FINAL REGISTRATION REPORT

Part B

Section 6

Mammalian Toxicology

Detailed summary of the risk assessment

Product code: CHR/H/FDF 574 SC

Product name(s): Cezaro 574 SC, Huron 574 SC

Chemical active substance(s):

Florasulam, 12 g/L
Diflufenican, 250 g/L
Flufencaet, 312 g/L

Central Zone

Zonal Rapporteur Member State: Poland

CORE ASSESSMENT

(authorization)

Applicant: Innvigo Sp. z o.o.

Submission date: November 2021

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Version history

When	What
March 2022	Dossier sent for evaluation
June 2022	Updates based on feedback from zRMS Poland
July 2022	Updates based on feedback from zRMS Poland
September 2022	zRMS evaluation of dRR
November 2022	Final version prepared by zRMS after Commenting period

zRMS comments:	The applicant´s text in this Section has not been amended by the zRMS. If necessary zRMS has crossed text and/or inserted new text written in gray.

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6 Mammalian Toxicology (KCP 7)

In the following document, data for active substances - diflufenican and flufenacet - was described during its inclusion on Annex 1 process in respectively 2009 and 2004 . Were reference to active substance data in the current risk assessment has been made, it was based on the data which protection for expired 10 years from date of inclusion of active substances on Annex I.
Data matching studies for florasulam have been evaluated by Poland. As a result of the assessment all reports were accepted and considered as equivalent to protected studies. Therefore, to support the authorization of CHR/H/FDF 574 SC INNVIGO is allowed to refer to EU approved reports.

6.1 Summary

Table 6.1-1: Information on CHR/H/FDF 574 SC *

Product name and code	CHR/H/FDF 574 SC
Formulation type	Suspension concentrate [SC]
Active substance(s) (incl. content)	Florasulam: ~~4.8~~ 12 g/L Diflufenican: 250 g/L Flufenacet 312 g/L
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 CHR/H/FDF 574 SC 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 CHR/H/PENDIF according to Regulation (EC) No 1272/2008

Hazard class(es), categories	Acute Tox. 4, H302, Skin Sens 1, H317, STOT RE 2, H373
Hazard pictograms or Code(s) for hazard pictogram(s)	
Signal word	Warning
Hazard statement(s)	Acute Tox.4, H302 – Harmful if swallowed Skin Sens.1, H317 – May cause an allergic skin reaction STOT RE 2, H373 – May cause damage to organs through prolonged or repeated exposure.
Precautionary statement(s)	P260 – Do not breathe dust/fume/gas/mist/vapours/spray. P272 – Contaminated work clothing should not be allowed out of the workplace. P280 – Wear protective gloves/~~protective clothing/eye protection/face protection~~ ~~P 305 + P351 + P338 IF IN EYES: Rinse cautiously with water for~~

	~~several minutes. Remove contact lenses, if present and easy to do. Continue rinsing~~ ~~P310 – Immediately call a Poison center/doctor/…~~ P301+P312 – IF SWALLOWED: Call a POISON CENTER or doctor if you feel unwell P302 + P352 – IF ON SKIN: Wash with plenty of soap and water. P333 + P313 – IF skin irritation or rash occurs: Get medical advice/attention P314 – Get medical advice/attention if you feel unwell. **Other section of the label:** ~~P201: Obtain special instructions before use.~~ P264: Wash hands thoroughly after handling. P272 – Contaminated work clothing should not be allowed out of the workplace P270: Do not eat, drink or smoke when using this product. P362+364: Take off contaminated clothing and wash before reuse. ~~P405: Store locked up.~~ ~~P403 + P233: Store in a well ventilated place. Keep container tightly closed.~~ P501: Dispose of contents/container to… ~~And P280 as follows:~~ WORKER: Inspection: Work wear (arms, body and legs covered) ~~"Stosować rękawice ochronne oraz odzież ochronną".~~ ~~"Wear protective gloves and protective clothing"~~ **Section "First Aid"** ~~P301+P310, P331~~, P330 ~~P332 + P313~~ ~~P304+P340~~ P301 + P312 ~~P308 + P313~~ P302 + P352 P333 + P313 For polish version: see the label
Additional labelling phrases	To avoid risks to man and the environment, comply with the instructions for use. [EUH401]
	~~EUH208 Contains 1,2-Benzisothiazol-3(2H)-one. May produce an allergic reaction.~~ Hazardous ingredients, other than the active substance: 1,2-benzisothiazol-3(2H)-one.

Table 6.1-3: Summary of risk assessment for operators, workers, residents and bystanders for CHR/H/FDF 574 SC

	Result	PPE / Risk mitigation measures
Operators	Acceptable	~~With gloves and work wear during mix/loading~~ Work wear and gloves during mix/loading
Workers	Acceptable	~~With PPE~~ Inspection: work wear (arms, body and legs covered)
Residents	Acceptable	5 meters buffer zone
Bystanders	Acceptable	

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

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

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

1	2	3	4	5	6	7	8	9	10			
Use-No.*	**Crops and situation (e.g. growth stage of crop)**	**F, Fn, Fpn G, Gn, Gpn or I ****	**Application**		**Application rate**		**PHI (d)**	**Remarks:** **(e.g. safener/synergist (L/ha))** **critical gap for operator, worker, resident or bystander exposure based on [Exposure model]**	**Acceptability of exposure assessment**			
			Method / Kind **(incl. application technique *****	**Max. number (min. interval between applications)** **a) per use** **b) per crop/ season**	**Max. application rate kg as/ha** **a) a.s. 1** **b) a.s. 2**	**Water L/ha** **min / max**			**Operator**	**Worker**	**Residents**	**Bystander**
	Cereals BBCH 11-25	F	Spray LCTM	1:1	a) Florasulam 0.0048 kg/ha b) Diflufenican 0.1 kg/ha c) Flufenacet 0.1248 kg/ha	200 - 400			R	A	R	R

* 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

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)

	Florasulam	**Diflufenican**	**Flufenacet**
Common Name	Florasulam	Diflufenican	Flufenacet
CAS-No.	145701-23-1	79277-27-3	142459-58-3
Classification and proposed labelling			
With regard to toxicological endpoints (according to the criteria in Reg. 1272/2008, as amended)	**Hazard classes (s), categories:** Aquatic Chronic 1 Aquatic Acute 1 **Code(s) for hazard pictogram(s):** GHS09 GHS07 **Signal word:** Warning **Hazard statement(s):** H400 – Very toxic to aquatic life. H410 – Very toxic to aquatic life with long lasting effects. **Precautionary statement(s):** P391 – Collect spillage. P273 – Avoid release to the environment. P501: Dispose of contents/container to…	**Hazard classes (s), categories:** Aquatic Acute 1 Aquatic Chronic 1 **Code(s) for hazard pictogram(s):** GHS09 **Signal word**: Warning **Hazard statement(s):** H400 – Very toxic to aquatic life. H410 – Very toxic to aquatic life with long lasting effects. **Precautionary statement(s):** P391 – Collect spillage. P273 – Avoid release to the environment.	**Hazard classes (s), categories**: Acute Tox. 4 STOT RE 2 Skin Sens. 1 Aquatic Acute 1 Aquatic Chronic 1 **Code(s) for hazard pictogram(s):** GHS08, GHS07, GHS09 **Signal word**: Warning **Hazard statement(s):** H302 – Harmful if swallowed. H373 – May cause damage to organs through prolonged or repeated exposure. H317 – May cause an allergic skin reaction. **Precautionary statement(s):** P280 - Wear protective gloves/ P260 - Do not breathe spray. P264 – Wash hands thoroughly after handling P270 – Do no eat, drink or smoke when using this product P272 - Contaminated work clothing should not be allowed out of the workplace. P301 + P312 – IF SWALLOWED: Call a POISON CENTER or doctor/physician if you feel unwell. P330 - Rinse mouth. P302 + P352 – IF ON SKIN: Wash with plenty of soap and water. P314 - Get medical advice/attention if you feel unwell. P333 + P313 – If skin irritation or rash occurs: Get medical advice/attention. P363 – Wash contaminated clothing before reuse. P501 - Dispose of contents/container to …
Additional C&L proposal	Not required	Not required	Not required
Agreed EU endpoints			
AOEL systemic	0.05 mg/kg bw/d	0.11 mg/kg bw/d	~~0.05~~ 0.017 mg/kg bw/d
Reference	EFSA Journal 2015;	EFSA Scientific Re-	Addendum to Annex B.5 mammalian toxicology,

<table>
<tr><th></th><th>Florasulam</th><th>Diflufenican</th><th>Flufenacet</th></tr>
<tr><td></td><td>13(1), 3984</td><td>port (2007) 122, 1-84, Conclusion on the peer review of diflufenican</td><td>January 2001
7469/VI/98-Final 3 July 2003 Review report for the active substance flufenacet</td></tr>
<tr><td colspan="4">Conditions to take into account/critical areas of concern with regard to toxicology</td></tr>
<tr><td></td><td>Operators
Use: cereals, maize, pasture and new leys; 1 L container, tractor mounted equipment, application rate 0.125L/ha

Exposure estimates (model): % of AOEL

- with UK-POEM
Without PPE:
43
PPE (gloves during mixing/loading):
29

- with German model
Without PPE:
2.7
PPE (gloves during mixing/loading):
1.7

Workers
<1% of AOEL even without PPE (worker wearing shoes, socks, long-sleeved shirt and long trousers) (Hoernicke, 1998)

Bystanders and residents[a]
<1% of AOEL (Martin, 2008)

(a): It is noted that, even for active substances still covered by the data requirements under Commission Regulation (EU) 545/2011, the approval criteria under Regulation (EC) No 1107/2009 are applicable, implying a risk</td><td>Operator:

Application in cereals
POEM % of AOEL (tractor, 0.12 kg a.s./ha, without PPE) 19.7%
(tractor, 0.12 kg a.s./ha, PPE = gloves during mix ing/loading) 19.5%
BBA (tractor, 0.12 kg a.s./ha, without PPE) 3.3%
(tractor, 0.12 kg a.s./ha, PPE = gloves during mixing/loading) 3.2%

Worker:
According to van Hemmen et al, 2002 and using EUROPOEM dislodgeable foliar residue and transfer coefficient values : 3 % of AOEL (no PPE)

Bystender:
According to Lloyd and Bell, 1983: 0.1% of AOEL

Not required</td><td>Operator exposure
Rate: 0.6 kg as/ha (corn, soybeen, sunflower)
<table><tr><td></td><td colspan="2">German</td><td colspan="2">Uk</td></tr><tr><td></td><td>No PPE</td><td>With PPE</td><td>No PPE</td><td>With PPE</td></tr><tr><td>Total absorbes dose (mg/kg bw/d</td><td>0.0817</td><td>0.0065</td><td>0.719</td><td>0.071</td></tr><tr><td>% AOEL syst</td><td>480.7</td><td>38.5</td><td>4229.4</td><td>417.6</td></tr></table>Rate: 0.24 kg as/ha (cereals)
<table><tr><td></td><td colspan="2">German</td><td colspan="2">Uk</td></tr><tr><td></td><td>No PPE</td><td>With PPE</td><td>No PPE</td><td>With PPE</td></tr><tr><td>Total absorbes dose (mg/kg bw/d</td><td>0.0327</td><td>0.0026</td><td>0.2872</td><td>0.0282</td></tr><tr><td>% AOEL syst</td><td>192.4</td><td>15.5</td><td>1689.4</td><td>165.9</td></tr></table>should pay particular attention to the protection of operators</td></tr>
</table>

	Florasulam	Diflufenican	Flufenacet
	~~assessment for vulnerable groups, which include residents. Therefore an assessment of the residential exposure according to the intended use of the plant protection product has to be provided.~~ Not required.		

6.3 Toxicological Evaluation of Plant Protection Product

A summary of the toxicological evaluation for CHR/H/FDF 574 SC 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 CHR/H/FDF 574 SC

Type of test, species, model system (Guideline)	Result	Acceptability	Classification (acc. to the criteria in Reg. 1272/2008)	Reference
LD_{50} oral, rat (calculation method)	~~1914.4~~ 1915.7 mg/kg bw	Yes	Acute Tox.4, H302	K. Żero
LC_{50} inhalation, rat (calculation method)	> 20 mg/L air	Yes	None	K. Żero
Skin irritation, (calculation method)	Non Irritant	Yes	None	K. Żero
Eye irritation, (calculation method)	Non Irritant	Yes	None	K. Żero
Skin sensitisation, (calculation method)	Sensitizatie	Yes	Skin Sens.1, H317	K. Żero
~~Specific target organ toxicity - single exposure (calculation method)~~	~~May cause damage to organs~~	~~-~~	~~STOT RE 2, H373.~~	~~K. Żero~~
Supplementary studies for combinations of plant protection products	No data – not required	-	None	K. Żero

Table 6.3-2: Additional toxicological information relevant for classification/labelling of CHR/H/FDF 574 SC

	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	Flufenacet (25.99%)	Acute Tox. 4, H302 (the ATE of the mixture =	Reg. 1272/2008	Acute Tox. 4, H302 Skin Sens. 1, H317

	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)
substance(s) (relevant for classification of product)		1916) Skin Sens. 1, H317 the ATE of the mixture = 1924) STOT RE 2, H373 (criteria ≥10%) Aquatic Acute 1, H400 Aquatic Chronic 1, H410*		STOT RE 2, H373
Toxicological properties of non-active substance(s) (relevant for classification of product)	Detailed information provided in Part C			
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.

zRMS comment:	**5-OH florasulam, ASTCA, TSA** 5-OH hydroxyl florasulam was assessed at EU level for toxicity and based on the studies it is not genotoxic and not acutely toxic by oral route. ASTCA and TSA were assessed at EU level for toxicity and based on the studies available these are not genotoxic. Results of these studies are included in the EFSA Conclusions (EFSA Journal 2015; 13(1):3984). **FOE sulfonic acid** The metabolites FOE sulfonic acid was screened for genotoxicity activity by the following data package of *in vitro* genotoxicity studies: Ames test, gene mutation test with mammalian cells and *in vitro* mammalian cell micronucleus test. The results are negative. It can be concluded that FOE sulfonic acid is considered to be non-genotoxic.

6.4.1 ASTCA

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

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

Type of test, species (Guideline)	Result	Acceptability	Reference*
Salmonella Escherichia coli/ Mammalian – microsome Reverse Muta-	non-genotoxic	Yes	Michael S. Mecchi (13 March 2008)

Type of test, species (Guideline)	Result	Acceptability	Reference*
tion Assay Preincubation Method with a Confirmatory Assay with ASTCA Metabolite of Florasulam (OECD 471 & 472)			
Evaluation of Florasulam ASTCA Metabolite In The Chinese Hamster Ovary Cell/Hypoxanthine-Guanine-Phosphoribosyl Transferase (CHO/HGPRT) Forward Mutation Assay. (OECD 476)	Non-genotoxic	Yes	M.R. Schisler, B.S. and D.R. Geter Ph.D. (30 April 2008)
Evaluation Of Florasulam ASTCA Metabolite In An In Vitro Chromosomal Aberration Assay Utilizing Rat Lymphocytes (OECD 473)	Non-genotoxic	Yes	M.R. Schisler, B.S., K.M. Kleinert B.S., D.R. Geter Ph. D. (2008)

* indicates that a study was reviewed at EU level

6.4.2 TSA

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

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

Type of test, species (Guideline)	Result	Acceptability	Reference*
Bacterial Reverse Mutation Test of TSA Metabolite of Florasulam using Salmonella typhimurium. (OECD 471)	non-genotoxic	Yes	Nagane R.M. (2011)
In vitro Mammalian Cell Gene Forward Mutation Test at the HGPRT Locus of the Chinese Hamster Ovary (CHO)-K1 Cell Line using TSA metabolite of florasulam. (OECD 476)	Non-mutagenic	Yes	Nagane R.M. (2011)
In vitro Mammalian Chromosome Aberration Test of TSA Metabolite of Florasulam in Human Peripheral Blood Lymphocytes. (OECD 473)	Non-genotoxic	Yes	Nagane R.M. (2011)

* indicates that a study was reviewed at EU level

6.4.3 5-OH-Florasulam

An overview of the results of the accepted toxicological studies for groundwater metabolite 5-OH-Florasulam is given in the following table. Full summaries of studies on the metabolite that have not previously been considered within an EU peer review process are described in detail in Appendix 2 (A 2.11 Other/Special Studies).

Table 6.4-3: Summary of the results of toxicity studies for 5-OH Florasulam

~~Type of test, species (Guideline)~~	~~Result~~	~~Acceptability~~	~~Reference*~~
~~Acute Oral Toxicity (OECD 401)~~	~~> 5000 mg~~		
~~Bacterial Reverse Mutation Test of~~	~~non-genotoxic~~		~~Bowles, A.J. (2011)~~

~~Type of test, species (Guideline)~~	~~Result~~	~~Acceptability~~	~~Reference*~~
~~TSA Metabolite of Florasulam using Salmonella typhimurium. (OECD 471)~~			
~~In vitro Mammalian Cell Gene Forward Mutation Test at the HGPRT Locus of the Chinese Hamster Ovary (CHO) K1 Cell Line using TSA metabolite of florasulam. (OECD 476)~~	~~Non-mutagenic~~		~~Linscombe, V.A; (2011)~~
~~In vitro Mammalian Chromosome Aberration Test of TSA Metabolite of Florasulam in Human Peripheral Blood Lymphocytes. (OECD 473)~~	~~Non-genotoxic~~		~~Linscombe, V.A.; (2011)~~

~~* indicates that a study was reviewed at EU level~~

Type of test, species (Guideline)	Result	Acceptability	Reference*
Acute Oral Toxicity (OECD 401)	> 5000 mg	Yes	
5-Hydroxy Florasulam: Reverse Mutation Assay "Ames Test" Using Salmonella Typhimurium And Escherichia Coli. (OECD 471)	non-genotoxic	Yes	Bowles, A.J. (2000)
Evaluation Of 5-Hydroxy-Florasulam In The Chinese Hamster Ovary Cell/Hypoxanthine-Guanine-Phosphoribosyl Transferase (CHO/HGPRT) Forward Mutation Assay. (OECD 476)	Non-mutagenic	Yes	V. A. Linscombe, MLT (A.M.T.), CLSp (CG) M. R. Schisler, B.S. D.J. Beuthin,(2000)
Evaluation Of 5-Hydroxy-Florasulam In An In Vitro Chromo-somal Aberration Assay Utilizing Rat Lymphocytes (OECD 473)	Non-genotoxic	Yes	V. A. Linscombe, MLT (A.M.T.), CLSp (CG) K. M. Jackson, A.A.S. K. E. Engle, A.A.S. (2000)

zRMS comment:	Genotoxic and acute data on 5-OH florasulam: - Acute oral in rat – LD50 >5000 mg/kg bw – K. J. Brooks et al 2000 - Ames test – negative- A. J. Bowles 2000 - In vitro chromosome aberration in rat lymphocytes – negative – V. A. Linscombe, Jackson and Eagle; 2000 - In vitro Chinese Hamster ovary gene mutation assay – negative – V. A. Linscombe, Schisler and Beuthin Studies evaluated in Florasulam RAR volume B6 July 2013

6.4.4 FOE sulfonic acid

Type of test, species (Guideline)	Result	Acceptability	Reference*
Bacterial reverse mutation assay (OECD 471)	Non-mutagenic	Yes	Herbold, 2000 * M-019064-01-1
In vitro evaluation of Flufenacet oxalate, Flufenacet sulfonic acid, Trifluoroethanesulfonic acid, Tri-fluoroacetic acid and Flufenacet	Non-mutagenic	Yes	J.Antonik, 2016.;. Study Number: K81/JA/01.

Type of test, species (Guideline)	Result	Acceptability	Reference*
methylsulfone genotoxicity using the micronucleus assay (MNA) (OECD 487)			
In vitro Mammalian Cell Gene Mutation test (OECD 490)	Non-genotoxic	Yes	J.Antonik; Study number: K82/JA/01
Rat, Acute Oral	LD50> 2000 mg/kg	Yes	xxxxxxxxxx 1998, M-004749-01-1*
Rat, Plasma kinetics and excretion	Low oral absorption (<10%) rapid renal clearance (i.v: t1/2 □ 30 min)	Yes	xxxxxxxxxxxx M-042251-01-1*

* indicates that a study was reviewed at EU level

~~FOE 5043 sulfonic acid was initially investigated using the salmonella/microsome plate incorporation test (Salmonella/microsome test with FOE 5043 sulfonic acid. Report Bayer PH 29473. GLP. Unpublished. B. Herbold, 2000.) for point mutagenic effects in doses of up to and including 5000 µg per plate on five Salmonella typhimurium LT2 mutants. These comprised the histidine auxotrophic strains TA 1535, TA 100, TA 1537, TA 98 and TA 102. The independent repeat was performed as preincubation for 20 minutes at 37°C. Other co ditions remained unchanged.~~
~~Doses up to and including 5000µg per plate did not cause any bacteriotoxic effects : total bacteria counts remained unchanged and no inhibition of growth was observed. Evidence of mutagenic ac tivity of FOE 5043 sulfonic acid was not seen. No biologically relevant increase in the mutant co unt, in comparison with the negative controls was observed.~~

~~The positive controls sodium azide, nitrofurantoin, 4 nitro 1,2 phenylene diamine, cumene hydro peroxyde and 2 aminoanthracene had a marked mutagenic effect, as was seen by a biologically relevant increase in mutant colonies compared to the corresponding negative controls.~~

~~Additional two studies were provided by PUH Chemirol:~~

~~- In vitro evaluation of Flufenacet oxalate, Flufenacet sulfonic acid, Trifluoroethanesulfonic acid, Trifluoroacetic acid and Flufenacet methylsulfone genotoxicity using the micronucleus assay (MNA). J.Antonik, 2016.; SELVITA. Study Number: K81/JA/01.Method: OECD 487~~
~~- In vitro Mammalian Cell Gene Mutation test (OECD 490) – genotoxicity determination of Flufena cet oxalate, Flufenacet sulfonic acid, Trifluoroethanesulfonic acid and Trifluoroacetic acid by Mo use Lymphoma Assay. J.Antonik; 2016; J.Antonik; Study number: K82/JA/01; SELVITA; OECD 490~~

~~The formation of MN is a consequence of chromosomal breakage and/or spindle fiber dysfunction induced by clastogens and/or aneuploidogens. The present study was performed in accordance with the OECD 487 and under GLP requirements. In order to assess genotoxic potential CHO K1 cells were exposed to test items (Flufenacet oxalate, Flufenacet sulfonic acid, Trifluoroethanesulfonic acid, Trifluoroacetic acid and Flufenacet methylsulfone) and appropriate reference items in system with (+S9) and without (S9 short and extended treatment) an exogenous metabolic activation. Stati stical analysis of the MN frequency and binucleate cells with MN was performer using the Chi square test with Yates' correction. To examine the dose response relationship in frequencies of the micronuclei Chi-square test for trend was performed.~~
~~None of tested concentration of Flufenacet oxalate, Flufenacet sulfonic acid, Trifluoroethanesulfo nic acid, Trifluoroacetic acid and Flufenacet methylsulfone exhibit a statistically significant increa se in MN frequency compared with the concurrent negativecontrol (P>0.05, T bles IX XIII, Figure I VII). Chi square test for trend revealed no dose related increase in MN frequency (P>0.05).~~
~~Results for positive reference items (mitomycin C and cyclophosphamide) demonstrated reprodu cibility and sensitivity of system.~~

~~In summary, the present research has demonstrated that items Flufenacet oxalate, Flufenacet sulfonic acid, Trifluoroethanesulfonic acid, Trifluoroacetic acid and Flufenacet methylsulfone did not produce dose dependent genetic toxicity in the CHO K1 cells.~~

~~Mutagenic potential of Flufenacet oxalate, Flufenacet sulfonic acid, Trifluoroethanesulfonic acid and Trifluoroacetic acid was evaluated trough Mouse Lymphoma Assay (MLA) in L5178Y cells. Tested items were analyzed in MLA,~~

in the presence and absence of exogenous metabolic activa tion.Obtained results have shown that tested item did not exceed MF above a value termed as
Global Evaluation Factor 126 ×10=6 in any of the tested doses both in the presence and absence of S9 exogenous activation system.
Obtained results indicate that tested items (Flufenacet oxalate, Flufenacet sulfonic acid, Trifluo roethanesulfonic acid and Trifluoroacetic acid) or their metabolic derivatives were not positive in Mouse Lymphoma Assay under the protocol described and according to the acceptability criteria defined in OECD guideline 490 and SPB 19.

Conclusion:

FOE 5043 sulfonic acid is considered to bee non mutagenic and have no genotoxicity potential in all of these assays.
FOE 5043 sulfonic acid plasmakinetics and excretion in urine in a rat study with single oral vs in travenous admin istration. Report PH 30052. GLP. Unpublished. xxxxxxxxxxxxxxx, 2000.
A study for the comparison of the plasmakinetics and excretion in urine after the single oral versus intravenous ad ministration of FOE 5043 sulfonic acid, a metabolite of FOE 5043, was conducted in male Wistar rats.
The treatment and observation time of the study has been designed to follow the principles of the following guide lines : OECD Guideline for Testing of Chemicals No 423.
The oral AUC was despite the 10 fold higher dose slightly lower than the intravenous AUC, which also argued in favour of low oral absorption.
The t1/2 after iv administration was short (about 30mn) which suggests the major role of the renal clearance.
FOE 5043 Sulfonsäure : study for acute oral toxicity in rats. Report 27137. GLP. Unpublished. xxxxxxxxxxx, 1998.

A study for acute oral toxicity in male and female Wistar rats was conducted with the test substance FOE 5043 Sul fonsäure (soil metabolite of FOE 5043).
The method used complied with the OCDE guideline for Testing of Chemicals; section4: Health effects, No. 401 – "Acute oral Toxicity".
Clinical findings :
Doses of 500 and 2000 mg/kg body weight were tolerated by male and female rats without mortali ties and 500mg/kg b.w. also without clinical signs. At 2000 mg/kg b.w. in both sexes diarrhea oc curred and anuses were moistened. The signs observed started 4 hours and lasted up to 5 hours after administration.
Body weight and body weight gain were not affected by treatment.
The acute oral LD50 of FOE 5043 sulfonic acid is > 2000 mg /kg b.w.

Conclusion on toxicological significance of the metabolite FOE sulfonic acid:
The goal of the additional physico chemical and biological experiments which were requested from the applicant was to demonstrate that the metabolite M2 (FOE sulfonic acid) was poorly absorbed orally, and had a low potential toxicity.

Based firstly on the physical properties that show a high hydrosolubility which suggests a low bio logical absorp tion,
The solubility in water is 55g/l at 20°C at pH 4 to 9 ; under the same conditions, its Kow is 0.0019, leading to a log Kow = -2.72 ; the pKa of sulfonic acid is <1 and secondly on the biological investigations that show poor biological disposition and low toxicity, the metabolite FOE 5043 sulfonic acid is considered of no toxicological relevance.

6.5 Dermal Absorption (KCP 7.3)

A summary of the dermal absorption rates for the active substances in CHR/H/FDF 574 SC are presented in the following table.

Table 6.5-1: Dermal absorption rates for active substances in CHR/H/FDF 574 SC

	Florasulam		Diflufenican		Flufenacet	
	Value	**Reference**	**Value**	**Reference**	**Value**	**Reference**
Concentrate	50% (nominal content of florasulam in CHR/H/FDF 574 SC is 12 g/L and	Guidance on Dermal Absorption EFSA, EFSA Journal 2017;15(6):4873	10%	Guidance on Dermal Absorption EFSA, EFSA Journal 2017;15(6):4873	10%	Guidance on Dermal Absorption EFSA, EFSA Journal 2017;15(6):4873

	Florasulam		Diflufenican		Flufenacet	
	Value	**Reference**	**Value**	**Reference**	**Value**	**Reference**
	therefore this active substance should be treat like dilution.)					
Dilution	50%		50%		50%	

6.5.1 Justification for proposed values - florasulam

No data on dermal absorption for florasulam in CHR/H/FDF 574 SC is available. Justifications for default values according to Guidance on Dermal Absorption (EFSA Journal 2017; 15(6):4873) are presented in the following table.

Table 6.5-2: Default dermal absorption rates for florasulam

	Value	Justification for value	Acceptability of justification
Concentrate	50%	A default dermal absorption value of 50% may be applied for concentrated products that are water-based/dispersed or solid-formulated, because nominal content of florasulam in CHR/H/FDF 574 SC is 12 g/L and therefore this active substance should be treat like dilution.	Yes
Dilution	50%	A default dermal absorption value of 50% may be applied for (in use) dilutions water-based/dispersed or solid-formulated.	Yes

6.5.2 Justification for proposed values – diflufenican

No data on dermal absorption for diflufenican in CHR/H/FDF 574 SC is available. Justifications for default values according to Guidance on Dermal Absorption (EFSA Journal 2017; 15(6):4873) are presented in the following table.

Table 6.5-3: Default dermal absorption rates for diflufenican

	Value	Justification for value	Acceptability of justification
Concentrate	10%	A default dermal absorption value of 10% may be applied for concentrated products that are water-based/dispersed or solid-formulated.	Yes
Dilution	50%	A default dermal absorption value of 50% may be applied for (in use) dilutions water-based/dispersed or solid-formulated.	Yes

6.5.3 Justification for proposed values - flufenacet

No data on dermal absorption for flufenacet in CHR/H/FDF 574 SC is available. Justifications for default values according to Guidance on Dermal Absorption (EFSA Journal 2017; 15(6):4873) are presented in the following table.

Table 6.5-4: Default dermal absorption rates for flufenacet

	Value	Justification for value	Acceptability of justification
Concentrate	10%	A default dermal absorption value of 10% may be applied for concentrated products that are water-based/dispersed or solid-formulated.	Yes
Dilution	50%	A default dermal absorption value of 50% may be applied for (in use) dilutions water-based/dispersed or solid-formulated.	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	CHR/H/FDF 574 SC		
Formulation type	SC		
Category	Herbicide		
Active substance(s) (incl. content)	**Florasulam** 12 g/L	**Diflufenican** 250 g/L	**Flufenacet** 312 g/L
AOEL systemic	0.05 mg/kg bw/d	0.11 mg/kg bw/d	0.017 mg/kg bw/d
Inhalation absorption	100%	100%	100%
Oral absorption	100%	100%	100%
Dermal absorption	Concentrate: 50 % Dilution: 50 %	Concentrate: 10 % Dilution: 50 %	Concentrate: 10 % Dilution: 50 %

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 is given in Part B, Section 0.

6.6.2 Operator exposure (KCP 7.2.1)

6.6.2.1 Estimation of operator exposure

A summary of the exposure models used for estimation of operator exposure to the active substances during application of CHR/H/FDF 574 SC 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 (acute exposure) and **Błąd! Nie można odnaleźć źródła odwołania.** (longer term exposure). Detailed calculations are in 0.

Table 6.6-2: Exposure models for intended uses

Critical use(s)	CHR/H/FDF 574 SC (max. 0.4 L product/ha)
Model(s)	Guidance on the assessment of exposure of operators, workers, residents and bystanders in risk assessment for plant protection products; EFSA Journal

	2014;12(10):3874 calculator version: 30/03/2015

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

		Florasulam		Diflufenican		Flufenacet	
Model data	**Level of PPE**	**Total absorbed dose (mg/kg/day)**	**% of systemic AOEL**	**Total absorbed dose (mg/kg/day)**	**% of systemic AOEL**	**Total absorbed dose (mg/kg/day)**	**% of systemic AOEL**
Tractor mounted boom spray application outdoors to low crops Application rate: 0.4 L prod./ha							
"EFSA Model" version 30.03.2015	no PPE*	0.0250153	50.03	0.0567433	51.58	0.0675940	397.61
	+ type of PPE (e.g. Gloves + work wear during mixing/loading)	0.0007921	1.58	0.0106982	9.73	0.0133080	78.28
	Work wear (ML&A)	0.014	28.02	0.03511	31.93	0.04206	247.45
	Work wear (ML&A) + gloves (ML)	0.00063	1.26	0.00733	6.67	0.00911	53.61

6.6.2.2 Measurement of operator exposure

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

6.6.3 Worker exposure (KCP 7.2.3)

6.6.3.1 Estimation of worker exposure

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 CHR/H/FDF 574 SC according to the critical use(s). Outcome of the estimation is presented in Table 6.6-5. Detailed calculations are in 0.

Table 6.6-4: Exposure models for intended uses

Critical use(s)	CHR/H/FDF 574 SC (max. 0.4 L product/ha)
Model	Guidance on the assessment of exposure of operators, workers, residents and bystanders in risk assessment for plant protection products; EFSA Journal 2014;12(10):3874 calculator version: 30/03/2015

Table 6.6-5: Estimated worker exposure

		Florasulam		Diflufenican		Flufenacet	
Model data	**Level of PPE**	**Total absorbed dose (mg/kg/day)**	**% of systemic AOEL**	**Total absorbed dose (mg/kg/day)**	**% of systemic AOEL**	**Total absorbed dose (mg/kg/day)**	**% of systemic AOEL**
Number of applications and application rate:		0.0048 kg a.s./ha		0.1 kg a.s./ha		0.1248 kg a.s. / ha	
~~8~~ 2 hours/day(1), ~~TC: 0.25 cm²/person/h (2)~~ Body weight: 60 kg	no PPE(3) TC 12500 cm^2/hr	0.003000	6.00	0.0625	56.82	0.0780	458.82
	~~with PPE(4)~~ work wear TC 1400 cm^2/hr	0.0003360	0.67	0.0070	6.36	0.008736	51.39

According to Guidance on Pesticides Exposure Assessment of Operators, Workers, Residents and Bystanders, (EFSA Journal 2014;12(10):3874) to the calculation used the value of ~~2500~~ 1400 transfer coefficient (TC (cm^2/h) arms, body and legs covered - workwear; bare hands) and ~~8~~ 2 hours work/day (only crop inspection and irrigation-type). Having regard to the above values, the predicted exposure values for ~~CHR/H/PENDIF~~ CHR/H/FDF 574 SC without PPP are ~~above~~ below100% of systemic AOEL and therefore exposure of the worker with using PPP is acceptable

6.6.3.2 Refinement of generic DFR value (KCP 7.2)

Not required

6.6.3.3 Measurement of worker exposure

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

6.6.4 Resident and bystander exposure (KCP 7.2.2)

6.6.4.1 Estimation of resident and bystander exposure

Table 6.6.-8 shows the exposure model(s) used for estimation of bystander and resident exposure to florasulam, diflufenican and flufenacet. Outcome of the estimation is presented in 9. Detailed calculations are in 0.

Table 6.6-6: Exposure models for intended uses

Critical use(s)	CHR/H/FDF 574 SC (max.0.4L product/ha)
Model	"EFSA Model" version 30.03.2015

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

	Florasulam		Diflufenican		Flufenacet		Flufenacet with 5 meters buffer zone	
Model data	**Total absorbed dose (mg/kg/day)**	**% of systemic AOEL**	**Total absorbed dose (mg/kg/day)**	**% of systemic AOEL**	**Total absorbed dose (mg/kg/day)**	**% of systemic AOEL**	**Total absorbed dose (mg/kg/day)**	**% of systemic AOEL**
Tractor mounted boom spray application outdoors to low crops Application rate: 0.4 L prod./ha								
Bystanders (adult) Drift rate: 2.77 % (1 m) Body weight: 60 kg	0.0004580	0.92	0.0049802	4.43	0.0061582	36.22	0.0055554	32.68
Bystanders (children) Drift rate: 2.77 % (1 m) Body weight: 10 kg	0.0015989	3.20	0.0120885	10.33	0.0148210	87.18	0.0128693	75.70
Residents (adult) Drift rate: 2.77 % (1 m) Body weight: 60 kg	0.0004580	0.92	0.0049802	4.43	0.0061582	36.22	0.0055554	32.68
Residents (children) Drift rate: 2.77 % (1 m) Body weight: 10 kg	0.0015989	3.20	0.0120885	10.33	0.0148210	87.18	0.0128693	75.70

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 florasulam, diflufenican and flufenacet 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

The product is a mixture of three active substances.

6.6.5.1 Exposure assessment of florasulam, diflufenican and flufenacet in CHR/H/FDF 574 SC

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: Risk assessment from combined exposure

Application scenario	Active ingredient	Estimated exposure / AAOEL (HQ)
Operators – work wear during mix/loading & application + gloves during mix/loading	Florasulam	0.0126
	Diflufenican	0.0667
	Flufenacet	0.5361
	Cumulative risk operators (HI)	0.615
Operators –with PPE (glove + work wear during mix/loading)	Florasulam	0.0158
	Diflufenican	0.0973
	Flufenacet	0.7828
	Cumulative risk operators (HI)	**0.8959**
Workers – with PPE	Florasulam	0.0067
	Diflufenican	0.0636
	Flufenacet	0.5139
	Cumulative risk workers (HI)	**0.5842**
Bystander – child with 5 meters buffer zone	Florasulam	0.0320
	Diflufenican	0.1033
	Flufenacet	0.7570
	Cumulative risk bystander – child (HI)	**0.8923**
Bystander - adult with 5 meters buffer zone	Florasulam	0.0092
	Diflufenican	0.0443
	Flufenacet	0.3268
	Cumulative risk bystander – adult (HI)	**0.3803**
Resident – child with 5 meters buffer zone	Florasulam	0.0320
	Diflufenican	0.1033
	Flufenacet	0.7570
	Cumulative risk bystander – child (HI)	**0.8923**
Resident - adult with 5 meters buffer zone	Florasulam	0.0092
	Diflufenican	0.0443
	Flufenacet	0.3268
	Cumulative risk bystander – adult (HI)	**0.3803**

The Hazard Index is < 1. Thus, combined exposure to all active substances in CHR/H/FDF 574 SC is not expected to present a risk for operators, workers, residents and bystanders. No further refinement of the assessment is required.

Appendix 1 Lists of data considered in support of the evaluation

List of data submitted by the applicant and relied on

Data point	Author(s)	Year	Title Company Report No. Source (where different from company) GLP or GEP status Published or not	Vertebrate study Y/N	Owner
KCP 7.1.1 KCP 7.1.2 KCP 7.1.4 KCP 7.1.5 KCP 7.1.6 KCP 7.1.7	K. Żero	2022	Toxicological classification of product CHR/H/FDF 574 SC based on calculation method taking into consideration health hazards of constituent substances; Chemirol Sp. z o.o. Non GLP Unpublished	N	Chemirol Sp. z o.o.
KCP 7.0/01	J. Antonik	2016	In vitro evaluation of Flufenacet oxalate, Flufenacet sulfonic acid, Trifluoroethanesulfonic acid, Trifluoroacetic acid and Flufenacet methylsulfone genotoxicity using the micronucleus assay (MNA). Selvita S.A. Park Life Science, Poland Study code: K81/JA/01 GLP Unpublished	N	Chemirol
KCP 7.0/02	J.Antonik	2016	In vitro Mammalian Cell Gene Mutation test (OECD 490) - genotoxicity determination of Flufenacet oxalate, Flufenacet sulfonic acid, Trifluoroethanesulfonic acid and Trifluoroacetic acid by Mouse Lymphoma Assay Selvita S.A. Park Life Science, Poland Study code: K82/JA/01 GLP Unpublished	N	Chemirol

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 7/01	xxxxxxxxxxxxxxxx	2000	DOE 5043 sulfonic acid plasmakinetics and excreation in urine in a rat study with single oral vs intravenous PH 30052 GLP Unpublished	Y	Bayer
KCP 7/02	xxxxxxxxxxxxxxxx	1998	FOE 5043 Sulfosaure: study for acute oral toxicity in rats 2137 GLP Unpublished	Y	Bayer
KCP 7/03	B. Herbold ~~fmecchi~~	2000	Salmonella/microsome test with FOE 5043 sulfonic acid PH 29473 GLP Unpublished	N	Bayer
KCP 7 /04	Michael, S.M.	2008	Salmonella Escherichia coli/ Mammalian-Microsome Reverse Mutation Assay Preincubation Method with a Confirmatory Assay with ASTCA Metabolite of Florasulam Covance Laboratories Inc DAS Report No.: 071120 (Accession Number) 257169 GLP/GEP (Y/N): Y Published: N	~~Y~~ N	DAS
KCP 7/05	Schisler, M.R. and Geter, D.R.	2008	Evaluation of Florasulam ASTCA Metabolite in the Chinese Hamster ovary Ell/hypoxanthine-guanine-phosphoribosyl Transferase (cho/hgprt) Forward Mutation Assay Toxicology & Environmental Research and Consulting DAS Report No.: 071133 (Accession Number) 25174 GLP/GEP: Y Published: N	~~Y~~ N	DAS
KCP 7/06	Schisler, M.R, Kleinert, K.M. and Geter, D.R.	2008	Evaluation of Florasulam ASTCA Metabolite in an in vitro Chromosomal Aberration Assay Utilizing Rat Lymphocytes Toxicology & Environmental	~~Y~~ N	DAS

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
			Research and Consulting DAS Report No.: 071132 (Accession Number) 257142 GLP/GEP: Y Published: No		
KCP 7/07	Nagane, R.M.	2011	Bacterial Reverse Mutation Test of TSA Metabolite of Florasulam using Salmonella typhimurium Jai Research Foundation DAS Report No.: 110432 (Accession Number) 2010127 GLP: Y Published: N	~~Y~~ N	DAS
KCP 7/08	Nagane, R.M.	2011	In vitro Mammalian Cell Gene Forward Mutation Test at the hgprt Locus of the Chinese Hamster Ovary (CHO)-K1 Cell Line using TSA metabolite of florasulam JAI Research Foundation DAS Report No: 110430 (Accession Number) 2010107 GLP/GEP: Y Published: N	~~Y~~ N	DAS
KCP 7/09	Nagane, R.M.	2011	In vitro Mammalian Chromosome Aberration Test of TSA Metabolite of Florasulam in Human Peripheral Blood Lymphocytes Jai Research Foundation DAS Report No: 110431 (Accession Number) 2010112 GLP/GEP: Y Published: N	~~Y~~ N	DAS
KCP 7/10	Bowles, A.J.	~~2011~~ 2000	5-Hydroxy Florasulam: Reverse Mutation Assay "Ames Test" Using Salmonella Typhimurium And Escherichia Coli. Safepharm Laboratories Limited P.O. Box No. 45 DERBY, DE1 2BT, UK GLP Unpublished	N	DAS
KCP 7/11	V. A. Linscombe, MLT (A.M.T.), CLSp (CG) M. R. Schisler, B.S. D.J. Beuthin,	~~2011~~ 2000	**Evaluation Of 5-Hydroxy-Florasulam In The Chinese Hamster Ovary Cell/Hypoxanthine-Guanine-Phosphoribosyl Transferase (CHO/HGPRT) Forward Mutation Assay**	N	DAS

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
	A.S.		Toxicology & Environmental Research and Consulting The Dow Chemical Company Midland, Michigan 48674 GLP Y		
KCP 7/12	V. A. Linscombe, MLT (A.M.T.), CLSp (CG) K. M. Jackson, A.A.S. K. E. Engle, A.A.S.	2000	**Evaluation Of 5-Hydroxy-Florasulam In An *In Vitro* Chromosomal Aberration Assay Utilizing Rat Lymphocytes** Toxicology & Environmental Research and Consulting The Dow Chemical Company Midland, Michigan 48674 **GLP** **Y**	N	DAS
KCP 7/13	-	~~2011~~ 2000	**5-Hydroxy-Florasulam: Acute oral toxicity study in Fischer 344 Rats** **GLP** **Y**	Y	DAS

Appendix 2 Detailed evaluation of the studies relied upon

A 2.1 Statement on bridging possibilities

Comments of zRMS:	Not applicable.

A 2.2 Acute oral toxicity (KCP 7.1.1)

Comments of zRMS:	The plant protection product CHR/H/FDF 574 SC was classified by calculation method as described in Regulation (EC) No 1272/2008. The product is classified as **Acute Tox. 4, H302**.

Reference: 7.1.1

Report: Toxicological classification of product CHR/H/FDF 574 SC based on calculation method taking into consideration health hazards of constituent substances; 2022; according to Part C, appendix 2

According to point 7.1.1 of Part A of Annex to the Commission Regulation (EU) No 284/2013 as regards the data requirements for plant protection products:
" A test for acute oral toxicity shall be carried out, unless the applicant can justify an alternative approach under Regulation (EC) No 1272/2008. In the latter case, acute oral toxicity of all components shall be provided or reliably predicted with a validated method. Consideration shall be given to the possible effects of components on the toxic potential of the total mixture."

The complete composition of the formulation with the classification of individual ingredients is available in part C.
Due to the fact, that all components of the formulation CHR/H/FDF 574 SC are known, the acute oral toxicity test is not necessary.

Materials and methods

We use the summation method using the formula:

$$ATE_{mix} = \frac{100}{\sum_{i=1}^{n} \frac{C_i}{ATE_i}}$$

Where:

- Ci - concentration of ingredient i (% w/w or % v/v)
- i – the individual ingredient from 1 to n
- n – the number of ingredients
- ATEi - Acute Toxicity Estimate of ingredient i.

We use the table:

Table 3.1.2
Conversion from experimentally obtained acute toxicity range values (or acute toxicity hazard categories) to acute toxicity point estimates for classification for the respective routes of exposure.

Exposure routes	Classification Category or experimentally obtained acute toxicity range estimate	Converted acute toxicity point estimate (see Note 1)
Oral (mg/kg body-weight)	0 < Category 1 ≤ 5 5 < Category 2 ≤ 50	0,5 5

	50 < Category 3 ≤ 300 300 < Category 4 ≤ 2 000	100 500
Dermal (mg/kg bodyweight)	0 < Category 1 ≤ 50 50 < Category 2 ≤ 200 200 < Category 3 ≤ 1 000 1 000 < Category 4 ≤ 2 000	5 50 300 1 100
Gases (ppmV)	0 < Category 1 ≤ 100 100 < Category 2 ≤ 500 500 < Category 3 ≤ 2 500 2 500 < Category 4 ≤ 20 000	10 100 700 4 500
Vapours (mg/l)	0 < Category 1 ≤ 0,5 0,5 < Category 2 ≤ 2,0 2,0 < Category 3 ≤ 10,0 10,0 < Category 4 ≤ 20,0	0,05 0,5 3 11
Dust/mist (mg/l)	0< Category 1 ≤ 0,05 0,05 < Category 2 ≤ 0,5 0,5 < Category 3 ≤ 1,0 1,0 < Category 4 ≤ 5,0	0,005 0,05 0,5 1,5

Note 1
These values are designed to be used in the calculation of the ATE for classification of a mixture based on its components and do not represent test results.

~~1.1. By ingestion (Acute Tox. 4, H302; Acute Tox. 3, H301)~~
~~Ingredients A, I1 and K2 are classified in this class of hazard.~~
~~• A – 26.1 % (Acute Tox. 4, H302)~~
~~• I1 - 0.0164 % (Acute Tox. 4, H302)~~
~~• K2 - 0.000246 % (Acute Tox. 3, H301)~~
~~For all ingredients the estimated values were taken..~~

~~$ATEmix = 100\Sigma CiATEmixni = 1 = 10026.1500 + 0.0164\,500 + 0.000246100$~~
~~$= 1000.0522 + 0.0000326 + 0.00000245 = 1000.052235 = 1914.4\,mgkgb.w.$~~

~~According to the table 3.1.2, a result (1914.4 mg/kg bw < 2 000 mg/kg bw) **classifies** the whole formulation as **Acute Tox. 4, H302.**.~~

Only ingredient A is relevant in this class of hazard:

- A – 26.1 % (Acute Tox. 4, H302)

$$ATE_{mix} = \frac{100}{\sum_{i=1}^{n} \frac{C_i}{ATE_{mix}}} = \frac{100}{\frac{26.1}{500}} = \frac{100}{0.0522} = 1915.7\ \frac{mg}{kg\ b.w.}$$

Results:
According to the table 3.1.2, a result (1915.7 mg/kg bw < 2 000 mg/kg bw) **classifies** the whole formulation as **Acute Tox. 4, H302.**

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

Comments of zRMS:	The plant protection product CHR/H/FDF 574 SC was classified by calculation method. According to Regulation (EC) No 1272/2008, no classification for acute dermal toxicity is required. For details, please refer to Part C.

A 2.3.1 Study 1

. According to point 7.1.2 of Part A of Annex to the Commission Regulation (EU) No 284/2013 as regards the data requirements for plant protection products:
”A test for dermal toxicity shall be carried out on a case by case basis, unless the applicant can jus-tify an alternative approach under Regulation (EC) No 1272/2008. In the latter case, acute dermal toxicity of all components shall be provided or reliably predicted with a validated method. Consid-eration shall be given to the possible effects of components on the toxic potential of the total mix-ture. Findings of severe skin irritation or corrosion in the dermal study may be used instead of per-forming a specific irritation study.”
The complete composition of the formulation with the classification of individual ingredients is available in part C.
The active substances and the other co-formulants are not classified as acute dermal toxic, it can be assumed that entire formulation is not classified in this class. According to point 7.1.2 of part A of Annex Regulation No 284/2014, it is possible to waive from acute dermal toxicity test. Due to the fact, that all components of the formulation CHR/H/FDF 574 SC are known, the acute dermal tox-icity test is not necessary.

A 2.4 Acute inhalation toxicity (KCP 7.1.3)

Comments of zRMS:	The plant protection product CHR/H/FDF 574 SC was classified by calculation method. According to Regulation (EC) No 1272/2008, no classification for acute inhalation toxicity is required. For details, please refer to Part C

~~Reference:~~ ~~7.1.2~~

~~Report~~ ~~Toxicological classification of product CHR/H/FDF 574 SC based on calculation method taking into consideration health hazards of constituent substances; 2021; according to Part C, appendix 2~~

~~According to point 7.1.1 of Part A of Annex to the Commission Regulation (EU) No 284/2013 as regards the data requirements for plant protection products:~~
~~” A test for dermal toxicity shall be carried out on a case by case basis, unless the applicant can justify an alternative approach under Regulation (EC) No 1272/2008. In the latter case, acute dermal toxicity of all components shall be provided or reliably predicted with a validated method. Consideration shall be given to the possible effects of components on the toxic potential of the total mixture.”~~

~~Ingredient K2 is classified in this hazard class.~~
~~• K2 – 0.000246 % (Acute Tox. 2, H330)~~
~~Estimated values were used to calculation.~~

~~$ATE_{mix}=100/\Sigma C_i ATE_{mixni=1}=100/(0.000246/0.5)=100/0.000492=203\,252.033\ mg/L$~~

~~According to the table 3.1.2, the result (203 252.033 mg/L) is significantly higher than generic concentration level (20 mg/L). Therefore the whole formulation is not toxic by inhalation..~~

.

Reference: 7.1.3

Report Toxicological classification of product CHR/H/FDF 574 SC based on calculation method taking into consideration health hazards of constituent substances; 2022; according to Part C, appendix 2

Inhalation study on CHR/F/PF 469 SC is not required according to point 7.1.3 of Part A of Annex to the Commission Regulation (EU) No 284/2013 as regards the data requirements for plant protection products the inhalation test must be carried out since the preparation is:

- a gas or liquefied gas,
- a smoke generating formulation or fumigant,
- used with fogging equipment,
- a vapor releasing preparation,
- an aerosol,
- a powder containing a significant proportion of particles of diameter <50 µm (> 1% on a weight basis),
- to be applied from aircraft in cases where inhalation exposure is relevant,
- contains an active substance with a vapor pressure > 1x10-2 Pa and is to be used in enclosed spaces such as warehouses or glasshouses,
- to be applied in a manner which generates a significant proportion of particles or droplets of diameter < 50 µm (> 1% on a weight basis).

The active substances and the other co-formulants are not classified as acute inhalation toxic, it can be assumed that entire formulation is not classified in this class. According to point 7.1.3 of part A of Annex Regulation No 284/2014, it is possible to waive from acute inhalation toxicity test.

The complete composition of the formulation with the classification of individual ingredients is available in part C.

Only ingredient K_2 is classified in this class of hazard. However, according to Guidance on the Application of the CLP criteria (version 5.0 July 2017) ingredients classified as categories 1-3 in a concentration <0.1% and category 4 <1% are not taken into account. The concentration of ingredient K_2 is less than 0.1%. Therefore this ingredient is not relevant and the whole mixture will not be classified as toxic by inhalation

A 2.5 Skin irritation (KCP 7.1.4)

Comments of zRMS:	The plant protection product CHR/H/FDF 574 SC was classified by calculation method. According to Regulation (EC) No 1272/2008, no classification for skin irritation is required. For details, please refer to Part C

A 2.5.1 Study 1

Reference:	7.1.4
Report	Toxicological classification of product CHR/H/FDF 574 SC based on calculation method taking into consideration health hazards of constituent substances; 2022; according to Part C, appendix 2

According to point 7.1.4 of Part A of Annex to the Commission Regulation (EU) No 284/2013 as regards the data requirements for plant protection products:
” The skin irritancy of the plant protection product shall be reported based on the tiered approach, unless the applicant can justify an alternative approach under Regulation (EC) No 1272/2008. In the latter case, skin irritation properties of all components shall be provided or reliably predicted with a validated method. Consideration shall be given to the possible effects of components on the irritant potential of the total mixture.”

The complete composition of the formulation with the classification of individual ingredients is available in part C.
For consideration of corrosive and irritant properties the following table applies:

Table 3.2.3
Generic concentration limits of ingredients classified for skin corrosive/irritant hazard (Category 1 or 2) that trigger classification of the mixture as corrosive/irritant to skin.

Sum of ingredients classified as:	Concentration triggering classification of a mixture as:	
	Skin Corrosive	Skin Irritant
	Category 1 (see note below)	Category 2
Skin Corrosive Categories 1A, 1B, 1C	≥ 5 %	≥ 1 % but < 5 %
Skin irritant Category 2		≥ 10 %
10 × Skin Corrosive Category 1A, 1B, 1C) + Skin irritant Category 2		≥ 10 %

Note
The sum of all ingredients of a mixture classified as Skin Corrosive Category 1A, 1B or 1C respectively, shall each be ≥ 5 % respectively in order to classify the mixture as either Skin Corrosive Category 1A, 1B or 1C. If the sum of the Skin Corrosive Category 1A ingredients is < 5 % but the sum of Category 1A+1B ingredients is ≥ 5 %, the mixture shall be classified as Skin Corrosive Category 1B. Similarly, if the sum of Skin Corrosive Category 1A+1B ingredients is < 5 % but the sum of Category 1A+1B+1C ingredients is ≥ 5 % the mixture shall be classified as Skin Corrosive Category 1C.

~~A) Irritant effect to skin:~~

- ~~Ingredients I2, K2, E1, F1, F2, H1, I3, J1 are relevant.~~
- ~~I2 - 0.00492 % (Skin. Corr. 1A, H314) SCL: 0,5 % ≤ C < 2 %~~
- ~~K2 - 0.000246 % (Skin Corr. 1B, H314)~~
- ~~E1 - 4.92 % (Skin Irrit. 2, H315)~~
- ~~F1 - 0.574 % (Skin Irrit. 2, H315)~~
- ~~F2 - 0.00205 % (Skin Irrit. 2, H315)~~
- ~~H1 - 0.0123 % (Skin Irrit. 2, H315)~~
- ~~J1 - 0.0738 % (Skin Irrit. 2, H315)~~

$$10\,x \sum C_{SkinCorr.} + \sum C_{SkinIrrit.}$$
$$= 10\,x \left(\frac{0.00492\%}{0.5\%} + \frac{0.000246\%}{10\%}\right) + \frac{4.92\%}{10\%} + \frac{0.574\%}{10\%} + \frac{0.00205\%}{10\%} + \frac{0.0123\%}{10\%} + \frac{0.0738\%}{10\%}$$
$$= 0.657$$

~~The sum of concentrations (5.69 %) is lower than generic concentration level (10%). Therefore the formulation is not classified as skin irritant.~~

~~b) Corrosive effect to skin:~~
~~Ingredients I2 and K2 are relevant.~~
~~• I2 - 0.00492 % (Skin. Corr. 1A, H314) SCL: 2 % ≤ C < 5 %~~
~~• K2 - 0.000246 % (Skin Corr. 1B, H314)~~

$$\sum C_{SkinCorr.} = \frac{0.00492\ \%}{2\%} + \frac{0.000246\ \%}{5\%} = 0.00246 + 0.0000492 = 0.00251$$

~~According to the table 3.2.3, the result (0.00251 %) is lower than generic concentration level (5 %). Therefore the whole formulation is not classified as skin corrosive.~~

a) Corrosive effect to skin:

Ingredient I_2 and K_2 are classified in this class of hazard. However according to Guidance on the Application of th CLP criteria (version 5.0 July 2017) the 'relevant ingredients' of a mixture are those which are present in concentrations ≥ 1% (w/w for solids, liquids, dusts, mists and vapours and v/v for gases), unless there is a presumption (e.g., in the case of corrosive ingredients) that an ingredient present at a concentration < 1% can still be relevant for classifying the mixture for skin corrosion/irritation. No ingredient classified as skin corrosive exceeds 1% its concentration. Therefore these ingredients are not relevant and mixture will not be classified as skin corrosive as well.

b) Irritant effect to skin:

Ingredients I_2, K_2, E_1, F_1, F_2, H_1, I_3, J_1 are classified as harmful to the skin. However, because of low concentration in the mixture ingredients F_1, F_2, H_1, J_1, K_2 are not relevant (according to Guidance on the Application of th CLP criteria (version 5.0 July 2017)). Ingredient I_2 is classified as skin corrosive and has specific concetration limit, so despite of low concentration, there is an presumption of possibility it can be relevant in these calculations.

- I_2 - 0.00492 % (Skin. Corr. 1A, H314) SCL Skin Irrit., H315: 0,5 % ≤ C < 2 %
- E_1 - 4.92 % (Skin Irrit. 2, H315)

$$10\ x \sum C_{SkinCorr.} + \sum C_{SkinIrrir.} = 10\ x \left(\frac{0.00492\%}{0.5\%}\right) + \frac{4.92\%}{10\%} = 0.0984 + 0.492 = 0.59$$

Results:
Since component I_2 has a specific concentration limit for the Skin Irrit. 2; H315 classification (0,5 % ≤ C < 2 %), the classification was calculated using this concentration as well as the generic concentration limit for E_1 component (10%). The result is less than 1, so the whole mixture will not be classified as skin irritant.

A 2.6 Eye irritation (KCP 7.1.5)

Comments of zRMS:	The plant protection product CHR/H/FDF 574 SC was classified by calculation method. According to Regulation (EC) No 1272/2008, no classification for eye irritation is required. All comments have been posted in Part C. For details, please refer to Part C.

A 2.6.1 Study 1

Reference:	7.1.5
Report	Toxicological classification of product CHR/H/FDF 574 SC based on calculation method taking into consideration health hazards of constituent substances; 2022; according to Part C, appendix 2

According to point 7.1.5 of Part A of Annex to the Commission Regulation (EU) No 284/2013 as regards the data requirements for plant protection products:
" Eye irritation tests shall be provided, unless it is likely that severe effects on the eyes may be produced or the applicant can justify an alternative approach under Regulation (EC) No 1272/2008. In the latter case, eye irritation properties of all components shall be provided or reliably predicted with a validated method. Consideration shall be given to the possible effects of components on the irritant potential of the total mixture."

Due to the fact, that all components of the formulation CHR/H/FDF 574 SC are known, eye corrosion test is not necessary.

Materials and methods

For consideration of corrosive and irritant properties the following table applies:

Table 3.3.3
Generic concentration limits of ingredients of a mixture classified as Skin corrosive Category 1 and/ or eye Category 1 or 2 for effects on the eye that trigger classification of the mixture for effects on the eye (Category 1 or 2).

Sum of ingredients classified as:	Concentration triggering classification of a mixture as:	
	Irreversible Eye Effects	Reversible Eye Effects
	Category 1	Category 2
Eye Effects Category 1 or Skin Corrosive Category 1A, 1B, 1C	≥ 3 %	≥ 1 % but < 3 %
Eye Effects Category 2		≥ 10 %
(10 × Eye Effects Category 1) + Eye effects Category 2		≥ 10 %
Skin Corrosive Category 1A, 1B, 1C + Eye effects Category 1	≥ 3 %	≥ 1 % but < 3 %
10 × (Skin Corrosive Category 1A, 1B, 1C + Eye Effects Category 1) + Eye Effects Category 2		≥ 10 %

The complete composition of the formulation with the classification of individual ingredients is available in part C.

~~a) Irritant effects to eyes:~~

~~Ingredients K2, I2, F1, I1, F2, H1 and J1 are relevant.~~
~~K2 - 0.000246 % (Eye Dam. 1, H318; Skin Corr. 1B, H314)~~
~~I2 - 0.00492 % (Eye Dam. 1, H318; Skin Corr. 1A, H314) SCL: 0,5 % ≤ C < 2 %~~
~~F1 - 0.574 % (Eye Dam. 1, H318)~~
~~I1 - 0.0164 % (Eye Dam. 1, H318)~~
~~F2 - 0.00205 % (Eye Irrit. 2, H319)~~
~~H1 - 0.0123 % (Eye Irrit. 2, H319)~~
~~J1 - 0.0738 % (Eye Irrit. 2, H319)~~

~~$10 x \left(\sum C_{SkinCorr.} + \sum C_{EyeDam.}\right) + \sum C_{EyeIrrit.}$~~

~~$= 10 x \left(\left(\frac{0.000246\ \%}{10\%} + \frac{0.00492\ \%}{0.5\%}\right) + \left(\frac{0.574\ \%}{10\%} + \frac{0.0164\ \%}{10\%}\right)\right)$~~

~~$+ \left(\frac{0.00205\ \%}{10\%} + \frac{0.0123\ \%}{10\%} + \frac{0.0738\ \%}{10\%}\right) = 10 x\ (0.009865 + 0.059) + 0.008815$~~

~~$= 0.68865 + 0.008815 = 0.697465$~~

~~Since component I2 has a specific concentration limit for the Eye Irrit. 2, H319 classification (0,5 % ≤ C < 2 %), the classification was recalculated using this concentration as well as the generic concentration limit rest of components classified in this category (10%). The result is less than 1, so the whole mixture will not be classified as Eye Irrit. 2, H319.~~

~~b) Corrosive effects to eyes:~~

~~Ingredients F_1, I_1, I_2 and K_2 are relevant.~~

- ~~F_1 – 0.574 % (Eye Dam. 1, H318)~~
- ~~I_1 – 0.0164% (Eye Dam. 1, H318)~~
- ~~I_2 – 0.00492 % (Eye Dam. 1, H318; Skin Corr. 1A, H314)~~
- ~~K_2 - 0.000246 % (Eye Dam. 1 H318; Skin Corr. 1B, H314)~~

~~We use the summation method, consisting in adding up the percentages of all ingredients classified in the each class.~~

~~$\sum C_{SkinCorr.} + \sum C_{EyeDam} = 0.00492\ \% + 0.000246\ \% + 0.574\ \% + 0.0164\% = 0.5956\ \%$~~

~~The sum of concentration of relevant ingredients (0.5956 %) is lower than a generic concentration limit (3%). Therefore the whole formulation is not classified as corrosive to eyes~~

a) Corrosive effects to eyes:

Ingredients F_1, I_1, I_2 and K_2 are classified as corrosive to eyes. However according to Guidance on the Application of th CLP criteria (version 5.0 July 2017) the 'relevant ingredients' of a mixture are those which are present in concentrations ≥ 1% (w/w for solids, liquids, dusts, mists and vapours and v/v for gases), unless there is a presumption (e.g. in the case of corrosive ingredients) that an ingredient present at a concentration < 1% can still be relevant for classifying the mixture for serious eye damage/eye irritation. No ingredient classified as eye corrosive exceeds 1% its concentration. Therefore these ingredients are not relevant and mixture will not be classified as eye corrosive as well.

b) Irritant effects to eyes:

Ingredients I_1, I_2, K_2, F_1, F_2, H_1 and J_1 are classified as harmful to the eyes. Because of low concentration in the mixture ingredients F_2, H_1, J_1 and K_2 are not relevant (according to Guidance on the Application of th CLP criteria (version 5.0 July 2017)). Ingredients F_1, I_1, I_2 are classified as eye corrosive, so despite of low concentration, there is an presumption of possibility that these ingredients can be relevant in the calculations:

- I_2 - 0.00492 % (Eye Dam. 1, H318; Skin Corr. 1A, H314) SCL: 0,5 % ≤ C < 2 %
- F_1 - 0.574 % (Eye Dam. 1, H318)
- I_1 - 0.0164 % (Eye Dam. 1, H318)

$$10\ x\ \left(\sum C_{SkinCorr.} + \sum C_{EyeDam.}\right) + \sum C_{EyeIrrit.} = 10\ x\ \left(\frac{0.00492\%}{0.5\%} + \frac{0.574\%}{10\%} + \frac{0.0164\%}{10\%}\right)$$
$$= 10\ x\ (0.00984 + 0.0574 + 0.00164) = 0.69$$

Since component I_2 has a specific concentration limit for the Eye Irrit. 2, H319 classification (0,5 % ≤ C < 2 %), the classification was calculated using this concentration as well as the generic concentration limit rest of components classified in this category (10%). The result is less than 1, so the whole mixture will not be classified as Eye Irrit. 2, H319.

A 2.7 Skin sensitisation (KCP 7.1.6)

Comments of zRMS:	In accordance with the provisions of the Regulation EC 1272/2008, the formulation **requires classification in respect to skin sensitisation as Skin Sens. 1, H317**. All comments have been posted in Part C. For details please see part C of dRR.

Reference: 7.1.6

Report: Toxicological classification of product CHR/H/FDF 574 SC based on calculation method taking into consideration health hazards of constituent substances; 2022; according to Part C, appendix 2

According to point 7.1.46of Part A of Annex to the Commission Regulation (EU) No 284/2013 as regards the data requirements for plant protection products:

” The skin sensitisation of the plant protection product shall be reported based on the tiered approach, unless the applicant can justify an alternative approach under Regulation (EC) No 1272/2008. In the latter case, skin irritation properties of all components shall be provided or reliably predicted with a validated method. Consideration shall be given to the possible effects of components on the irritant potential of the total mixture.”Due to the fact, that all components of the formulation CHR/H/FDF 574 SC are known, eye corrosion test is not necessary.

Materials and methods

We use the table:

Table 3.4.5
Generic concentration limits of ingredients of a mixture classified as either skin sensitisers or respiratory sensitisers that trigger classification of the mixture

Ingredient classified as:	Concentration triggering classification of a mixture as:		
	Skin Sensitiser	Respiratory Sensitiser	
	All physical states	Solid/Liquid	Gas
Skin Sensitiser Category 1	≥ 1,0 %	-	-
Skin Sensitiser Category 1A	≥ 0,1 %	-	-
Skin Sensitiser Category 1B	≥ 1,0 %		
Respiratory Sensitiser Category 1	-	≥ 1,0 %	≥ 0,2 %

Respiratory Sensitiser Category 1A	-	≥ 0,1 %	≥ 0,1 %
Respiratory Sensitiser Category 1B		≥ 1,0 %	≥ 0,2 %

3.1. Skin sensitizing (Skin Sens. 1, H317; Skin Sens. 1A, H317; Skin Sens. 1B, H317)

Ingredients A, H_1, I_1 and K_2 are relevant:

- A – 26.1 % (Skin Sens. 1, H317)
- H_1 - 0.0123 % (Skin Sens. 1B, H317)
- I_1 - 0.0164 % (Skin Sens. 1, H317; Skin Sens. 1, H317 C ≥ 0,05 %)
- K_2 - 0.000246 % (Skin Sens. 1A, H317)

The concentration of ingredient A (26.1 %) classified as Skin Sens. 1, H317 is significantly higher that triggering concentration level. Therefore whole formulation will be classified as Skin Sens. 1, H317.

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

Not required

A 2.9 Data on co-formulants (KCP 7.4)

A 2.9.1 Material safety data sheet for each co-formulant

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

A 2.9.2 Available toxicological data for each co-formulant

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

A 2.10 Studies on dermal absorption (KCP 7.3)

For the dermal absorption of the active substance the Applicant refers to Guidance on Dermal Absorption1 EFSA, EFSA Journal 2017;15(6):4873.
Based on an evaluation of agreed dermal absorption values for a range of concentrated pesticide formulations and their dilutions, the following default values are recommended (see opinion section 4.1.1.for details).
A default dermal absorption value of 25% may be applied for concentrated products that are organic solvent-formulated or in other types of formulations.
A default dermal absorption value of 70% may be applied for (in use) dilutions of organic solvent-formulated or in other types of formulation.

A 2.11 Other/Special Studies

A 2.11.1 Specific target organ toxicity

A 1.11.1 Study 1

Reference:	7.1.1
Report	Toxicological classification of product CHR/H/FDF 574 SC based on calculation method taking into consideration health hazards of constituent substances; 2021; according to Part C, appendix 2

According to point 3.8.3 of Regulation (EC) No 1272/2008 as regards the data requirements for plant protection products:
" Mixtures are classified using the same criteria as for substances, or alternatively as described below. As with substances, mixtures shall be classified for specific target organ toxicity following single exposure. Where there is no reliable evidence or test data for the specific mixture itself, and the bridging principles cannot be used to enable classification, then classification of the mixture is based on the classification of the ingredient substances. In this case, the mixture shall be classified as a specific target organ toxicant (specific organ specified), following single exposure, when at least one ingredient has been classified as a Category 1 or Category 2 specific target organ toxicant and is present at or above the appropriate generic concentration limit as mentioned in Table 3.8.3 for Category 1 and 2 respectively"

Due to the fact, that all components of the formulation CHR/H/FDF 574 SC are known, eye corrosion test is not necessary.

Materials and methods

For consideration of specific target organ properties the following table applies:
Table 3.8.3
Generic concentration limits of ingredients of a mixture classified as a specific target organ toxicant that trigger classification of the mixture as Category 1 or 2.

Ingredient classified as:	Generic concentration limits triggering classification of the mixture as:	
	Category 1	Category 2
Category 1 Specific Target Organ Toxicant	Concentration ≥ 10 %	1,0 % ≤ concentration < 10 %
Category 2 Specific Target Organ Toxicant		Concentration ≥ 10 % [(Note 1)]

Note 1
If a Category 2 specific target organ toxicant is present in the mixture as an ingredient at a concentration ≥ 1,0 % a SDS shall be available for the mixture upon request.

We also took into account the point 3.8.3.4.5.: "Care shall be exercised when extrapolating toxicity of a mixture that contains Category 3 ingredient(s). A generic concentration limit of 20 % is appropriate; however, it shall be recognised that this concentration limit may be higher or lower depending on the Category 3 ingredient(s) and that some effects such as respiratory tract irritation may not occur below a certain concentration while other effects such as narcotic effects may occur below this 20 % value. Expert judgement shall be exercised."

Results and discussions

The ingredient A is classified as STOT RE 2, H373. The concentration of the ingredient (26.1%) is higher than concentration triggering classification 10%. According to table 3.8.3. the formulation is classified as STOT RE 2, H373.

Comments of zRMS:	The plant protection product CHR/H/FDF 574 SC was classified by calculation method as described in Regulation (EC) No 1272/2008. The product is classified as STOT RE 2, H373. All comments have been posted in Part C. For details please see part C of dRR.

A 2.11.1 Study 2

Reference: 7.1.1

Report: Toxicological classification of product CHR/H/FDF 574 SC based on calculation method taking into consideration health hazards of constituent substances; 2021; according to Part C, appendix 2

For consideration of carcinogenicity the following table applies:

Table 3.7.2

Generic concentration limits of ingredients of a mixture classified as reproduction toxicants or for effects on or via lactation that trigger classification of the mixture

Ingredient classified as:	Generic concentration limits triggering classification of a mixture as:			
	Category 1A reproductive toxicant	Category 1B reproductive toxicant	Category 2 reproductive toxicant	Additional category for effects on or via lactation
Category 1A reproductive toxicant	≥ 0,3 % [Note 1]			
Category 1B reproductive toxicant		≥ 0,3 % [Note 1]		
Category 2 reproductive toxicant			≥ 3,0 % [Note 1]	
Additional category for effects on or via lactation				≥ 0,3 % [Note 1]

Note
The concentration limits in the table above apply to solids and liquids (w/w units) as well as gases (v/v units).
Note 1
If a Category 1 or Category 2 reproductive toxicant or a substance classified for effects on or via lactation is present in the mixture as an ingredient at a concentration above 0,1 %, a SDS shall be available for the mixture upon request.

Results and discussions

Ingredient L_1 is relevant:

- K_1 – 0.000246 % (Repr. 2, H361f)

A concentration of this compound is lower than concentration triggering classification (3%). Therefore the formulation is not classified as toxic for reproduction

~~**KCP 7.0/01 In vitro evaluation of Flufenacet oxalate, Flufenacet sulfonic acid, Trifluoroethanesulfonic acid, Trifluoroacetic acid and Flufenacet methylsulfone genotoxicity using the micronucleus assay (MNA). J.Antonik, 2016.; SELVITA. Study Number: K81/JA/01.Method: OECD 487 GLP, Unpublished**~~

~~The formation of MN is a consequence of chromosomal breakage and/or spindle fiber dysfunction induced by clastogens and/or aneuploidogens. The present study was performed in accordance with the OECD 487 and under GLP requirements. In order to assess genotoxic potential CHO-K1 cells were exposed to test items (Flufenacet oxalate, Flufenacet sulfonic acid, Trifluoroethanesulfonic acid, Trifluoroacetic acid and Flufenacet methylsulfone) and appropriate reference items in system with (+S9) and without (S9 short and extended treatment) an exogenous metabolic activation. Stati stical analysis of the MN frequency and binucleate cells with MN was performer using the~~

~~Chi square test with Yates' correction. To examine the dose response relationship in frequencies of the micronuclei Chi square test for trend was performed.~~
~~None of tested concentration of Flufenacet oxalate, Flufenacet sulfonic acid, Trifluoroethanesulfo nic acid, Trifluoroacetic acid and Flufenacet methylsulfone exhibit a statistically significant increa se in MN frequency compared with the concurrent negativecontrol (P>0.05, T bles IX XIII, Figure I VII). Chi square test for trend revealed no dose related increase in MN frequency (P>0.05).~~
~~Results for positive reference items (mitomycin C and cyclophosphamide) demonstrated reprodu cibility and sensitivity of system.~~

~~In summary, the present research has demonstrated that items Flufenacet oxalate, Flufenacet sul fonic acid, Trifluoroethanesulfonic acid, Trifluoroacetic acid and Flufenacet methylsulfone did not produce dose dependent genetic toxicity in the CHO K1 cells.~~

Reference:	KCP 7.0/01
Report	In vitro evaluation of Flufenacet oxalate, Flufenacet sulfonic acid, Trifluoroethanesulfonic acid, Trifluoroacetic acid and Flufenacet methylsulfone genotoxicity using the micronucleus assay (MNA) Justyna Antonik, 2016 Selvita S.A. Park Life Science, Poland Study code: K81/JA/01 GLP Unpublished
Guideline(s):	Organization for Economic Cooperation and Development (OECD) 487 and under GLP requirements
Deviations:	No
GLP:	Yes
Acceptability:	Yes
Duplication (if vertebrate study)	-

Materials and Methods:
Test System:
CHO-K1 cell line was cultivated according to the previously established SOP-01 in 25 cm2 or 75 cm2 tissue culture flasks at 37ºC in a humidified atmosphere containing 5% CO2 using Ham's F12 medium supplemented with 10% v/v h.i. FBS and antibiotics (Penicillin and Streptomycin). The doubling time of CHO-K1 determined at Selvita is approximately 18h. The cultures were tested regularly for the absence of mycoplasma infections.
Test Item:

Item	Provider	CAS	Batch no	MW [g/mol]	Mfg. date	Exp. date
Flufenacet oxalate	Key Organics	201668-31-7	EXP-15-EE1619	225.2	01.12.2015	12.2017
Flufenacet sulfonic acid	Key Organics	n/a	EXP-15-DFO394	275.3	01.12.2015	12.2017
Trifluoroethanesulfonic acid	Apollo Scientific	1827-97-0	A5457345	164.1	10.2015	10.2017

Method:
The in vitro Micronucleus Assay (MNA) is a mutagenic test system for the detection of chemicals that induce the formation of small membrane-bound DNA fragments (micronuclei - MN) in the cytoplasm of interphase cells. The MNA, used for regulatory purposes measures formation of chromosomal changes following DNA damage induced by the items under test, and is used to predict the genotoxic potential of pharmaceuticals, industrial chemicals, food additives and cosmetic ingredients. MN originate from chromosome fragments or whole chromosomes that are not included in the main daughter nuclei during nuclear division. They reflect chromosome damage and may thus provide a marker of genotoxicity and even

early-stage carcinogenesis. The most commonly used method in mammalian cells is the cytokinesis-block micronucleus (CBMN) assay. In the CBMN assay, MN are scored after a single cell division using binucleated cultured cells (accumulated using cytochalasin B) to eliminate the confounding effect of altered cell division kinetics on the MN index.

Test procedure:

1. CHO-K1 cells were maintained in Ham's F12 medium supplemented with 10% v/v h.i. FBS , 1000 U/mL penicillin and 1000 U/mL streptomycin.
2. For experiments cells were plated at 50 000 cells/well into the wells of a 24-well plate, in a volume of 500 µL per well (-S9 incubation), 100 000 cells/well into the wells of a 12-well plate, in a volume of 1000 µL per well (+S9 incubation) and cultured overnight (18–22h) prior to the start of the assay.
3. The following day, the medium was removed and replaced with 500 µL (-S9 incubation) or 600 µL (+S9 incubation) per well of medium with test items and appropriate positive and negative controls. For details see Table 1.
4. For the short treatment (+/- S9), cells were treated with items for 3h, after which the medium was removed, the cells were washed once with warm medium, and fresh medium containing cytochalasin B (3 µg/mL) was added for 27h.
5. At the end of the incubation period, the medium was removed, the cells were washed once with warm PBS, than were detached by trypsinization, collected to 15- ml falcons in 3 mL medium and centrifuged for 8 minutes in 160 x g.
6. Medium was discarded and cells were washed with 2 mL of PBS. Cultures were centrifuged for 8 minutes in 160 x g.
7. Cells were treated with 1 mL of warm 75 mM KCl hypotonic solution for 20-30 seconds and then they were fixed by adding 2 mL of cold fixative (acetic acid:methanol in proportions 1:3 v/v).
8. Cultures were centrifuged for 8 minutes in 160 x g, then treated with 3 mL of fixative and centrifuged again.
9. The cells were incubated in fresh fixative for 30 minutes at room temperature, after which they were centrifuged for 8 minutes in 160 x g.
10. After last centrifugation, the supernatant was gently discarded, whilst cel suspension (approx. 150 µL fixative) was gently resuspended and a few drops of suspension was placed on a cold clean glass slide in humid chamber (45°C in water bath) and air dried.
11. Next day, the slides were stained by with 15% Giemsa stain for approx. 5 minutes, then washed twice in distilled water and air dried.

Results:

The formation of MN is a consequence of chromosomal breakage and/or spindle-fiber dysfunction induced by clastogens and/or aneuploidogens. The present study was performed in accordance with the OECD 487 and under GLP requirements.

In order to assess genotoxic potential CHO-K1 cells were exposed to test items (Flufenacet oxalate, Flufenacet sulfonic acid, Trifluoroethanesulfonic acid, Trifluoroacetic acid and Flufenacet methylsulfone) and appropriate reference items in system with (+S9) and without (-S9 short and extended treatment) an exogenous metabolic activation.

Statistical analysis of the MN frequency and binucleate cells with MN was performer using the Chi-square test with Yates' correction. To examine the dose-response relationship in frequencies of the micronuclei Chi-square test for trend was performed.

None of tested concentration of Flufenacet oxalate, Flufenacet sulfonic acid, Trifluoroethanesulfonic acid, Trifluoroacetic acid and Flufenacet methylsulfone exhibit a statistically significant increase in MN frequency compared with the concurrent negative
control ($P>0.05$, Tables IX-XIII, Figure I-VII). Chi-square test for trend revealed no dose-related increase in MN frequency ($P>0.05$). Results for positive reference items (mitomycin C and cyclophosphamide) demonstrated reproducibility and sensitivity of system.

In summary, the present research has demonstrated that items Flufenacet oxalate, Flufenacet sulfonic acid, Trifluoroethanesulfonic acid, Trifluoroacetic acid and Flufenacet methylsulfone did not produce dose-dependent genetic toxicity in the CHO-K1 cells.

Cytotoxicity test results for Flufenacet sulfonic acid.

Flufenacet sulfonic acid - Cytotoxicity test

Test item	CBPI	RI [%]	Cytotoxicity [%]	MN [‰]	P value	Cells with MN [‰]	P value
3h (-S9)							
PBS control	1.88	100.0	0.0	5	NA	4.5	NA
0.2 µg/mL MMC	1.76	86.3	13.7	34	<0. 0001 (****)	32	<0. 0001 (****)
0.4 µg/mL MMC	1.69	77.9	22.1	36	<0.0001 (****)	34	<0.0001 (****)
DMSO control	1.90	100.0	0.0				
0.9 µg/mL Flufenacet sulfonic acid	1.89	98.7	1.3				
2.7 µg/mL Flufenacet sulfonic acid	1.90	100.4	-0.4				
8.2 µg/mL Flufenacet sulfonic acid	1.88	98.6	1.4				
24.7 µg/mL Flufenacet sulfonic acid	1.91	101.4	-1.4				
74.1 µg/mL Flufenacet sulfonic acid	1.88	98.7	1.3				
222.2 µg/mL Flufenacet sulfonic acid	1.91	101.2	-1.2				
666.7 µg/mL Flufenacet sulfonic acid	1.93	103.6	-3.6				
2000.0 µg/mL Flufenacet sulfonic acid	1.91	100.9	-0.9				
27h (-S9)							
PBS control	1.89	100.0	0.0	4	NA	4	NA
0.1 µg/mL MMC	1.81	91.0	9.0	27	<0. 0001 (****)	26	<0.0001 (****)
0.2 µg/mL MMC	1.72	81.3	18.7	31	<0.0001 (****)	28	<0.0001 (****)
DMSO control	1.98	100.0	0.0				
0.9 µg/mL Flufenacet sulfonic acid	1.94	96.8	3.2				
2.7 µg/mL Flufenacet sulfonic acid	1.92	94.1	5.9				
8.2 µg/mL Flufenacet sulfonic acid	1.97	99.6	0.4				
24.7 µg/mL Flufenacet sulfonic acid	1.97	99.5	0.5				
74.1 µg/mL Flufenacet sulfonic acid	1.91	92.9	7.1				
222.2 µg/mL Flufenacet sulfonic acid	1.90	92.2	7.8				
666.7 µg/mL Flufenacet sulfonic acid	1.92	93.7	6.3				
2000.0 µg/mL Flufenacet sulfonic acid	1.84	86.4	13.6				
3h (+S9)							
PBS control	1.81	100.0	0.0	7	NA	6.5	NA
5 µg/mL CP	1.81	99.3	0.7	24	<0.0001 (****)	20	0.0004 (***)
10 µg/mL CP	1.80	98.0	2.0	29	<0.0001 (****)	27	<0.0001 (****)
DMSO control	1.85	100.0	0.0				
0.9 µg/mL Flufenacet sulfonic acid	1.77	90.8	9.2				
2.7 µg/mL Flufenacet sulfonic acid	1.78	92.2	7.8				
8.2 µg/mL Flufenacet sulfonic acid	1.79	92.9	7.1				
24.7 µg/mL Flufenacet sulfonic acid	1.78	92.1	7.9				
74.1 µg/mL Flufenacet sulfonic acid	1.79	93.3	6.7				
222.2 µg/mL Flufenacet sulfonic acid	1.81	95.0	5.0				
666.7 µg/mL Flufenacet sulfonic acid	1.77	90.1	9.9				
2000.0 µg/mL Flufenacet sulfonic acid	1.83	97.3	2.7				

Statistically significant level: ns P>0.05; * P≤0.05; ** P≤0.01; *** P≤0.001, **** P<0.0001.

MNA test results for Flufenacet-sulfonic acid .

Flufenacet-sulfonic acid – Genotoxicity test

Test item	CBPI	RI [%]	Cytotoxicity [%]	MN [‰]	P value	Cells with MN [‰]	P value	Result
3h (-S9)								
PBS control	1.92	100.0	0.0	4	NA	4	NA	NA
0.2 µg/mL MMC	1.78	85.4	14.6	32	<0.0001 (****)	36	<0.0001 (***)	positive
0.4 µg/mL MMC	1.66	72.5	27.5	39	<0.0001 (****)	31	<0.0001 (****)	positive
DMSO control	2.00	100.0	0.0	6	NA	6	NA	NA
250 µg/mL Flufenacet sulfonic acid	2.01	101.2	-1.2	9	0.2868	9	0.2704	negative
500 µg/mL Flufenacet sulfonic acid	2.02	102.4	-2.4	9	0.3674	9	0.3504	negative
1000 µg/mL Flufenacet sulfonic acid	2.03	103.3	-3.3	9	0.3674	9	0.2704	negative
2000 µg/mL Flufenacet sulfonic acid	2.05	105.7	-5.7	11	0.1107	10	0.1335	negative
27h (-S9)								
PBS control	2.05	100.0	0.0		NA		NA	NA
0.1 µg/mL MMC	1.91	86.7	13.3	37	0.0007 (***)	35	0.0008 (***)	positive
0.2 µg/mL MMC	1.80	76.1	23.9	47	<0.0001 (****)	43	<0.0001 (****)	positive
DMSO control	2.03	100.0	0.0	7	NA	6	NA	NA
250 µg/mL Flufenacet sulfonic acid	1.97	93.8	6.2	6	0.9940	6	0.8425	negative
500 µg/mL Flufenacet sulfonic acid	2.04	101.0	-1.0	8	0.7373	8	0.5954	negative
1000 µg/mL Flufenacet sulfonic acid	2.03	99.3	0.7	8	0.8671	8	0.7166	negative
2000 µg/mL Flufenacet sulfonic acid	2.01	97.5	2.5	9	0.4751	9	0.3638	negative
3h (+S9)								
PBS control	1.87	100.0	0.0	8	NA	8	NA	NA
5 µg/mL CP	1.81	92.3	7.7	17	0.0166 (*)	17	0.0201 (**)	positive
10 µg/mL CP	1.81	92.4	7.6	20	0.0031 (**)	19	<0.0001 (****)	positive
DMSO control	1.91	100.0	0.0	8	NA	8	NA	NA
250 µg/mL Flufenacet sulfonic acid	1.80	99.1	0.9	9	0.7245	9	0.7245	negative
500 µg/mL Flufenacet sulfonic acid	1.94	103.6	-3.6	9	0.8613	8	0.8613	negative
1000 µg/mL Flufenacet sulfonic acid	1.91	100.2	-0.2	11	0.3992	10	0.3992	negative
2000 µg/mL Flufenacet sulfonic acid	1.89	98.5	1.5	10	0.5993	9	0.8503	negative

Statistically significant level: ns P>0.05; * P≤0.05; ** P≤0.01; *** P≤0.001, **** P<0.0001.

Comments of zRMS:	The study is considered acceptable. Deviations to OECD 487, 2016 : no historical control data for negative and positive controls. Flufenacet sulfonic acid is negative in the *in vitro* micronucleus test. **MATERIALS** Test material: Flufenacet sulfonic acid Lot/Batch no: EXP-1-5-DFO394 Expiry date: 12/2017 Test system: CHO-K1: Chinese hamster ovary cell line Origin: CLS Cat. No: 603480

	Schedule of the MNA test -S9 short treatment – Treatment for 3h with test items (at 37°C) – Removal the treatment medium – Addition of fresh medium and cytochalasin B (cytoB) – Harvesting 1.5 – 2.0 normal cell cycles later (27h) -S9 extended treatment – Treatment for 1.5 – 2 normal cell cycles (27h) – with test items in the presence of cytoB (at 37°C) – Harvesting at the end of the exposure period +S9 short treatment – Treatment for 3h with test items in the presence of S9 (at 37°C) – Removal the S9 and treatment medium – Addition fresh medium and cytoB – Harvesting 1.5 – 2.0 normal cell cycles later (27h) **Test item concentration** -S9/ +S9: 250, 500, 1000, 2000 µg/mL in DMSO **Results** MN frequency and binucleate cells: Chi-square test with Yates' correction for a=0.05. MN scoring: light microscope using criteria defined by Fenech et al. (2003) Cytotoxicity assessment: cytotoxicity block proliferation index (CBPI) The highest tested concentrations of Flufenacet sulfonic acid at any tested concentration did not reduce CBPI or RI to 45±5% of the concurrent negative control (1% v/v DMSO) in test with and without (-S9 short and extended treatment) metabolic activation. The items tested under condition with and without metabolic activation at analyzed concentrations did not exhibit statistically significant increase in micronucleus frequency per culture compared with the concurrent negative control. A significant concentration-related increase in frequency of MN was not observed in cultures treated with Flufenacet sulfonic acid.

~~**KCP 7.0/02** In vitro Mammalian Cell Gene Mutation test (OECD 490) - genotoxicity determination of Flufenacet oxalate, Flufenacet sulfonic acid, Trifluoroethanesulfonic acid and Trifluoroacetic acid by Mouse Lymphoma Assay. J.Antonik; 2016; Study number: K82/JA/01; SELVITA; OECD 490, GLP, Unpublished~~

~~Mutagenic potential of Flufenacet oxalate, Flufenacet sulfonic acid, Trifluoroethanesulfonic acid and Trifluoroacetic acid was evaluated trough Mouse Lymphoma Assay (MLA) in L5178Y cells. Tested items were analyzed in MLA, in the presence and absence of exogenous metabolic activa tion.Obtained results have shown that tested item did not exceed MF above a value~~

~~Mouse Lymphoma Assay under the protocol described and according to the acceptability criteria defined in OECD guideline 490 and SPB 19~~

Reference: KCP 7.0/02

Report	In vitro Mammalian Cell Gene Mutation test (OECD 490) - genotoxicity determination of Flufenacet oxalate, Flufenacet sulfonic acid, Trifluor ethanesulfonic acid and Trifluoroacetic acid by Mouse Lymphoma Assay Justyna Antonik, 2016 Selvita S.A. Park Life Science, Poland Study code: K82/JA/01 GLP Un-published
Guideline(s):	Organization for Economic Cooperation and Development (OECD) 490 and under GLP requirements
Deviations:	No
GLP:	Yes
Acceptability:	Yes
Duplication (if vertebrate study)	-

Materials and Methods:

Test System:

The L5178Y TK+/− (clone 3.7.2C) cell line was purchased from American Type Culture Collection (ATCC) and maintained in log phase growth by serial subculturing. The cells were routinely cultured in RPMI 1640 supplemented with 10% (v/v) heat inactivated horse serum hereafter referred to as the medium growth (Medium10). To reduce the frequency of spontaneous TK−/− mutants, cell cultures were cleansed of the pre-existing TK−/− mutants by exposing them to the thymidine, hypoxanthine, methotrexate and glutamine (THMG) for approximately 24 hours to select against the TK−/− phenotype. The concentration of heat inactivated horse serum was reduced to 5% (v/v) prior to treatment with tested item.

The cloning medium (Medium 20) consisted of RPMI 1640 supplemented with 20% (v/v) heat inactivated horse serum. For selection, the cloning media were supplemented with 3 µg/mL 3-trifluorothymidine (TFT).

Test Item:

Samples of the test items were provided by the Study Sponsor (Table 1). Dimethyl sulfoxide (DMSO) was selected as a solvent for compounds: Flufenacet oxalate, Flufenacet sulfonic acid, and Trifluoroethanesulfonic acid, while water (H2O) was selected as a solvent for Trifluoroacetic acid.

Flufenacet oxalate and Flufenacet sulfonic acid were soluble at 2000 µg/mL concentration – the highest concentration recommended by OECD 490 for compounds with molecular mass above 200 g/M. However, it was noted that Flufenacet sulfonic acid at this concentration quickly polymerizes in DMSO, while after addition to culture medium it rapidly dissolutes. Trifluoroethanesulfonic acid was soluble at 10 mM concentration – the highest concentration recommended by OECD 490 for compounds with molecular mass below 200 g/M. Compound was soluble at all concentrations used. Trifluoroacetic acid was tested at concentrations up to 2 µL/mL – the highest concentration recommended by OECD 490 for liquid compounds. It was noted that Trifluoroacetic acid at 2 µL/mL concentration rapidly changes pH of the culture medium.

Name	Provider	CAS	Batch no	MW [g/mol]	Mfg. date	Exp. date
Flufenacet oxalate	Key Organics	201668-31-7	EXP-15-EE1619	225.2	01.12.2015	12.2017
Flufenacet sulfonic acid	Key Organics	n/a	EXP-15-DFO394	275.3	01.12.2015	12.2017
Trifluoroethanesulfonic acid	Apollo Scientific	1827-97-0	A5457345	164.1	10.2015	10.2017
Trifluoroacetic acid	FluoroChem	76-05-1	20120730	114.0	n/a	n/a

Control item

Methyl methanosulfonate (MMS) and Cyclophosphamide (Cp) were selected to be used in the assay as positive controls.

MMS was used in the absence of metabolic activation (−S9) and Cp in the presence of metabolic activation (+S9). MMS is a direct acting mutagen, while Cp is promutagen that requires biotransformation with the liver enzymes to elicit a mutagenic response. PBS without or with S9 treated cultures were used as vehicle (negative) controls for tested item.

Positive controls demonstrated effectiveness of the assay.

Method:
The Mouse Lymphoma Assay (MLA) is a short-term assay designed to detect forward gene mutations induced by mutagens at the heterozygous thymidine kinase (TK) locus. It is capable of quantifying genetic alterations. The system recommended by OECD 490 employed L5178Y TK+/− cells and the TK (thymidine kinase) locus. 5-Trifluorothymidine (TFT) is a toxic pyrimidine analogue that interferes with DNA metabolism causing cell death. However, if the functional copy of the TK gene is lost (TK−/−) through mutation, the TFT is not metabolized and is no longer toxic. The L5178Y TK+/− cells are sensitive to the cytotoxic effects of the TFT. When L5178Y TK+/− cells are exposed on mutagenic and/or carcinogenic agents, TK+/− is mutated to the TK−/− genotype which is causing TFT resistance. The mutant cells when cloned in medium containing the selective agent TFT, proliferate and form colonies. The mouse lymphoma TK assay uses the thymidine kinase (TK) gene (reporter of mutation) d tects a broad spectrum of genetic damage, including point mutations, large scale chromosomal changes and recombination. That is why it is often recommended and widely used to determine the genotoxic potential of various chemicals. This is also the Gene Mutation Assay of choice at Selvita laboratory as a suitable short-term mutagenicity screening assay to predict chemical carcinogenicity. The studies were performed according to Standard Research Procedure SPB-19.

Exposure:
On day 1, L5178Y TK−/−-clean cells growing in logarithmic phase were treated in individual 50mL falcon tubes for 4 hours exposition and in T75 cm2 culture flasks for extended exposition. Each tube contained 8.5 mL of cell suspension (6×106 cells in total) in Medium 5. In the next step, 0.5 mL of S9 mixture or medium 5 was added. Then 100 µL solution of test items (20 µL for Trifluoroacetic acid), 100 µL of positive control or vehicle was added. Each tube was fulfilled to the 10 mL volume (short incubation). Each culture flask contained 19.8 mL of cell suspension (4×106 cells in total) in Medium 5. Then 200 µL solution of vehicle and test items (40 µL for Trifluoroacetic acid), 200 µL of positive control or vehicle was added. Each culture flask was fulfilled to the 20 mL volume. Following addition of the test item, the cell suspensions were gently mixed and placed in a CO2 incubator at 37°C for the exposure period. At the end of the exposure time, the cells were pelleted, washed with Medium A and collected by centrifugation, and then resuspended in 20 mL of Medium 10. Cultures were transferred to flasks for growth through the expression period and placed in the CO2 incubator (5% CO2, 37°C).
Cell suspension from each culture was used for counting (post-treatment) and for plating immediately after treatment to obtain Relative Viability (RV) and Relative Total Growth (RTG) values. Portion from the cell suspension was used to prepare 3-step dilution with non-selective (without TFT) Medium 20 to obtain concentration of 8 cells/mL. Using a multichannel pipette, 200 µL of cell suspension was dispensed to each well of two 96-well sterile flat-bottom plates for each tested dose and controls.

Results:
Mutagenic potential of Flufenacet oxalate, Flufenacet sulfonic acid, Trifluoroethanesulfonic acid and Trifluoroacetic acid was evaluated trough Mouse Lymphoma Assay (MLA) in L5178Y cells. Tested items were analyzed in MLA, in the presence and absence of exogenous metabolic activation. Obtained results have shown that tested item did not exceed MF above a value termed as Global Evaluation Factor 126 ×10−6 in any of the tested doses both in the presence and absence of S9 exogenous activation system (Table 9-11).
Obtained results indicate that tested items (Flufenacet oxalate, Flufenacet sulfonic acid, Trifluoroethanesulfonic acid and Trifluoroacetic acid) or their metabolic derivatives were not positive in Mouse Lymphoma Assay under the protocol described and according to the acceptability criteria defined in OECD guideline 490 and SPB-19.

Evaluation of the potential cytotoxic activity of Flufenacet oxalate, Flufenacet sulfonic acid, Trifluoroethanesulfonic acid and Trifluoroacetic acid in the Mouse LymphomaAssay in the presence of S9 fraction – 4h (initial dose range-finding assay).

Cpd.	Conc.	RSG	RTG	RV	RS	Colony counts	% Small colonies	Mutation Frequency [1x10^{-6}]	Fold increase	Induced MF [1x10^{-6}]
Flufenacet sulfonic acid	2000.00 µg/mL	0.64	0.38	119%	60%	51	41%	112.34	0.82	-25
Flufenacet sulfonic acid	666.67 µg/mL	0.49	0.22	100%	46%	53	30%	154.37	1.12	17
Flufenacet sulfonic acid	222.22 µg/mL	1.21	0.97	97%	80%	33	45%	93.14	0.68	-44
Flufenacet sulfonic acid	74.07 µg/mL	1.45	1.32	94%	91%	42	36%	125.90	0.92	-12
Flufenacet sulfonic acid	24.69 µg/mL	0.60	0.52	148%	87%	72	36%	151.31	1.10	14
Flufenacet sulfonic acid	8.23 µg/mL	1.20	0.70	89%	58%	38	29%	117.91	0.86	-20
Flufenacet sulfonic acid	2.74 µg/mL	1.02	0.74	98%	72%	43	49%	123.19	0.90	-14
Flufanecet sulfonic acid	0.00 µg/mL*	1.00	1.00	100%	100%	50	46%	137.48	1.00	0.00
Trifluoroethane sulfonic acid	10.00 mM	0.58	0.55	132%	96%	35	46%	88.29	1.32	21
Trifluoroethane sulfonic acid	3.33 mM	0.75	0.67	83%	89%	28	54%	105.74	1.58	39
Trifluoroethane sulfonic acid	1.11 mM	0.60	0.58	102%	97%	35	43%	114.40	1.71	48
Trifluoroethane sulfonic acid	0.37 mM	0.50	0.49	100%	99%	35	60%	112.47	1.68	46
Trifluoroethane sulfonic acid	0.12 mM	0.67	0.66	111%	99%	36	36%	107.59	1.61	41
Trifluoroethane sulfonic acid	0.04 mM	0.51	0.55	115%	107%	40	35%	113.96	1.70	47
Trifluoroethane sulfonic acid	0.01 mM	0.65	0.77	132%	119%	35	46%	88.29	1.32	21
Trifluoroethane sulfonic acid	0.00 mM*	1.00	1.00	100%	100%	21	48%	66.84	1.00	0

Evaluation of the potential cytotoxic activity of Flufenacet oxalate, Flufenacet sulfonic acid, Trifluoroethanesulfonic acid and Trifluoroacetic acid in the Mouse Lymphoma Assay in the absence of S9 fraction – 4h (initial dose range-finding assay).

Cpd.	Conc.	RSG	RTG	RV	RS	Colony counts	% Small colonies	Mutation Frequency [1x10^{-6}]	Fold increase	Induced MF [1x10^{-6}]
Flufenacet sulfonic acid	2000.00 µg/mL	1.10	1.06	108%	97%	21	57%	59.07	1.16	8
Flufenacet sulfonic acid	666.67 µg/mL	0.71	0.76	135%	107%	23	35%	52.04	1.02	1
Flufenacet sulfonic acid	222.22 µg/mL	0.82	1.09	128%	132%	21	48%	49.92	0.98	-1
Flufenacet sulfonic acid	74.07 µg/mL	0.74	1.00	130%	135%	23	39%	54.00	1.06	3
Flufenacet sulfonic acid	24.69 µg/mL	0.68	0.69	135%	102%	25	64%	56.89	1.11	6
Flufenacet sulfonic acid	8.23 µg/mL	0.56	0.57	112%	102%	19	37%	48.62	0.95	-3
Flufenacet sulfonic acid	2.74 µg/mL	0.64	0.64	138%	100%	22	50%	48.69	0.95	-2
Flufanecet sulfonic acid	0.00 µg/mL*	1.00	1.00	100%	100%	18	56%	51.12	1.00	0

Evaluation of the potential cytotoxic activity of Flufenacet oxalate, Flufenacet sulfonic acid, Trifluoroethanesulfonic acid and Trifluoroacetic acid in the Mouse Lymphoma Assay in the absence of S9 fraction – 24h (initial dose range-finding assay).

Cpd.	Conc.	RSG	RTG	RV	RS	Colony counts	% Small colonies	Mutation Frequency [1x10^{-6}]	Fold increase	Induced MF [1x10^{-6}]

Flufenacet sulfonic acid	2000.00 µg/mL	1.17	1.23	111%	104%	42	50%	106.39	0.88	-15
Flufenacet sulfonic acid	666.67 µg/mL	1.02	1.01	129%	99%	53	49%	116.63	0.96	-5
Flufenacet sulfonic acid	222.22 µg/mL	1.18	1.16	88%	99%	47	47%	152.45	1.26	31
Flufenacet sulfonic acid	74.07 µg/mL	0.76	1.07	80%	141%	42	38%	146.78	1.21	26
Flufenacet sulfonic acid	24.69 µg/mL	0.46	0.51	161%	109%	37	54%	63.60	0.52	-58
Flufenacet sulfonic acid	8.23 µg/mL	0.80	1.12	141%	139%	44	41%	87.97	0.73	-33
Flufenacet sulfonic acid	2.74 µg/mL	1.00	1.57	107%	156%	46	52%	122.29	1.01	1
Flufanecet sulfonic acid	0.00 µg/mL*	1.00	1.00	100%	100%	43	44%	121.17	1.00	0

Evaluation of the potential mutagenic activity of Flufenacet oxalate, Flufenacet sulfonic acid, Trifluoroethanesulfonic acid and Trifluoroacetic acid in the Mouse Lymphoma Assay in the presence of S9 - 4h (Definitive Mutagenicity Assay).

Cpd.	Conc.	RSG	RTG	RV	RS	Colony counts	% Small colonies	Mutation Frequency [1x10^{-6}]	Fold increase	Induced MF [1x10^{-6}]
Flufenacet sulfonic acid	2000 µg/mL	1.26	1.55	96%	123%	23	26%	55.98	0.70	-24
Flufenacet sulfonic acid	1000 µg/mL	1.41	1.77	89%	126%	27	33%	72.43	0.91	-7
Flufenacet sulfonic acid	500 µg/mL	0.88	0.84	100%	95%	32	47%	74.53	0.93	-5
Flufenacet sulfonic acid	250 µg/mL	1.35	1.35	98%	100%	35	57%	86.73	1.09	7
Flufanecet sulfonic acid	0.00 µg/mL*	1.00	1.00	100%	100%	35	49%	79.82	1.00	0

Evaluation of the potential mutagenic activity of Flufenacet oxalate, Flufenacet sulfonic acid, Trifluoroethanesulfonic acid and Trifluoroacetic acid in the Mouse Lymphoma Assay in the absence of S9- 4h (Definitive Mutagenicity Assay).

Cpd.	Conc.	RSG	RTG	RV	RS	Colony counts	% Small colonies	Mutation Frequency [1x10^{-6}]	Fold increase	Induced MF [1x10^{-6}]
Flufenacet sulfonic acid	2000 µg/mL	1.45	1.59	116%	110%	32	56%	106.80	0.93	-8
Flufenacet sulfonic acid	1000 µg/mL	0.75	0.58	135%	78%	34	59%	94.65	0.82	-21
Flufenacet sulfonic acid	500 µg/mL	1.25	1.20	111%	96%	20	60%	67.37	0.58	-48
Flufenacet sulfonic acid	250 µg/mL	1.24	1.01	123%	81%	30	63%	90.29	0.78	-25
Flufanecet sulfonic acid	0.00 µg/mL*	1.00	1.00	100%	100%	31	52%	115.19	1.00	0

Evaluation of the potential mutagenic activity of Flufenacet oxalate, Flufenacet sulfonic acid, Trifluoroethanesulfonic acid and Trifluoroacetic acid in the Mouse Lymphoma Assay in the absence of S9 - 24h (Definitive Mutagenicity Assay).

Cpd.	Conc.	RSG	RTG	RV	RS	Colony counts	% Small colonies	Mutation Frequency [1x10^{-6}]	Fold increase	Induced MF [1x10^{-6}]
Flufenacet sulfonic acid	2000 µg/mL	0.89	0.80	102%	90%	23	57%	57.97	0.94	-4
Flufenacet sulfonic acid	1000 µg/mL	0.89	0.87	75%	98%	17	65%	56.78	0.92	-5
Flufenacet sulfonic acid	500 µg/mL	0.79	0.75	102%	95%	20	70%	49.97	0.81	-12
Flufenacet sulfonic acid	250 µg/mL	0.84	0.89	73%	106%	21	48%	73.05	1.18	11
Flufanecet sulfonic acid	0.00 µg/mL*	1.00	1.00	100%	100%	24	58%	61.71	1.00	0

Comments of zRMS:	The study is considered acceptable. Deviations to OECD 490, 2016 : no historical control data for negative and positive controls. Flufenacet sulfonic acid is negative in the *in vitro* mammalian cell gene mutation test . **Materials** Test material: Flufenacet sulfonic acid Lot/Batch no: EXP-1-5-DFO394 Expiry date: 12/2017 Test system: Cell line: L5178Y TK+/− clone (3.7.2C) Origin: American type culture collection (ATCC) Cat. No: CRL-9518 Lot No: 607 979 977 **MLA test** +S9 - 4 h -S9 - 4 h -S9 - 24 h **Test item concentration** 250, 500, 1000, 2000 µg/mL in DMSO [1% v/v] **Results** None of doses Flufenacet sulfonic acid induced dose-related cytotoxic and mutagenic effects in mouse lymphoma cells under experimental conditions in definitive mutagenicity assays. In the absence and presence of metabolic activation induced mutation frequency level did not exceed 126 $\times 10^{-6}$ in any of the doses tested. MMS and Cp were used in different concentrations as positive controls without or with S9, respectively. Both positive controls yielded MF above 300 $\times 10^{-6}$ in TFT-resistant colonies, therefore indicating the assay sensitivity and responsiveness to mutagens. Negative controls, PBS (for MMS and Cp), DMSO met acceptability criteria defined in OECD 490. Obtained results indicate that the tested item is considered as non-mutagenic under the conditions employed and according to the acceptability criteria defined in OECD guideline 490 and SPB-19.

A 2.12 Operator exposure calculations (KCP 7.2.1.1)

A 2.12.1 Calculations for florasulam

Table A 1: Estimation of operator exposure towards florasulam using the EFSA Model without PPP

Operator exposure for outdoor spray applications

Application rate of active substance	0.0048 kg a.s./ha		*i_AppRate*
Assumed area treated	50 ha/day		*d_AreaTreated*
Amount of active substance applied	0.24 kg a.s./day		*i_AmoutAS*
Dermal absorption of the product	50.00%		*i_AbsorpProduct*
Dermal absorption of in-use dilution	50.00%		*i_AbsorInuse*
Formulation type	Soluble concentrates, emulsifiable concentrate, etc.		
Indoor or Outdoor application	Outdoor		
Application method	Downward spraying		
Application equipment	Vehicle-mounted		
Season	not relevant		

OutdoorSoluble concentrates, emulsifiable concentrate, etc.Downward sprayingVehicle-mounted

	Exposure values	µg exposure/day mixed and loaded		Reference	Comment
		75th centile	95th centile		
Mixing and loading	Hands	1619	5858	AOEM	
	Body	1308	47579	AOEM	
	Head	12	68	AOEM	
	Protected hands (gloves)	14	48	AOEM	
	Protected body (workwear or protective garment and sturdy footwear)	7	35	AOEM	
	Protected head (hood and face shield)	0	4	AOEM	
	Inhalation	2	28	AOEM	
	Protective Equipment	Select for inclusion		Penetration factor	Inhalation Protection factor
	Gloves	No			
	Clothing	Potential exposure		Incl. in AOEM model	
	Head and respiratory PPE	None		1	1
	Water soluble bag	No		1	

	Exposure values	µg exposure/day applied		Reference	Comment
		75th centile	95th centile		
Application	Hands	36	806	AOEM	
	Body	20	103	AOEM	
	Head	1	3	AOEM	
	Protected hands (gloves)	20	2822	AOEM	
	Protected body (workwear or protective garment and sturdy footwear)	1	1	AOEM	
	Inhalation	1	1	AOEM	
	Protective Equipment	Select for inclusion		Penetration factor	Inhalation Protection factor
	Gloves	No			
	Clothing	Potential exposure		Incl. in AOEM model	
	Head and respiratory PPE	None		1	1
	Closed cab	No		vehicle mounted upward spraying only	

1. Total

	Without RPE/PPE	With RPE/PPE	
Longer term			
Total systemic exposure from mixing, loading and application (mg a.s./day)	1.5009209	1.5009209	
Total systemic exposure from mixing, loading and application per kg body weight (mg/kg bw/day)	0.0250153	0.0250153	
% of RVNAS	50.03%	50.03%	

Table A 2: Estimation of operator exposure towards florasulam using the EFSA Model with gloves and protective clothing at mixing/loading

Operator exposure for outdoor spray applications

Application rate of active substance	0.0048 kg a.s./ha		*i_AppRate*
Assumed area treated	50 ha/day		*d_AreaTreated*
Amount of active substance applied	0.24 kg a.s./day		*i_AmoutAS*
Dermal absorption of the product	50.00%		*i_AbsorpProduct*
Dermal absorption of in-use dilution	50.00%		*i_AbsorInuse*
Formulation type	Soluble concentrates, emulsifiable concentrate, etc.		
Indoor or Outdoor application	Outdoor		
Application method	Downward spraying		
Application equipment	Vehicle-mounted		
Season	not relevant		

OutdoorSoluble concentrates, emulsifiable concentrate, etc.Downward sprayingVehicle-mounted

	Exposure values	µg exposure/day mixed and loaded		Reference	Comment
		75th centile	95th centile		
Mixing and loading	Hands	1619	5858	AOEM	
	Body	1308	47579	AOEM	
	Head	12	68	AOEM	
	Protected hands (gloves)	14	48	AOEM	
	Protected body (workwear or protective garment and sturdy footwear)	7	35	AOEM	
	Protected head (hood and face shield)	0	4	AOEM	
	Inhalation	2	28	AOEM	
	Protective Equipment	Select for inclusion		Penetration factor	Inhalation Protection factor
	Gloves	Yes		Incl. in AOEM model	
	Clothing	Work wear - arms, body and legs covered		Incl. in AOEM model	
	Head and respiratory PPE	None		1	1
	Water soluble bag	No		1	

	Exposure values	µg exposure/day applied		Reference	Comment
		75th centile	95th centile		
Application	Hands	36	806	AOEM	
	Body	20	103	AOEM	
	Head	1	3	AOEM	
	Protected hands (gloves)	20	2822	AOEM	
	Protected body (workwear or protective garment and sturdy footwear)	1	1	AOEM	
	Inhalation	1	1	AOEM	
	Protective Equipment	Select for inclusion		Penetration factor	Inhalation Protection factor
	Gloves	No			
	Clothing	Potential exposure		Incl. in AOEM model	
	Head and respiratory PPE	None		1	1
	Closed cab	No		vehicle mounted upward spraying only	

1. Total

	Without RPE/PPE	With RPE/PPE	
Longer term			
Total systemic exposure from mixing, loading and application (mg a.s./day)	1.5009209	0.0475286	
Total systemic exposure from mixing, loading and application per kg body weight (mg/kg bw/day)	0.0250153	0.0007921	
% of RVNAS	50.03%	1.58%	

Calculations for Diflufenican

Table A 1: Estimation of operator exposure towards diflufenican using the EFSA Model without PPP

Operator exposure for outdoor spray applications

Application rate of active substance	0.1	kg a.s./ha	*i_AppRate*
Assumed area treated	50	ha/day	*d_AreaTreated*
Amount of active substance applied	5	kg a.s./day	*i_AmoutAS*
Dermal absorption of the product	10.00%		*i_AbsorpProduct*
Dermal absorption of in-use dilution	50.00%		*i_AbsorInuse*
Formulation type	Soluble concentrates, emulsifiable concentrate, etc.		
Indoor or Outdoor application	Outdoor		
Application method	Downward spraying		
Application equipment	Vehicle-mounted		
Season	not relevant		

	Exposure values	µg exposure/day mixed and loaded 75th centile	95th centile	Reference	Comment
Mixing and loading	Hands	16767	62314	AOEM	
	Body	11058	114960	AOEM	
	Head	259	1423	AOEM	
	Protected hands (gloves)	98	990	AOEM	
	Protected body (workwear or protective garment and sturdy footwear)	99	731	AOEM	
	Protected head (hood and face shield)	4	81	AOEM	
	Inhalation	6	30	AOEM	
	Protective Equipment	Select for inclusion		Penetration factor	Inhalation Protection factor
	Gloves	No			
	Clothing	Potential exposure		Incl. in AOEM model	
	Head and respiratory PPE	None		1	1
	Water soluble bag	No		1	

	Exposure values	µg exposure/day applied 75th centile	95th centile	Reference	Comment
Application	Hands	742	7449	AOEM	
	Body	415	2138	AOEM	
	Head	20	59	AOEM	
	Protected hands (gloves)	102	4021	AOEM	
	Protected body (workwear or protective garment and sturdy footwear)	11	28	AOEM	
	Inhalation	2	7	AOEM	
	Protective Equipment	Select for inclusion		Penetration factor	Inhalation Protection factor
	Gloves	No			
	Clothing	Potential exposure		Incl. in AOEM model	
	Head and respiratory PPE	None		1	1
	Closed cab	No		vehicle mounted upward spraying only	

1. Total

	Without RPE/PPE	With RPE/PPE	
Longer term			
Total systemic exposure from mixing, loading and application (mg a.s./day)	3.4045985	3.4045985	
Total systemic exposure from mixing, loading and application per kg body weight (mg/kg bw/day)	0.0567433	0.0567433	
% of RVNAS	51.58%	51.58%	
Acute			
Total systemic exposure from mixing, loading and application (mg a.s./day)	22.7296048	22.7296048	
Total systemic exposure from mixing, loading and application per kg body weight (mg/kg bw/day)	0.3788267	0.3788267	
% of RVAAS	#DZIEL/0!	#DZIEL/0!	

Table A 2: Estimation of operator exposure towards diflufenican using the EFSA Model with gloves at mixing/loading

Operator exposure for outdoor spray applications

Application rate of active substance	0.1	kg a.s./ha	*i_AppRate*
Assumed area treated	50	ha/day	*d_AreaTreated*
Amount of active substance applied	5	kg a.s./day	*i_AmoutAS*
Dermal absorption of the product	10.00%		*i_AbsorpProduct*
Dermal absorption of in-use dilution	50.00%		*i_AbsorInuse*
Formulation type	Soluble concentrates, emulsifiable concentrate, etc.		
Indoor or Outdoor application	Outdoor		
Application method	Downward spraying		
Application equipment	Vehicle-mounted		
Season	not relevant		

OutdoorSoluble concentrates, emulsifiable concentrate, etc.Downward sprayingVehicle-mounted

	Exposure values	µg exposure/day mixed and loaded 75th centile	95th centile	Reference	Comment
Mixing and loading	Hands	16767	62314	AOEM	
	Body	11058	114960	AOEM	
	Head	259	1423	AOEM	
	Protected hands (gloves)	98	990	AOEM	
	Protected body (workwear or protective garment and sturdy footwear)	99	731	AOEM	
	Protected head (hood and face shield)	4	81	AOEM	
	Inhalation	6	30	AOEM	
	Protective Equipment	Select for inclusion		Penetration factor	Inhalation Protection factor
	Gloves	Yes		Incl. in AOEM model	
	Clothing	Work wear - arms, body and legs covered		Incl. in AOEM model	
	Head and respiratory PPE	None		1	1
	Water soluble bag	No		1	

	Exposure values	µg exposure/day applied 75th centile	95th centile	Reference	Comment
Application	Hands	742	7449	AOEM	
	Body	415	2138	AOEM	
	Head	20	59	AOEM	
	Protected hands (gloves)	102	4021	AOEM	
	Protected body (workwear or protective garment and sturdy footwear)	11	28	AOEM	
	Inhalation	2	7	AOEM	
	Protective Equipment	Select for inclusion		Penetration factor	Inhalation Protection factor
	Gloves	No			
	Clothing	Potential exposure		Incl. in AOEM model	
	Head and respiratory PPE	None		1	1
	Closed cab	No		vehicle mounted upward spraying only	

1. Total

	Without RPE/PPE	With RPE/PPE
Longer term		
Total systemic exposure from mixing, loading and application (mg a.s./day)	3.4045985	0.6418892
Total systemic exposure from mixing, loading and application per kg body weight (mg/kg bw/day)	0.0567433	0.0106982
% of RVNAS	51.58%	9.73%
Acute		
Total systemic exposure from mixing, loading and application (mg a.s./day)	22.7296048	5.1743629
Total systemic exposure from mixing, loading and application per kg body weight (mg/kg bw/day)	0.3788267	0.0862394
% of RVAAS	#DZIEL/0!	#DZIEL/0!

A 2.12.2 Calculations for Flufenacet

Table A 1: Estimation of operator exposure towards flufenacet using the EFSA Model without PPP

Operator exposure for outdoor spray applications

Application rate of active substance	0.1248	kg a.s./ha	*i_AppRate*
Assumed area treated	50	ha/day	*d_AreaTreated*
Amount of active substance applied	6.24	kg a.s./day	*i_AmoutAS*
Dermal absorption of the product	10.00%		*i_AbsorpProduct*
Dermal absorption of in-use dilution	50.00%		*i_AbsorInuse*
Formulation type	Soluble concentrates, emulsifiable concentrate, etc.		
Indoor or Outdoor application	Outdoor		
Application method	Downward spraying		
Application equipment	Vehicle-mounted		
Season	not relevant		

	Exposure values	µg exposure/day mixed and loaded 75th centile	95th centile	Reference	Comment
Mixing and loading	Hands	19885	74046	AOEM	
	Body	12921	122602	AOEM	
	Head	324	1776	AOEM	
	Protected hands (gloves)	113	1236	AOEM	
	Protected body (workwear or protective garment and sturdy footwear)	120	913	AOEM	
	Protected head (hood and face shield)	5	101	AOEM	
	Inhalation	6	30	AOEM	
	Protective Equipment	Select for inclusion		Penetration factor	Inhalation Protection factor
	Gloves	No			
	Clothing	Potential exposure		Incl. in AOEM model	
	Head and respiratory PPE	None		1	1
	Water soluble bag	No		1	

	Exposure values	µg exposure/day applied 75th centile	95th centile	Reference	Comment
Application	Hands	926	8761	AOEM	
	Body	517	2668	AOEM	
	Head	24	74	AOEM	
	Protected hands (gloves)	115	4126	AOEM	
	Protected body (workwear or protective garment and sturdy footwear)	14	35	AOEM	
	Inhalation	3	8	AOEM	
	Protective Equipment	Select for inclusion		Penetration factor	Inhalation Protection factor
	Gloves	No			
	Clothing	Potential exposure		Incl. in AOEM model	
	Head and respiratory PPE	None		1	1
	Closed cab	No		vehicle mounted upward spraying only	

1. Total

	Without RPE/PPE	With RPE/PPE	
Longer term			
Total systemic exposure from mixing, loading and application (mg a.s./day)	4.0556382	4.0556382	
Total systemic exposure from mixing, loading and application per kg body weight (mg/kg bw/day)	0.0675940	0.0675940	
% of RVNAS	397.61%	397.61%	
Acute			
Total systemic exposure from mixing, loading and application (mg a.s./day)	25.6320504	25.6320504	
Total systemic exposure from mixing, loading and application per kg body weight (mg/kg bw/day)	0.4272008	0.4272008	
% of RVAAS	#DZIEL/0!	#DZIEL/0!	

Table A 2: Estimation of operator exposure towards flufenacet using the EFSA Model with gloves and protective clothing at mixing/loading

Operator exposure for outdoor spray applications

Application rate of active substance	0.1248	kg a.s./ha	*i_AppRate*
Assumed area treated	50	ha/day	*d_AreaTreated*
Amount of active substance applied	6.24	kg a.s./day	*i_AmoutAS*
Dermal absorption of the product	10.00%		*i_AbsorpProduct*
Dermal absorption of in-use dilution	50.00%		*i_AbsorInuse*
Formulation type	Soluble concentrates, emulsifiable concentrate, etc.		
Indoor or Outdoor application	Outdoor		
Application method	Downward spraying		
Application equipment	Vehicle-mounted		
Season	not relevant		

Outdoor;soluble concentrates, emulsifiable concentrate, etc;Downward spraying;Vehicle-mounted

	Exposure values	µg exposure/day mixed and loaded 75th centile	95th centile	Reference	Comment
Mixing and loading	Hands	19885	74046	AOEM	
	Body	12921	122602	AOEM	
	Head	324	1776	AOEM	
	Protected hands (gloves)	113	1236	AOEM	
	Protected body (workwear or protective garment and sturdy footwear)	120	913	AOEM	
	Protected head (hood and face shield)	5	101	AOEM	
	Inhalation	6	30	AOEM	
	Protective Equipment	Select for inclusion		Penetration factor	Inhalation Protection factor
	Gloves	Yes		Incl. in AOEM model	
	Clothing	Work wear - arms, body and legs covered		Incl. in AOEM model	
	Head and respiratory PPE	None		1	1
	Water soluble bag	No		1	

	Exposure values	µg exposure/day applied 75th centile	95th centile	Reference	Comment
Application	Hands	926	8761	AOEM	
	Body	517	2668	AOEM	
	Head	24	74	AOEM	
	Protected hands (gloves)	115	4126	AOEM	
	Protected body (workwear or protective garment and sturdy footwear)	14	35	AOEM	
	Inhalation	3	8	AOEM	
	Protective Equipment	Select for inclusion		Penetration factor	Inhalation Protection factor
	Gloves	No			
	Clothing	Potential exposure		Incl. in AOEM model	
	Head and respiratory PPE	None		1	1
	Closed cab	No		vehicle mounted upward spraying only	

1. Total

	Without RPE/PPE	With RPE/PPE	
Longer term			
Total systemic exposure from mixing, loading and application (mg a.s./day)	4.0556382	0.7984812	
Total systemic exposure from mixing, loading and application per kg body weight (mg/kg bw/day)	0.0675940	0.0133080	
% of RVNAS	397.61%	78.28%	
Acute			
Total systemic exposure from mixing, loading and application (mg a.s./day)	25.6320504	6.1820099	
Total systemic exposure from mixing, loading and application per kg body weight (mg/kg bw/day)	0.4272008	0.1030335	
% of RVAAS	#DZIEL/0!	#DZIEL/0!	

A 2.13 Worker exposure calculations (KCP 7.2.3.1)

A 2.13.1 Calculations for florasulam

Worker exposure from residues on foliage for			
Crop type	Cereals		
Indoor or outdoor	Outdoor		
Application method	Downward spraying		
Application equipment	Vehicle-mounted		
Worker's task	Inspection, irrigation		
Main body parts in contact with foliage	Hand and body		
Application rate of active substance	0.0048	kg a.s./ha	*i_AppRate*
Number of applications	1		*i_AppNo*
Interval between multiple applications	365	days	*i_AppInt*
Half-life of active substance	30	days	*d_HalflifeAS*
Multiple application factor	1.0		*d_MAF*
Dermal absorption of the product	50.00%		*i_AbsorpProduct*
Dermal absorption of the in-use dilution	50.00%		*i_AbsorpInuse*
Dislodgeable foliar residue (i_AppRate*i_DFR)	0.0144	µg a.s./cm^2	*d_DFR*
Working hours	2	hr	*d_WorkHr*
Dermal transfer coefficient - Total potential exposure	12500	cm^2/hr	*d_DermTcUCV*
Dermal transfer coefficient - arms, body and legs covered	1400	cm^2/hr	*d_DermTcCV1*
Dermal transfer coefficient - hands, arms, body and legs covered	no TC available for this assessment	cm^2/hr	*d_DermTcCV2*
Inhalation transfer coefficient for automated applications	NA	ha/hr*10^(-3)	*d_InhalTcAut*
Inhalation transfer coefficient for cutting ornamentals	NA	ha/hr*10^(-3)	*d_InhalTcCut*
Inhalation transfer coefficient for sorting / bundling ornamentals	NA	ha/hr*10^(-3)	*d_InhalTcSort*

1. Total

	Potential exposure	Work wear - arms, body and legs covered	Working wear and gloves	Comments
Total systemic exposure (mg a.s./day)	0.1800000	0.0201600	no TC available for this assessment	
Total systemic exposure per kg body weight (mg/kg bw/day)	0.0030000	0.0003360		
% of RVNAS	6.00%	0.67%		

A 2.13.2 Calculations for diflufenican

Worker exposure from residues on foliage for			
Crop type	Cereals		
Indoor or outdoor	Outdoor		
Application method	Downward spraying		
Application equipment	Vehicle-mounted		
Worker's task	Inspection, irrigation		
Main body parts in contact with foliage	Hand and body		
Application rate of active substance	0.1	kg a.s./ha	*i_AppRate*
Number of applications	1		*i_AppNo*
Interval between multiple applications	365	days	*i_AppInt*
Half-life of active substance	30	days	*d_HalflifeAS*
Multiple application factor	1.0		*d_MAF*
Dermal absorption of the product	10.00%		*i_AbsorpProduct*
Dermal absorption of the in-use dilution	50.00%		*i_AbsorpInuse*
Dislodgeable foliar residue (i_AppRate*i_DFR)	0.3	µg a.s./cm^2	*d_DFR*
Working hours	2	hr	*d_WorkHr*
Dermal transfer coefficient - Total potential exposure	12500	cm^2/hr	*d_DermTcUCV*
Dermal transfer coefficient - arms, body and legs covered	1400	cm^2/hr	*d_DermTcCV1*
Dermal transfer coefficient - hands, arms, body and legs covered	no TC available for this assessment	cm^2/hr	*d_DermTcCV2*
Inhalation transfer coefficient for automated applications	NA	ha/hr*10^(-3)	*d_InhalTcAut*
Inhalation transfer coefficient for cutting ornamentals	NA	ha/hr*10^(-3)	*d_InhalTcCut*
Inhalation transfer coefficient for sorting / bundling ornamentals	NA	ha/hr*10^(-3)	*d_InhalTcSort*

1. Total

	Potential exposure	Work wear - arms, body and legs covered	Working wear and gloves	Comments
Total systemic exposure (mg a.s./day)	3.7500000	0.4200000	no TC available for this assessment	
Total systemic exposure per kg body weight (mg/kg bw/day)	0.0625000	0.0070000		
% of RVNAS	56.82%	6.36%		

A 2.13.3 Calculations for flufenacet

Worker exposure from residues on foliage for			
Crop type	Cereals		
Indoor or outdoor	Outdoor		
Application method	Downward spraying		
Application equipment	Vehicle-mounted		
Worker's task	Inspection, irrigation		
Main body parts in contact with foliage	Hand and body		
Application rate of active substance	0.1248	kg a.s./ha	*i_AppRate*
Number of applications	1		*i_AppNo*
Interval between multiple applications	365	days	*i_AppInt*
Half-life of active substance	30	days	*d_HalflifeAS*
Multiple application factor	1.0		*d_MAF*
Dermal absorption of the product	10.00%		*i_AbsorpProduct*
Dermal absorption of the in-use dilution	50.00%		*i_AbsorpInuse*
Dislodgeable foliar residue (i_AppRate*i_DFR)	0.3744	µg a.s./cm^2	*d_DFR*
Working hours	2	hr	*d_WorkHr*
Dermal transfer coefficient - Total potential exposure	12500	cm^2/hr	*d_DermTcUCV*
Dermal transfer coefficient - arms, body and legs covered	1400	cm^2/hr	*d_DermTcCV1*
Dermal transfer coefficient - hands, arms, body and legs covered	no TC available for this assessment	cm^2/hr	*d_DermTcCV2*
Inhalation transfer coefficient for automated applications	NA	ha/hr*10^(-3)	*d_InhalTcAut*
Inhalation transfer coefficient for cutting ornamentals	NA	ha/hr*10^(-3)	*d_InhalTcCut*
Inhalation transfer coefficient for sorting / bundling ornamentals	NA	ha/hr*10^(-3)	*d_InhalTcSort*

1. Total

	Potential exposure	Work wear - arms, body and legs covered	Working wear and gloves	Comments
Total systemic exposure (mg a.s./day)	4.6800000	0.5241600	no TC available for this assessment	
Total systemic exposure per kg body weight (mg/kg bw/day)	0.0780000	0.0087360		
% of RVNAS	458.82%	51.39%		

A 2.14 Resident and bystander exposure calculations (KCP 7.2.2.1)

A 2.14.1 Calculations for florasulam

Resident exposure for				
Croptype	Cereals			
Application method	Downward spraying			
Application equipment	Vehicle-mounted			*i_AppEquip*
Formulation type	Soluble concentrates, emulsifiable concentrate, etc.			*i_FormVal*
Buffer strip	2-3	m		*i_Buffer*
Application rate of the product	0.0048	kg a.s./ha		*i_AppRate*
Concentration of active substance (in-use dilution for liquid applications)	0.024	g a.s./l		*d_ConcAS*
Dermal absorption of product	50.00%			*i_AbsorpProduct*
Dermal absorption of in-use dilution	50.00%			*i_AbsorpInuse*
Oral absorption	100.00%			*i_AbsorpOralInuse*
Dislodgeable foliar residue (i_AppRate*i_DFR)	0.0144	µg a.s./cm^2		*d_DFR*
Vapour pressure of in-use dilution	low volatile substances having a vapour pressure of <5*10-3Pa	Pa		*i_Volat*
Concentration in air	0.001	mg/m^3		*d_AirCon*
Resident dermal spray drift exposure 75th percentile - adult	0.47	ml spray dilution/person		
Resident dermal spray drift exposure 75th percentile - child	0.327	ml spray dilution/person		
Resident inhal. spray drift exposure 75th percentile - adult	0.00010	ml spray dilution/person		
Resident inhal. spray drift exposure 75th percentile - child	0.00022	ml spray dilution/person		
Resident dermal spray drift exposure mean - adult	0.22318	ml spray dilution/person		
Resident dermal spray drift exposure mean - child	0.18	ml spray dilution/person		
Resident inhal. spray drift exposure mean - adult	0.00009	ml spray dilution/person		
Resident inhal. spray drift exposure mean - child	0.00017	ml spray dilution/person		
Exposure duration dermal	2	hours		*d_ReExpDur*
Exposure duration inhalation	24	hours		*d_ReExpDurInhal*
Exposure duration entry into treated crops	0.25	hours		*d_ExpDurTreatCrop*
Light clothing adjustment factor	18.0%			*d_ClothAF*
Breathing rate adult	0.23	m^3/day/kg		*d_BreathRAd*
Breathing rate child (1-3 year old)	1.07	m^3/day/kg		*d_BreathRCh*
Drift percentage on surface (75th percentile)	5.60%			
Drift percentage on surface (mean)	4.10%			
Turf transferable residues percentage	5.00%			*d_Turf*
Transfer coeff. of surface deposits-adult	7300	cm^2/hour		*d_ReTCAd*
Transfer coeff. of surface deposits-child (1-3 year old)	2600	cm^2/hour		*d_ReTCCh*
Saliva extraction percentage	50.00%			*d_SalExt*
Surface area of hands mouthed	20	cm^2		*d_AreaHM*
Frequency of hand to mouth activity	9.5	events/hour		*d_ReFreqHM*
Ingestion rate for mouthing of grass per day	25	cm^2		*d_MouthGrass*
Dislodgeable residues percentage transferability for object to mouth	20.00%			*d_DRP*
Transfer coefficient for entry into treated crops (75th percentile) - ad	7500	cm^2/h		*d_TcEntryAd*
Transfer coefficient for entry into treated crops (75th percentile) - ch	2250	cm^2/h		*d_TcEntryCh*
Transfer coefficient for entry into treated crops (mean) - adult	5980	cm^2/h		*d_TcEntryAd*
Transfer coefficient for entry into treated crops (mean) - child	1794	cm^2/h		*d_TcEntryCh*

1. Total

1.1 1-3 year old child

	Spray drift (75th percentile)	Vapour (75th percentile)	Surface deposits (75th percentile)	Entry into treated crops (75th percentile)	All pathways (mean)
Total systemic exposure (mg a.s./day)	0.0032230	0.0107000	0.0003884	0.0040500	0.0159889
Total systemic exposure per kg body weight	0.0003223	0.0010700	0.0000388	0.0004050	0.0015989
% of RVNAS	0.64%	2.14%	0.08%	0.81%	3.20%

1.2 Adult

	Spray drift	Vapour	Surface deposits	Entry into treated crops	All pathways (mean)
Total systemic exposure (mg a.s./day)	0.0046272	0.0138000	0.0009811	0.0135000	0.0274806
Total systemic exposure per kg body weight	0.0000771	0.0002300	0.0000164	0.0002250	0.0004580
% of RVNAS	0.15%	0.46%	0.03%	0.45%	0.92%

A 2.14.2 Calculations for diflufenican

Resident exposure for				
Croptype	Cereals			
Application method	Downward spraying			
Application equipment	Vehicle-mounted			*i_AppEquip*
Formulation type	Soluble concentrates, emulsifiable concentrate, etc.			*i_FormVal*
Buffer strip	2-3	m		*i_Buffer*
Application rate of the product	0.1	kg a.s./ha		*i_AppRate*
Concentration of active substance (in-use dilution for liquid applications)	0.5	g a.s./l		*d_ConcAS*
Dermal absorption of product	10.00%			*i_AbsorpProduct*
Dermal absorption of in-use dilution	50.00%			*i_AbsorpInuse*
Oral absorption	100.00%			*i_AbsorpOralInuse*
Dislodgeable foliar residue (i_AppRate*i_DFR)	0.3	µg a.s./cm^2		*d_DFR*
Vapour pressure of in-use dilution	low volatile substances having a vapour pressure of <5*10-3Pa	Pa		*i_Volat*
Concentration in air	0.001	mg/m^3		*d_AirCon*
Resident dermal spray drift exposure 75th percentile - adult	0.47	ml spray dilution/person		
Resident dermal spray drift exposure 75th percentile - child	0.327	ml spray dilution/person		
Resident inhal. spray drift exposure 75th percentile - adult	0.00010	ml spray dilution/person		
Resident inhal. spray drift exposure 75th percentile - child	0.00022	ml spray dilution/person		
Resident dermal spray drift exposure mean - adult	0.22318	ml spray dilution/person		
Resident dermal spray drift exposure mean - child	0.18	ml spray dilution/person		
Resident inhal. spray drift exposure mean - adult	0.00009	ml spray dilution/person		
Resident inhal. spray drift exposure mean - child	0.00017	ml spray dilution/person		
Exposure duration dermal	2	hours		*d_ReExpDur*
Exposure duration inhalation	24	hours		*d_ReExpDurInhal*
Exposure duration entry into treated crops	0.25	hours		*d_ExpDurTreatCrop*
Light clothing adjustment factor	18.0%			*d_ClothAF*
Breathing rate adult	0.23	m^3/day/kg		*d_BreathRAd*
Breathing rate child (1-3 year old)	1.07	m^3/day/kg		*d_BreathRCh*
Drift percentage on surface (75th percentile)	5.60%			
Drift percentage on surface (mean)	4.10%			
Turf transferable residues percentage	5.00%			*d_Turf*
Transfer coeff. of surface deposits-adult	7300	cm^2/hour		*d_ReTCAd*
Transfer coeff. of surface deposits-child (1-3 year old)	2600	cm^2/hour		*d_ReTCCh*
Saliva extraction percentage	50.00%			*d_SalExt*
Surface area of hands mouthed	20	cm^2		*d_AreaHM*
Frequency of hand to mouth activity	9.5	events/hour		*d_ReFreqHM*
Ingestion rate for mouthing of grass per day	25	cm^2		*d_MouthGrass*
Dislodgeable residues percentage transferability for object to mouth	20.00%			*d_DRP*
Transfer coefficient for entry into treated crops (75th percentile) - ad	7500	cm^2/h		*d_TcEntryAd*
Transfer coefficient for entry into treated crops (75th percentile) - ch	2250	cm^2/h		*d_TcEntryCh*
Transfer coefficient for entry into treated crops (mean) - adult	5980	cm^2/h		*d_TcEntryAd*
Transfer coefficient for entry into treated crops (mean) - child	1794	cm^2/h		*d_TcEntryCh*

1. Total

1.1 1-3 year old child

	Spray drift (75th percentile)	Vapour (75th percentile)	Surface deposits (75th percentile)	Entry into treated crops (75th percentile)	All pathways (mean)
Total systemic exposure (mg a.s./day)	0.0671450	0.0107000	0.0080920	0.0843750	0.1208845
Total systemic exposure per kg body weight	0.0067145	0.0010700	0.0008092	0.0084375	0.0120885
% of RVNAS	6.10%	0.97%	0.74%	7.67%	10.99%

1.2 Adult

	Spray drift	Vapour	Surface deposits	Entry into treated crops	All pathways (mean)
Total systemic exposure (mg a.s./day)	0.0964000	0.0138000	0.0204400	0.2812500	0.2988119
Total systemic exposure per kg body weight	0.0016067	0.0002300	0.0003407	0.0046875	0.0049802
% of RVNAS	1.46%	0.21%	0.31%	4.26%	4.53%

A 2.14.3 Calculations for flufenacet

Resident exposure for				
Croptype	Cereals			
Application method	Downward spraying			
Application equipment	Vehicle-mounted			*i_AppEquip*
Formulation type	Soluble concentrates, emulsifiable concentrate, etc.			*i_FormVal*
Buffer strip	2-3	m		*i_Buffer*
Application rate of the product	0.1248	kg a.s./ha		*i_AppRate*
Concentration of active substance (in-use dilution for liquid applications)	0.624	g a.s./l		*d_ConcAS*
Dermal absorption of product	10.00%			*i_AbsorpProduct*
Dermal absorption of in-use dilution	50.00%			*i_AbsorpInuse*
Oral absorption	100.00%			*i_AbsorpOralInuse*
Dislodgeable foliar residue (i_AppRate*i_DFR)	0.3744	µg a.s./cm^2		*d_DFR*
Vapour pressure of in-use dilution	low volatile substances having a vapour pressure of <5*10-3Pa	Pa		*i_Volat*
Concentration in air	0.001	mg/m^3		*d_AirCon*
Resident dermal spray drift exposure 75th percentile - adult	0.47	ml spray dilution/person		
Resident dermal spray drift exposure 75th percentile - child	0.327	ml spray dilution/person		
Resident inhal. spray drift exposure 75th percentile - adult	0.00010	ml spray dilution/person		
Resident inhal. spray drift exposure 75th percentile - child	0.00022	ml spray dilution/person		
Resident dermal spray drift exposure mean - adult	0.22318	ml spray dilution/person		
Resident dermal spray drift exposure mean - child	0.18	ml spray dilution/person		
Resident inhal. spray drift exposure mean - adult	0.00009	ml spray dilution/person		
Resident inhal. spray drift exposure mean - child	0.00017	ml spray dilution/person		
Exposure duration dermal	2	hours		*d_ReExpDur*
Exposure duration inhalation	24	hours		*d_ReExpDurInhal*
Exposure duration entry into treated crops	0.25	hours		*d_ExpDurTreatCrop*
Light clothing adjustment factor	18.0%			*d_ClothAF*
Breathing rate adult	0.23	m^3/day/kg		*d_BreathRAd*
Breathing rate child (1-3 year old)	1.07	m^3/day/kg		*d_BreathRCh*
Drift percentage on surface (75th percentile)	5.60%			
Drift percentage on surface (mean)	4.10%			
Turf transferable residues percentage	5.00%			*d_Turf*
Transfer coeff. of surface deposits-adult	7300	cm^2/hour		*d_ReTCAd*
Transfer coeff. of surface deposits-child (1-3 year old)	2600	cm^2/hour		*d_ReTCCh*
Saliva extraction percentage	50.00%			*d_SalExt*
Surface area of hands mouthed	20	cm^2		*d_AreaHM*
Frequency of hand to mouth activity	9.5	events/hour		*d_ReFreqHM*
Ingestion rate for mouthing of grass per day	25	cm^2		*d_MouthGrass*
Dislodgeable residues percentage transferability for object to mouth	20.00%			*d_DRP*
Transfer coefficient for entry into treated crops (75th percentile) - ad	7500	cm^2/h		*d_TcEntryAd*
Transfer coefficient for entry into treated crops (75th percentile) - ch	2250	cm^2/h		*d_TcEntryCh*
Transfer coefficient for entry into treated crops (mean) - adult	5980	cm^2/h		*d_TcEntryAd*
Transfer coefficient for entry into treated crops (mean) - child	1794	cm^2/h		*d_TcEntryCh*

1. Total

1.1 1-3 year old child

	Spray drift (75th percentile)	Vapour (75th percentile)	Surface deposits (75th percentile)	Entry into treated crops (75th percentile)	All pathways (mean)
Total systemic exposure (mg a.s./day)	0.0837970	0.0107000	0.0100988	0.1053000	0.1482103
Total systemic exposure per kg body weight	0.0083797	0.0010700	0.0010099	0.0105300	0.0148210
% of RVNAS	49.29%	6.29%	5.94%	61.94%	87.18%

1.2 Adult

	Spray drift	Vapour	Surface deposits	Entry into treated crops	All pathways (mean)
Total systemic exposure (mg a.s./day)	0.1203072	0.0138000	0.0255091	0.3510000	0.3694949
Total systemic exposure per kg body weight	0.0020051	0.0002300	0.0004252	0.0058500	0.0061582
% of RVNAS	11.79%	1.35%	2.50%	34.41%	36.22%

Resident exposure for				
Croptype	Cereals			
Application method	Downward spraying			
Application equipment	Vehicle-mounted			*i_AppEquip*
Formulation type	Soluble concentrates, emulsifiable concentrate, etc.			*i_FormVal*
Buffer strip	5	m		*i_Buffer*
Application rate of the product	0.1248	kg a.s./ha		*i_AppRate*
Concentration of active substance (in-use dilution for liquid applications)	0.624	g a.s./l		*d_ConcAS*
Dermal absorption of product	10.00%			*i_AbsorpProduct*
Dermal absorption of in-use dilution	50.00%			*i_AbsorpInuse*
Oral absorption	100.00%			*i_AbsorpOralInuse*
Dislodgeable foliar residue (i_AppRate*i_DFR)	0.3744	µg a.s./cm^2		*d_DFR*
Vapour pressure of in-use dilution	low volatile substances having a vapour pressure of <5*10-3Pa	Pa		*i_Volat*
Concentration in air	0.001	mg/m^3		*d_AirCon*
Resident dermal spray drift exposure 75th percentile - adult	0.23798	ml spray dilution/person		
Resident dermal spray drift exposure 75th percentile - child	0.2175	ml spray dilution/person		
Resident inhal. spray drift exposure 75th percentile - adult	0.00009	ml spray dilution/person		
Resident inhal. spray drift exposure 75th percentile - child	0.00017	ml spray dilution/person		
Resident dermal spray drift exposure mean - adult	0.12278	ml spray dilution/person		
Resident dermal spray drift exposure mean - child	0.12	ml spray dilution/person		
Resident inhal. spray drift exposure mean - adult	0.00008	ml spray dilution/person		
Resident inhal. spray drift exposure mean - child	0.00014	ml spray dilution/person		
Exposure duration dermal	2	hours		*d_ReExpDur*
Exposure duration inhalation	24	hours		*d_ReExpDurInhal*
Exposure duration entry into treated crops	0.25	hours		*d_ExpDurTreatCrop*
Light clothing adjustment factor	18.0%			*d_ClothAF*
Breathing rate adult	0.23	m^3/day/kg		*d_BreathRAd*
Breathing rate child (1-3 year old)	1.07	m^3/day/kg		*d_BreathRCh*
Drift percentage on surface (75th percentile)	2.30%			
Drift percentage on surface (mean)	1.80%			
Turf transferable residues percentage	5.00%			*d_Turf*
Transfer coeff. of surface deposits-adult	7300	cm^2/hour		*d_ReTCAd*
Transfer coeff. of surface deposits-child (1-3 year old)	2600	cm^2/hour		*d_ReTCCh*
Saliva extraction percentage	50.00%			*d_SalExt*
Surface area of hands mouthed	20	cm^2		*d_AreaHM*
Frequency of hand to mouth activity	9.5	events/hour		*d_ReFreqHM*
Ingestion rate for mouthing of grass per day	25	cm^2		*d_MouthGrass*
Dislodgeable residues percentage transferability for object to mouth	20.00%			*d_DRP*
Transfer coefficient for entry into treated crops (75th percentile) - ad	7500	cm^2/h		*d_TcEntryAd*
Transfer coefficient for entry into treated crops (75th percentile) - ch	2250	cm^2/h		*d_TcEntryCh*
Transfer coefficient for entry into treated crops (mean) - adult	5980	cm^2/h		*d_TcEntryAd*
Transfer coefficient for entry into treated crops (mean) - child	1794	cm^2/h		*d_TcEntryCh*

1. Total

1.1 1-3 year old child

	Spray drift (75th percentile)	Vapour (75th percentile)	Surface deposits (75th percentile)	Entry into treated crops (75th percentile)	All pathways (mean)
Total systemic exposure (mg a.s./day)	0.0557513	0.0107000	0.0041477	0.1053000	0.1286934
Total systemic exposure per kg body weight	0.0055751	0.0010700	0.0004148	0.0105300	0.0128693
% of RVNAS	32.79%	6.29%	2.44%	61.94%	75.70%

1.2 Adult

	Spray drift	Vapour	Surface deposits	Entry into treated crops	All pathways (mean)
Total systemic exposure (mg a.s./day)	0.0609410	0.0138000	0.0104770	0.3510000	0.3333253
Total systemic exposure per kg body weight	0.0010157	0.0002300	0.0001746	0.0058500	0.0055554
% of RVNAS	5.97%	1.35%	1.03%	34.41%	32.68%

A 2.15 Combined exposure calculations for florasulam, diflufenican and flufenacet

Application scenario	Active ingredient	Estimated exposure / AAOEL (HQ)
Operators –with PPE (glove + work wear during mix/loading)	Florasulam	0.0158
	Diflufenican	0.0973
	Flufenacet	0.7828
	Cumulative risk operators (HI)	**0.8959**

Application scenario	Active ingredient	Estimated exposure / AAOEL (HQ)
Workers – with PPE	Florasulam	0.0067
	Diflufenican	0.0636
	Flufenacet	0.5139
	Cumulative risk workers (HI)	**0.5842**
Bystander – child with 5 meters buffer zone	Florasulam	0.0320
	Diflufenican	0.1033
	Flufenacet	0.7570
	Cumulative risk bystander – child (HI)	**0.8923**
Bystander - adult with 5 meters buffer zone	Florasulam	0.0092
	Diflufenican	0.0443
	Flufenacet	0.3268
	Cumulative risk bystander – adult (HI)	**0.3803**
Resident – child with 5 meters buffer zone	Florasulam	0.0320
	Diflufenican	0.1033
	Flufenacet	0.7570
	Cumulative risk bystander – child (HI)	**0.8923**
Resident - adult with 5 meters buffer zone	Florasulam	0.0092
	Diflufenican	0.0443
	Flufenacet	0.3268
	Cumulative risk bystander – adult (HI)	**0.3803**

Calculation

Model AOEM - Operator – florasulam-workwear

Operator exposure for outdoor spray applications

Application rate of active substance	0,0048	kg a.s./ha	*i_AppRate*
Assumed area treated	50	ha/day	*d_AreaTreated*
Amount of active substance applied	0,24	kg a.s./day	*i_AmoutAS*
Dermal absorption of the product	50,00%		*i_AbsorpProduct*
Dermal absorption of in-use dilution	50,00%		*i_AbsorInuse*
Formulation type	Soluble concentrates, emulsifiable concentrate, etc.		
Indoor or Outdoor application	Outdoor		
Application method	Downward spraying		
Application equipment	Vehicle-mounted		
Season	not relevant		

OutdoorSoluble concentrates, emulsifiable concentrate, etc.Downward sprayingVehicle-mounted

	Exposure values	µg exposure/day mixed and loaded		Reference	Comment
		75th centile	95th centile		
Mixing and loading	Hands	1619	5858	AOEM	
	Body	1308	47579	AOEM	
	Head	12	68	AOEM	
	Protected hands (gloves)	14	48	AOEM	
	Protected body (workwear or protective garment and sturdy footwear)	7	35	AOEM	
	Protected head (hood and face shield)	0	4	AOEM	
	Inhalation	2	28	AOEM	
	Protective Equipment	Select for inclusion		Penetration factor	Inhalation Protection factor
	Gloves	No			
	Clothing	Work wear - arms, body and legs covered		Incl. in AOEM model	
	Head and respiratory PPE	None		1	1
	Water soluble bag	No		1	

	Exposure values	µg exposure/day applied		Reference	Comment
		75th centile	95th centile		
Application	Hands	36	806	AOEM	
	Body	20	103	AOEM	
	Head	1	3	AOEM	
	Protected hands (gloves)	20	2822	AOEM	
	Protected body (workwear or protective garment and sturdy footwear)	1	1	AOEM	
	Inhalation	1	1	AOEM	
	Protective Equipment	Select for inclusion		Penetration factor	Inhalation Protection factor
	Gloves	No			
	Clothing	Work wear - arms, body and legs covered		Incl. in AOEM model	
	Head and respiratory PPE	None		1	1
	Closed cab	No		vehicle mounted upward spraying only	

1. Total

	Without RPE/PPE	With RPE/PPE	
Longer term			
Total systemic exposure from mixing, loading and application (mg a.s./day)	1,5009209	0,8405147	
Total systemic exposure from mixing, loading and application per kg body weight (mg/kg bw/day)	0,0250153	0,0140086	
% of RVNAS	50,03%	28,02%	
Acute			
Total systemic exposure from mixing, loading and application (mg a.s./day)	27,2371291	3,4145049	
Total systemic exposure from mixing, loading and application per kg body weight (mg/kg bw/day)	0,4539522	0,0569084	
% of RVAAS	#DZIEL/0!	#DZIEL/0!	

Model AOEM - Operator – florasulam-workwear + gloves during M/L

Operator exposure for outdoor spray applications

Application rate of active substance	0,0048	kg a.s./ha	*i_AppRate*
Assumed area treated	50	ha/day	*d_AreaTreated*
Amount of active substance applied	0,24	kg a.s./day	*i_AmoutAS*
Dermal absorption of the product	50,00%		*i_AbsorpProduct*
Dermal absorption of in-use dilution	50,00%		*i_AbsorInuse*
Formulation type	Soluble concentrates, emulsifiable concentrate, etc.		
Indoor or Outdoor application	Outdoor		
Application method	Downward spraying		
Application equipment	Vehicle-mounted		
Season	not relevant		

OutdoorSoluble concentrates, emulsifiable concentrate, etc.Downward sprayingVehicle-mounted

	Exposure values	µg exposure/day mixed and loaded		Reference	Comment
		75th centile	95th centile		
Mixing and loading	Hands	1619	5858	AOEM	
	Body	1308	47579	AOEM	
	Head	12	68	AOEM	
	Protected hands (gloves)	14	48	AOEM	
	Protected body (workwear or protective garment and sturdy footwear)	7	35	AOEM	
	Protected head (hood and face shield)	0	4	AOEM	
	Inhalation	2	28	AOEM	
	Protective Equipment	Select for inclusion		Penetration factor	Inhalation Protection factor
	Gloves	Yes		Incl. in AOEM model	
	Clothing	Work wear - arms, body and legs covered		Incl. in AOEM model	
	Head and respiratory PPE	None		1	1
	Water soluble bag	No		1	

	Exposure values	µg exposure/day applied		Reference	Comment
		75th centile	95th centile		
Application	Hands	36	806	AOEM	
	Body	20	103	AOEM	
	Head	1	3	AOEM	
	Protected hands (gloves)	20	2822	AOEM	
	Protected body (workwear or protective garment and sturdy footwear)	1	1	AOEM	
	Inhalation	1	1	AOEM	
	Protective Equipment	Select for inclusion		Penetration factor	Inhalation Protection factor
	Gloves	No			
	Clothing	Work wear - arms, body and legs covered		Incl. in AOEM model	
	Head and respiratory PPE	None		1	1
	Closed cab	No		vehicle mounted upward spraying only	

1. Total

	Without RPE/PPE	With RPE/PPE	
Longer term			
Total systemic exposure from mixing, loading and application (mg a.s./day)	1,5009209	0,0378497	
Total systemic exposure from mixing, loading and application per kg body weight (mg/kg bw/day)	0,0250153	0,0006308	
% of RVNAS	50,03%	1,26%	
Acute			
Total systemic exposure from mixing, loading and application (mg a.s./day)	27,2371291	0,5094647	
Total systemic exposure from mixing, loading and application per kg body weight (mg/kg bw/day)	0,4539522	0,0084911	
% of RVAAS	#DZIEL/0!	#DZIEL/0!	

Model AOEM - Operator – diflufenican -workwear

Operator exposure for outdoor spray applications

Application rate of active substance	0,1	kg a.s./ha	*i_AppRate*
Assumed area treated	50	ha/day	*d_AreaTreated*
Amount of active substance applied	5	kg a.s./day	*i_AmoutAS*
Dermal absorption of the product	10,00%		*i_AbsorpProduct*
Dermal absorption of in-use dilution	50,00%		*i_AbsorInuse*
Formulation type	Soluble concentrates, emulsifiable concentrate, etc.		
Indoor or Outdoor application	Outdoor		
Application method	Downward spraying		
Application equipment	Vehicle-mounted		
Season	not relevant		

Outdoorsoluble concentrates, emulsifiable concentrate, etc.Downward sprayingvehicle-mounted

	Exposure values	µg exposure/day mixed and loaded		Reference	Comment
		75th centile	95th centile		
Mixing and loading	Hands	16767	62314	AOEM	
	Body	11058	114960	AOEM	
	Head	259	1423	AOEM	
	Protected hands (gloves)	98	990	AOEM	
	Protected body (workwear or protective garment and sturdy footwear)	99	731	AOEM	
	Protected head (hood and face shield)	4	81	AOEM	
	Inhalation	6	30	AOEM	
	Protective Equipment	Select for inclusion		Penetration factor	Inhalation Protection factor
	Gloves	No			
	Clothing	Work wear - arms, body and legs covered		Incl. in AOEM model	
	Head and respiratory PPE	None		1	1
	Water soluble bag	No		1	

	Exposure values	µg exposure/day applied		Reference	Comment
		75th centile	95th centile		
Application	Hands	742	7449	AOEM	
	Body	415	2138	AOEM	
	Head	20	59	AOEM	
	Protected hands (gloves)	102	4021	AOEM	
	Protected body (workwear or protective garment and sturdy footwear)	11	28	AOEM	
	Inhalation	2	7	AOEM	
	Protective Equipment	Select for inclusion		Penetration factor	Inhalation Protection factor
	Gloves	No			
	Clothing	Work wear - arms, body and legs covered		Incl. in AOEM model	
	Head and respiratory PPE	None		1	1
	Closed cab	No		vehicle mounted upward spraying only	

1. Total

	Without RPE/PPE	With RPE/PPE	
Longer term			
Total systemic exposure from mixing, loading and application (mg a.s./day)	3,4045985	2,1071020	
Total systemic exposure from mixing, loading and application per kg body weight (mg/kg bw/day)	0,0567433	0,0351184	
% of RVNAS	51,58%	31,93%	
Acute			
Total systemic exposure from mixing, loading and application (mg a.s./day)	22,7296048	10,2518936	
Total systemic exposure from mixing, loading and application per kg body weight (mg/kg bw/day)	0,3788267	0,1708649	
% of RVAAS	#DZIEL/0!	#DZIEL/0!	

Model AOEM - Operator – diflufenican -workwear plus gloves during M/L

Operator exposure for outdoor spray applications

Application rate of active substance	0,1	kg a.s./ha	*i_AppRate*
Assumed area treated	50	ha/day	*d_AreaTreated*
Amount of active substance applied	5	kg a.s./day	*i_AmoutAS*
Dermal absorption of the product	10,00%		*i_AbsorpProduct*
Dermal absorption of in-use dilution	50,00%		*i_AbsorInuse*
Formulation type	Soluble concentrates, emulsifiable concentrate, etc.		
Indoor or Outdoor application	Outdoor		
Application method	Downward spraying		
Application equipment	Vehicle-mounted		
Season	not relevant		

Outdoor;Soluble concentrates, emulsifiable concentrate, etc;Downward spraying;Vehicle-mounted

	Exposure values	µg exposure/day mixed and loaded 75th centile	95th centile	Reference	Comment
Mixing and loading	Hands	16767	62314	AOEM	
	Body	11058	114960	AOEM	
	Head	259	1423	AOEM	
	Protected hands (gloves)	98	990	AOEM	
	Protected body (workwear or protective garment and sturdy footwear)	99	731	AOEM	
	Protected head (hood and face shield)	4	81	AOEM	
	Inhalation	6	30	AOEM	
	Protective Equipment	Select for inclusion		Penetration factor	Inhalation Protection factor
	Gloves	Yes		Incl. in AOEM model	
	Clothing	Work wear - arms, body and legs covered		Incl. in AOEM model	
	Head and respiratory PPE	None		1	1
	Water soluble bag	No		1	

	Exposure values	µg exposure/day applied 75th centile	95th centile	Reference	Comment
Application	Hands	742	7449	AOEM	
	Body	415	2138	AOEM	
	Head	20	59	AOEM	
	Protected hands (gloves)	102	4021	AOEM	
	Protected body (workwear or protective garment and sturdy footwear)	11	28	AOEM	
	Inhalation	2	7	AOEM	
	Protective Equipment	Select for inclusion		Penetration factor	Inhalation Protection factor
	Gloves	No			
	Clothing	Work wear - arms, body and legs covered		Incl. in AOEM model	
	Head and respiratory PPE	None		1	1
	Closed cab	No		vehicle mounted upward spraying only	

1. Total

	Without RPE/PPE	With RPE/PPE	
Longer term			
Total systemic exposure from mixing, loading and application (mg a.s./day)	3,4045985	0,4402450	
Total systemic exposure from mixing, loading and application per kg body weight (mg/kg bw/day)	0,0567433	0,0073374	
% of RVNAS	51,58%	6,67%	
Acute			
Total systemic exposure from mixing, loading and application (mg a.s./day)	22,7296048	4,1195241	
Total systemic exposure from mixing, loading and application per kg body weight (mg/kg bw/day)	0,3788267	0,0686587	
% of RVAAS	#DZIEL/0!	#DZIEL/0!	

Model AOEM - Operator –flufenacet -workwear

Operator exposure for outdoor spray applications

Application rate of active substance	0,1248	kg a.s./ha	*i_AppRate*
Assumed area treated	50	ha/day	*d_AreaTreated*
Amount of active substance applied	6,24	kg a.s./day	*i_AmoutAS*
Dermal absorption of the product	10,00%		*i_AbsorpProduct*
Dermal absorption of in-use dilution	50,00%		*i_AbsorInuse*
Formulation type	Soluble concentrates, emulsifiable concentrate, etc.		
Indoor or Outdoor application	Outdoor		
Application method	Downward spraying		
Application equipment	Vehicle-mounted		
Season	not relevant		

	Exposure values	µg exposure/day mixed and loaded		Reference	Comment
		75th centile	95th centile		
Mixing and loading	Hands	19885	74046	AOEM	
	Body	12921	122602	AOEM	
	Head	324	1776	AOEM	
	Protected hands (gloves)	113	1236	AOEM	
	Protected body (workwear or protective garment and sturdy footwear)	120	913	AOEM	
	Protected head (hood and face shield)	5	101	AOEM	
	Inhalation	6	30	AOEM	
	Protective Equipment	Select for inclusion		Penetration factor	Inhalation Protection factor
	Gloves	No			
	Clothing	Work wear - arms, body and legs covered		Incl. in AOEM model	
	Head and respiratory PPE	None		1	1
	Water soluble bag	No		1	

	Exposure values	µg exposure/day applied		Reference	Comment
		75th centile	95th centile		
Application	Hands	926	8761	AOEM	
	Body	517	2668	AOEM	
	Head	24	74	AOEM	
	Protected hands (gloves)	115	4126	AOEM	
	Protected body (workwear or protective garment and sturdy footwear)	14	35	AOEM	
	Inhalation	3	8	AOEM	
	Protective Equipment	Select for inclusion		Penetration factor	Inhalation Protection factor
	Gloves	No			
	Clothing	Work wear - arms, body and legs covered		Incl. in AOEM model	
	Head and respiratory PPE	None		1	1
	Closed cab	No		vehicle mounted upward spraying only	

1. Total

	Without RPE/PPE	With RPE/PPE	
Longer term			
Total systemic exposure from mixing, loading and application (mg a.s./day)	4,0556382	2,5239524	
Total systemic exposure from mixing, loading and application per kg body weight (mg/kg bw/day)	0,0675940	0,0420659	
% of RVNAS	397,61%	247,45%	
Acute			
Total systemic exposure from mixing, loading and application (mg a.s./day)	25,6320504	12,1466233	
Total systemic exposure from mixing, loading and application per kg body weight (mg/kg bw/day)	0,4272008	0,2024437	
% of RVAAS	#DZIEL/0!	#DZIEL/0!	

Model AOEM - Operator –flufenacet -workwear plus gloves during M/L

Operator exposure for outdoor spray applications

Application rate of active substance	0,1248 kg a.s./ha		*i_AppRate*
Assumed area treated	50 ha/day		*d_AreaTreated*
Amount of active substance applied	6,24 kg a.s./day		*i_AmoutAS*
Dermal absorption of the product	10,00%		*i_AbsorpProduct*
Dermal absorption of in-use dilution	50,00%		*i_AbsorInuse*
Formulation type	Soluble concentrates, emulsifiable concentrate, etc.		
Indoor or Outdoor application	Outdoor		
Application method	Downward spraying		
Application equipment	Vehicle-mounted		
Season	not relevant		

Outdoorsoluble concentrates, emulsifiable concentrate, etc.Downward sprayingvehicle-mounted

	Exposure values	µg exposure/day mixed and loaded		Reference	Comment
		75th centile	95th centile		
Mixing and loading	Hands	19885	74046	AOEM	
	Body	12921	122602	AOEM	
	Head	324	1776	AOEM	
	Protected hands (gloves)	113	1236	AOEM	
	Protected body (workwear or protective garment and sturdy footwear)	120	913	AOEM	
	Protected head (hood and face shield)	5	101	AOEM	
	Inhalation	6	30	AOEM	
	Protective Equipment	Select for inclusion		Penetration factor	Inhalation Protection factor
	Gloves	Yes		Incl. in AOEM model	
	Clothing	Work wear - arms, body and legs covered		Incl. in AOEM model	
	Head and respiratory PPE	None		1	1
	Water soluble bag	No		1	

	Exposure values	µg exposure/day applied		Reference	Comment
		75th centile	95th centile		
Application	Hands	926	8761	AOEM	
	Body	517	2668	AOEM	
	Head	24	74	AOEM	
	Protected hands (gloves)	115	4126	AOEM	
	Protected body (workwear or protective garment and sturdy footwear)	14	35	AOEM	
	Inhalation	3	8	AOEM	
	Protective Equipment	Select for inclusion		Penetration factor	Inhalation Protection factor
	Gloves	No			
	Clothing	Work wear - arms, body and legs covered		Incl. in AOEM model	
	Head and respiratory PPE	None		1	1
	Closed cab	No		vehicle mounted upward spraying only	

1. Total

	Without RPE/PPE	With RPE/PPE	
Longer term			
Total systemic exposure from mixing, loading and application (mg a.s./day)	4,0556382	0,5468293	
Total systemic exposure from mixing, loading and application per kg body weight (mg/kg bw/day)	0,0675940	0,0091138	
% of RVNAS	397,61%	53,61%	
Acute			
Total systemic exposure from mixing, loading and application (mg a.s./day)	25,6320504	4,8655710	
Total systemic exposure from mixing, loading and application per kg body weight (mg/kg bw/day)	0,4272008	0,0810929	
% of RVAAS	#DZIEL/0!	#DZIEL/0!	

Appendix 3 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)