substances formulated in BAS 768 00 F

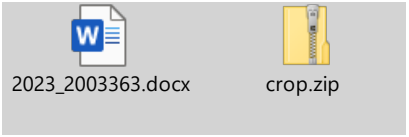
Non-dietary exposure estimations were conducted using default dermal absorption studies as recommended by the EFSA guidance on dermal absorption (EFSA Journal 2017; 15(6):4873) – see Chapter 6.5.

A 2.11 Other/Special Studies

None available.

Appendix 3 Exposure calculations

Opex report on exposure calculations:



A 3.1 Operator exposure calculations (KCP 7.2.1.1)

A 3.1.1 Calculations for mefentrifluconazole

Table A 4: Input parameters considered for the estimation of operator exposure

Formulation type	SC	**Name of active substance**	Mefentrifluconazole
Concentration of active substance [g a.s./l or kg]	25	**Crops**	Field crops
Area treated [ha/day]	50	**Application method**	Downward spraying
Dermal absorption [%] (concentrate)	50	**Application technique**	Vehicle-mounted
Dermal absorption [%] (dilution)	50	**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]	0.035		
AAOEL [mg/kg bw]	0.15		

Table A 5: Estimation of operator exposure (short-term) towards mefentrifluconazole using the EFSA Online Calculator

Activity	Systemic exposure per body part	With workwear	With workwear + PPE/RPE
Mixing and loading (µg/kg bw per day)	*Hand protection*	*None*	*Protected hands*
	Hands exposure	**190**	**1.1**
	Body protection	*Workwear*	*Workwear*
	Body exposure	**1.1**	**1.1**
	Head protection	*None*	*None*
	Head exposure	**2.6**	**2.6**
	Inhalation protection	*None*	*None*
	Inhalation exposure	**0.1**	**0.1**
Application (µg/kg bw per day)	*Hand protection*	*None*	*None*
	Hands exposure	**6.2**	**6.2**
	Body protection	*Workwear*	*Workwear*
	Body exposure	**0.09**	**0.09**
	Head protection	*None*	*None*
	Head exposure	**0.2**	**0.2**
	Inhalation protection	*None*	*None*

Activity	Systemic exposure per body part	With workwear	With workwear + PPE/RPE
	Inhalation exposure	**0.04**	**0.04**
Total	Total systemic exposure [mg/kg bw per day]	0.2	0.01
	% of AOEL	572	32.5

Table A 6: Estimation of operator exposure (acute) towards mefentrifluconazole using the EFSA Online Calculator

Activity	Systemic exposure per body part	With workwear	With workwear + PPE/RPE
Mixing and loading (µg/kg bw per day)	*Hand protection*	*None*	*Protected hands*
	Hands exposure	**713**	**25.8**
	Body protection	*Workwear*	*Workwear*
	Body exposure	**9.9**	**9.9**
	Head protection	*None*	*None*
	Head exposure	**15.8**	**15.8**
	Inhalation protection	*None*	*None*
	Inhalation exposure	**0.3**	**0.3**
Application (µg/kg bw per day)	*Hand protection*	*None*	*None*
	Hands exposure	**61.8**	**61.8**
	Body protection	*Workwear*	*Workwear*
	Body exposure	**0.2**	**0.2**
	Head protection	*None*	*None*
	Head exposure	**0.5**	**0.5**
	Inhalation protection	*None*	*None*
	Inhalation exposure	**0.1**	**0.1**
Total	Total systemic exposure [mg/kg bw per day]	0.8	0.1
	% of AAOEL	534	76.3

A 3.1.2 Calculations for sulfur

Table A 7: Input parameters considered for the estimation of operator exposure

Formulation type	SC	**Name of active substance**	Sulfur
Concentration of active substance [g a.s./l or kg]	600	**Crops**	Field crops
Area treated [ha/day]	50	**Application method**	Downward spraying
Dermal absorption [%] (concentrate)	10	**Application technique**	Vehicle-mounted
Dermal absorption [%] (dilution)	50	**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]	24
AAOEL [mg/kg bw]	

Table A 8: Estimation of operator exposure (short-term) towards sulfur using the EFSA Online Calculator

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	**290**	**290**
	Body protection	*Workwear*	*Workwear*
	Body exposure	**1.6**	**1.6**
	Head protection	*None*	*None*
	Head exposure	**12.6**	**12.6**
	Inhalation protection	*None*	*None*
	Inhalation exposure	**0.3**	**0.3**
Application (µg/kg bw per day)	*Hand protection*	*None*	*None*
	Hands exposure	**148**	**148**
	Body protection	*Workwear*	*Workwear*
	Body exposure	**2.2**	**2.2**
	Head protection	*None*	*None*
	Head exposure	**3.9**	**3.9**
	Inhalation protection	*None*	*None*
	Inhalation exposure	**0.2**	**0.2**
Total	Total systemic exposure [mg/kg bw per day]	0.5	0.5
	% of AOEL	1.9	1.9

Note: the EFSA calculator does not provide the correct figures for workwear and PPE/RPE instead figures for the scenario with workwear only are erroneously presented in both columns.

Table A 9: Estimation of operator exposure (acute) towards sulfur using the EFSA Online Calculator

Not applicable since no AAOEL is required for sulfur.

A 3.2 Worker exposure calculations (KCP 7.2.3.1)

A 3.2.1 Calculations for mefentrifluconazole

Table A 10: Input parameters considered for the estimation of worker exposure, outdoor scenario, normal crop density

Indoor/outdoor	Outdoor	**AOEL [mg/kg bw/day]**	0.035
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. product application rate of the product [l or kg/ha]	4	**DFR refined worker [µg/cm² foliage per kg a.s./ha]**	3
Max. no. of applications	2	**DT50 foliar worker [days]**	30
Interval between multiple applications [days]	14		
Multiple application factor	1.72		
Body weight (kg)	60		
Name of active substance	Mefentrifluconazole		
Dermal absorption [%] (dilution)	50		
Inhalation absorption [%]	100		
Time [hours per day]	2		

Table A 11: Estimation of worker exposure towards mefentrifluconazole using the EFSA online calculator

Exposure route	Description	Potential	Workwear	Workwear and gloves	Gloves
Dermal	Systemic dermal exposure [mg a.s. per day]	6.5	0.7	0.6	N.A.
Inhalation	Systemic inhalation exposure [mg a.s. per day]				N.A.
Total	Total systemic exposure [mg a.s. per day]	6.5	0.7	0.6	N.A.
	Total systemic exposure [mg/kg bw per day]	0.1	0.01	0.01	N.A.
	% of AOEL	307	34.4	30.7	N.A.

A 3.2.2 Calculations for sulfur

Table A 12: Input parameters considered for the estimation of worker exposure, outdoor scenario, normal crop density

Indoor/outdoor	Outdoor	**AOEL [mg/kg bw/day]**	24
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. product application rate of the product [l or kg/ha]	4	**DFR refined worker [µg/cm² foliage per kg a.s./ha]**	3
Max. no. of applications	2	**DT50 foliar worker [days]**	30
Interval between multiple applications [days]	14		
Multiple application factor	1.72		
Body weight (kg)	60		
Name of active substance	Sulfur		
Dermal absorption [%] (dilution)	50		
Inhalation absorption [%]	100		
Time [hours per day]	2		

Table A 13: Estimation of worker exposure towards sulfur using the EFSA online calculator

Exposure route	Description	Potential	Workwear	Workwear and gloves	Gloves
Dermal	Systemic dermal exposure [mg a.s. per day]	155	17.3	15.5	N.A.
Inhalation	Systemic inhalation exposure [mg a.s. per day]				N.A.
Total	Total systemic exposure [mg a.s. per day]	155	17.3	15.5	N.A.
	Total systemic exposure [mg/kg bw per day]	2.6	0.3	0.3	N.A.
	% of AOEL	10.8	1.2	1.1	N.A.

A 3.3 Bystander and resident exposure calculations (KCP 7.2.2.1)

The report of the EFSA online calculator does not provide further details on the bystander and resident exposure assessment, therefore no detailed tabulation can be provided.

A 3.4 Combined exposure calculations for mefentrifluconazole and sulfur

The estimates are presented in section 6.6.5 above based on the calculation for the individual compounds as presented in section 6.6.2 to 6.6.4 and further detailed.in A 3.1 to A 3.2.

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 studies available. None required.