REGISTRATION REPORT

Part B

Section 10
Assessment of the relevance of metabolites in groundwater

Detailed summary of the risk assessment

Product code: 102000007779

Product name(s): Flufenacet SC 508.8 G
(Active substance(s)) Flufenacet 508.8 g/L

Central Zone
Zonal Rapporteur Member State: Poland

CORE ASSESSMENT

(Authorization)

Applicant: Bayer Crop Science Division

Submission date: 30 June 2021

MS Finalisation date: February 2022, updated March 2023 (initial Core Assessment)
June 2023 (final Core Assessment)

Version history

When	What
June 2021	Original Bayer Crop Science Division submission
February 2022	Initial assessment by the zRMS The report in the dRR format has been prepared by the Applicant, therefore all comments, additional evaluations and conclusions of the zRMS are presented in grey commenting boxes. Minor changes are introduced directly in the text and highlighted in grey. Not agreed or not relevant information are ~~struck through and shaded for transparency~~.
March 2023	Updated after information from the fate and behaviour expert, within the scope of PECgw Minor changes are introduced directly in the text and highlighted in grey. Not agreed or not relevant information are ~~struck through and shaded for transparency~~.
June 2023	Final report (Core Assessment updated following the commenting period) Additional information/assessments included by the zRMS in the report in response to comments received from the cMS and the Applicant are highlighted in yellow. Information no longer relevant ~~is struck through and shaded~~.

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Reviewer comments:

This part of dossier has been submitted to support registration of the plant protection product FFA SC 508.8 G according art. 33 of 1107/2009.

Document refers data related to the forming of metabolites in the environment (see dRR B8). dRR Part B10 has been reviewed for the purposes of ongoing registration and also checked its compliance with the current guidelines. Information has been considered as sufficient and appropriate for concluding. For detailed assessment of genotoxicity of metabolite M01 and M02 refer dRR Part B6

10 Relevance of metabolites in groundwater

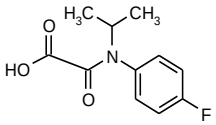
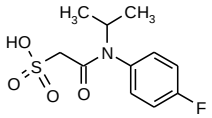
10.1 General information

Flufenacet

The metabolites FOE oxalate (M01) and FOE sulfonic acid (M02) are predicted to occur in groundwater at concentrations at or above 0.1 µg/L (see dRR Part B, Section 8 (Environmental fate and behaviour) chapter 8.8.2.1). Assessment of the relevance of these metabolites according to the stepwise procedure of the EC guidance document SANCO/221/2000 –rev.10 is therefore required.

General information on the metabolites is provided in Table 10.1-1. The impact of the relevance assessment on whether a particular GAP use leads to acceptable risk or not is presented in the summary of the cGAP evaluation in chapter 8.1 of the dRR Part B, Section 8 (Environmental fate and behaviour).

Table 10.1-1: General information on the metabolite(s)

Name of active substance	Metabolite name and code	Structural/molecular formula	Trigger for relevance assessmnent	
flufenacet (FOE 5043, FFA; formerly: fluthiamide	FOE oxalate (M01, BCS-AB16305)		Max PEC_{gw} Based on:	0.832 ug/L ~~0.745 µg/L~~ FOCUS PELMO and Porto/ winter cereals, pre-emergence, 1x244.2 g a.s./ha (Tier 2)
	FOE sulfonic acid[1] (M02, WAK6222)		Max PEC_{gw} Based on:	5.241 µg/L FOCUS PEARL & PELMO and Jokioinen/ winter cereals, pre-emergence, 1x244.2 g a.s./ha (Tier 2)

[1] The structures and report names of degradation products of flufenacet identified in environmental fate studies reflect in general their uncharged species. The degradation products FOE sulfonic acid has pKa-value < 2 and hence, are deprotonated (ionic) under environmental conditions. Therefore, the environmental relevant deprotonated species is used for all studies which were conducted to elucidate the toxicological and ecotoxicological properties of the degradation product as well as the fate in the environment, plants and animals

10.2 Relevance assessment of FOE oxalate (M01)

Summary:

In the Draft Assessment Report for flufenacet (1997) two lysimeter studies were performed. The RMS concluded that metabolite M1 oxalate does not pose a risk for groundwater if flufenacet is used according to the proposed use pattern.

The relevance of the groundwater metabolite FOE oxalate (M01) has already been assessed and the assessment agreed at EU level (see Addendum to DAR (Monograph), January 2003), but the relevance assessment is not applicable for the GAP and groundwater scenarios considered in this dRR (*i.e.* the conclusions made at the EU-level are not valid with regard to the PEC_{gw} calculated for the GAP and groundwater scenarios considered in this dRR). Therefore, the assessment and conclusions are presented here. FOE oxalate is not considered relevant according to the criteria laid down in the EC guidance document SANCO/221/2000 – rev.10. A summary of the relevance assessment is given in Table 10.2-1 and the corresponding studies are listed in the corresponding sections.

Studies supporting PEC_{gw} data are evaluated in Section 8 (Environmental fate and behaviour), the genotoxicity studies are evaluated in Section 6 (Mammalian Toxicology). Input data for the refined risk assessment in Step 5 taking into account food as an additional source of possible intake by consumers are reported in Section 7 (Metabolism and residues).
The dietary risk assessment for flufenacet is based on the "common moiety" residue definition for commodities of plant origin covering all metabolites which include the common fluorophenyl-acetamide moiety. All metabolites which own this common chemical fragment (i.e. also FOE oxalate) are captured by the same dietary risk assessment relative to food of plant origin. The data on biological activity are evaluated in Appendix 2 of this Section.

Table 10.2-1: Summary of the relevance assessment for FOE oxalate

	Assessment step		Result of assessment	
	STEP 1		Metabolite of no concern?	no
Quantification of groundwater contamination	STEP 2		Max PEC_{gw}	0.832 ug/L ~~0.745 µg/L~~
			Based on	Modelling data FOCUS PELMO and Porto/ winter cereals (pre-emergence), 1x244.2 g a.s./ha (Tier 2)
Hazard assessment	STEP 3	Stage 1	Biological activity comparable to the parent?	No biological activity
		Stage 2	Genotoxic properties of metabolite	Not genotoxic
		Stage 3	Toxic properties of metabolite;	Likely to be less toxic than parent compound
			Classification of parent	Acute toxicity Cat 4, H302 Skin sensi. Cat 1, H317 STOT RE Cat 2, H373
			Classification of metabolite	Metabolite does not require classification
Consumer health risk assessment	STEP 4		Estimated consumer exposure via drinking water and other sources; threshold of concern approach	Exposure via drinking water acceptable (< 0.75 µg/L), additional exposure via food may lead to overall exposure > 0.02 µg/kg bw/d.
	STEP 5		Refined risk assessment	acceptable
			Predicted exposure (% of ADI)	Adult: By drinking water 0.9% ~~0.8%~~ ADI All intake sources 20.9% ~~20.8 %~~ of ADI* Child: By drinking water 2.6% ~~2.4%~~ ADI All intake sources 37.6% ~~37.4 %~~ of ADI* Infant: By drinking water 4.0% ~~3.6%~~ ADI All intake sources 24.0% ~~23.6 %~~ of ADI*
			ADI based on	Flufenacet ADI of 0.005 mg/kg bw/day based on LOAEL of 1.2 mg/kg bw/day from the 2-year rat study with an AF of 250. (Review Report (7469/VI/98-Final – 3rd July 2003)

* Assuming that all flufenacet derived residues consist to 100% of the respective metabolite

10.2.1 STEP 1: Exclusion of degradation products of no concern

The major degradation product of flufenacet, FOE oxalate, contains a phenyl ring and is therefore not an aliphatic compound. Hence, FOE oxalate does not meet the criteria for products of no concern as defined in step 1 of the guidance and therefore needs further assessment.

10.2.2 STEP 2: Quantification of potential groundwater contamination

PEC_{gw} calculations after leaching from soil for FOE oxalate were performed (see Part B, Section 8, chapter 8.8). The uses for which concentrations of FOE oxalate were considered to exceed 0.1 µg/L are listed in Table 10.2-1. Details are given in Part B, Section 8, chapter 8.8.

10.2.3 STEP 3: Hazard assessment – identification of relevant metabolites

10.2.3.1 STEP 3, Stage 1: screening for biological activity

FOE-oxalate (code BCS-AB16305) does not have comparable target activity to the parent active compound as shown in biological screening data. In a direct comparison study, it could be shown that FOE oxalate, a metabolite of flufenacet, had no pre-emergence biological activity when tested on a range of weeds and crops under highly sensitive screening conditions. In these tests, it did not show any significant herbicidal activity, *i.e.* the observed activity was always less than 50% compared to the parent active substance flufenacet.

Since the activity threshold of 50%, as given in Guidance Document SANCO/221/2000 rev. 10, was not exceeded, the metabolite is considered to be non-relevant and is further evaluated in Stage 2.

Full summaries of biological screening studies on the metabolite that have not been previously considered within an EU peer review process are described in detail in Appendix 2.

10.2.3.2 STEP 3, Stage 2: screening for genotoxicity

FOE oxalate was screened for genotoxic activity by the following data package of *in vitro* genotoxicity studies: Ames test, gene mutation test with mammalian cells, and a chromosome aberration test. FOE oxalate was non-genotoxic as shown by a negative Ames test, negative gene mutation test with mammalian cells and a negative chromosome aberration test.
FOE oxalate is considered not relevant and is further evaluated in Stage 3. The genotoxicity studies not reviewed on EU level are evaluated in Part B, Section 6, studies referenced in chapter.6.4.1 and Appendix 2 (A 2.11).

Study	Dose	Result	Reference
Bacterial reverse mutation assay (S. typhimurium, TA1535, TA1537, TA98, TA100, TA102)	16 - 5000 µg/plate (+/- S9 mix)	Negative (+/- S9 mix)	Draft Registration Report Part B, Section 6 A2.11.1 Herbold, 2009, M-358953-01-1
Mammalian cell gene mutation test (Chinese hamster V79 cells)	150 - 2400 µg/mL (+/- S9 mix)	Negative (+/- S9 mix)	Draft Registration Report Part B, Section 6 A2.11.2 Wollny, 2010 M-361724-01-1
Mammalian chromosome aberration test (Chinese hamster V79 cells)	600 - 2400 µg/mL (+/- S9 mix)	Negative (+/- S9 mix)	Draft Registration Report Part B, Section 6 A2.11.3 Nern, 2009 M-358043-01-1

10.2.3.3 STEP 3, Stage 3: screening for toxicity

The parent flufenacet to FOE oxalate is not classified as acutely or chronically toxic or very toxic, is not classified for reproductive toxicity and is not classified as a carcinogen in category 1 or 2 according to CLP 1272/2008. There are no reasons to expect that FOE oxalate may be toxic or highly toxic. FOE oxalate has not been subject to targeted testing.

Quantitative Structure Analysis Relationship (QSAR) analysis (Derek Nexus: 3.0.1, Nexus: 1.5.0) revealed for FOE oxalate, as well as for the parent compound flufenacet an equivocal alert for nephrotoxicity in mammals, due to the presence of a halogenated benzene sub-structure contained in the metabolite and flufenacet.
Further structural analysis (Toxtree-v.2.5.0) revealed that this metabolite belongs to Cramer class III.

No acute or repeated dose toxicity studies were conducted with FOE oxalate.

FOE-oxalate (M01) is not a rat metabolite but is detected in plants and groundwater.

The bioavailability of FOE oxalate, as representative plant metabolite arising from the fluorophenyl-acetamide portion of the parent compound flufenacet, was investigated in rats after a single oral application of 1 mg/kg bw [Fluorophenyl-UL-14C] FOE 5043 oxalate (see Monograph of Flufenacet, Krolski, M. E.; Bosnak, L. L.; 1995; M-002278-01-1). The metabolite was rapidly excreted with the faeces 61 - 80% of the dose and with the urine 19 - 37% of the dose within 0-72 hours after administration; the main portion already within 24 hours. No radioactivity could be detected in tissues/carcass 24 hours after dosing. The only compound observed in urine and faeces was identified as the unchanged FOE oxalate. This demonstrates that even if FOE-oxalate is absorbed it is not metabolized and not retained (accumulated) in the body, but rapidly excreted. The short retention period and the metabolic stability of FOE oxalate suggest no relevant toxic effects after oral intake. Comparing absorption of FOE oxalate to the parent compound for which an absorption rate of 75-89% (low dose 1 mg/kg; m/f) of the applied rate was determined in the rat ADME study, the bioavailability of the metabolite is considerably less. On the basis of the findings from toxicological and animal metabolism studies it is concluded that the bioavailability for FOE oxalate is low compared to the parent substance.

The findings are well in line with the livestock metabolism studies conducted with FOE oxalate as the main plant metabolite (see Monograph of Flufenacet: Duah, F. K.; Freeseman, P. L.; Jett, C. M.; Minor, R. G.; 1995; M-004474-01-1; Duah, F. K.; Freeseman, P. L.; Jett, C. M.; Minor, R. G.; 1995; M-004478-01-1). FOE-oxalate was not further metabolised and found up to 99% TRR in kidney of the goat. The low levels in tissue, milk and eggs suggest that FOE-oxalate is minimally absorbed and rapidly excreted after oral administration (see Monograph).

Thus, even if exposure due to intake of water occurs, FOE-oxalate will rapidly be excreted unchanged. Therefore, FOE-oxalate is likely to be less toxic to humans than flufenacet. Further toxicity data for this metabolite are not considered to be necessary. As a worst-case assumption, the ADI of the parent compound (0.005 mg/kg) is considered as an adequate reference value for the assessment of consumer exposure to FOE oxalate.

FOE oxalate is not considered relevant and is further evaluated in Step 4.

10.2.4 STEP 4: Exposure assessment – threshold of concern approach

FOE oxalate was not considered relevant in the hazard assessment of Step 3.
The PEC_{gw} for FOE oxalate was < 0.75 µg/L. The potential exposure to FOE oxalate via all sources may exceed 0.02 µg/kg body weight/day since FOE oxalate is a main plant metabolite. A further assessment in Step 5 is required. Further calculations are presented in Step 5.

10.2.5 STEP 5: Refined risk assessment

FOE oxalate has a PEC_{gw} < 0.75 µg/L but the threshold of concern approach in Step 4 is not acceptable due to possible intakes via food of plant origin. A refined assessment of the potential toxicological significance including the selected ADI is presented here.

The metabolism of flufenacet in plants was found to be qualitatively similar in all the examined crops. Flufenacet was both rapidly and extensively metabolised, such that even at early sampling dates no parent compound was detected. The first metabolic step consists in the cleavage of the molecule into the thiadone and fluorophenyl¬acetamide moieties. Most of the fluorophenylacetamide moiety first forms conjugates with glutathione (M22) or homoglutathione, is further metabolised into the cysteine conjugate (M23) and then in various other hydrolysis and oxidation products including the sulfonic acid (M02), the thioglycolate sulfoxide (M04), the methylsulfoxide (M06), the methylsulfone (M07), and the sulfinyl lactic acid (M33). The sulfanyl lactic acid glucoside (M41) and the sulfinyl acid glucoside (M37) are also formed via the

cysteine conjugate (M23) but were only observed in the post-emergence studies. Alternately, direct hydrolysis and oxidation of the fluorophenylacetamide moiety yields the **oxalate** conjugate (M01) via the unobserved primary alcohol (M03).

Based on the findings from plant metabolism studies, the residue definition in plants was defined as **flufenacet (sum of all compounds containing the N fluorophenyl-N-isopropyl moiety expressed as flufenacet equivalent).** It covers all the metabolites derived from the fluorophenyl-acetamide moiety, *i.e.* including FOE oxalate (M01) and is suitable for both pre- and post-emergence uses. This definition is established for both risk assessment and post-registration control. The toxicological properties of the metabolites are considered to be covered by the toxicological studies conducted with the parent compound (EFSA Journal 2012;10(4):2689)).

A justification of an acceptable daily intake (ADI) for FOE oxalate derived from toxicological and metabolism studies is given in chapter 10.2.3.3 above. The ADI of the parent compound (0.005 mg/kg) is considered as an adequate reference value for the assessment of consumer exposure to FOE oxalate. EFSA concluded in their Reasoned Opinion on the review of existing MRLs (EFSA Journal 2012;10(4):2689): *"However, since none of the metabolites* [containing the N fluorophenyl-N-isopropyl moiety] *raised any particular concern it is considered acceptable to apply the toxicological reference values of the parent compound for the time being."*

Since plant residues may be determined by means of a common moiety method which is based on the conversion of the metabolites to a common chemical fragment (4-fluorophenyl-N-isopropyl benzamine) the metabolite cannot be measured individually in plant field samples.

Risk assessment: Consumer exposure via ground-or drinking water

The exposure assessments for FOE oxalate contained in groundwater are performed using the highest groundwater concentrations predicted by modelling for the pre-emergence use in/on winter cereals at a rate of 0.2442 kg a.s./ha (0.832 µg/L ~~0.745 µg/L~~ in FOCUS PELMO and Porto, Tier 2).
Because the groundwater concentrations are compared to a toxicological reference value expressed as flufenacet, also the concentration of the metabolite contained in drinking water must be expressed as parent equivalent.

Table 10.2-2: Upper limit intake of FOE oxalate via drinking water

	Consumption (L)	**Body weight (kg)**	**Upper limit gw conc (µg/L) expressed as metabolite**	**Upper limit gw conc (µg/L) expressed as parent**	**Intake (µg/person/day) expressed as parent**	**µg/kg bw/day expressed as parent**	**% ADI (5 µg/kg bw/d)**	**GAP/Model/ Scenario**
Adult	2	60	0.832 ~~0.745~~	1.342 ~~1.202~~	2.68 ~~2.40~~	0.04	0.89 ~~0.80~~	FOCUS PELMO and Porto/ winter cereals (pre-emergence), 1x244.2 g a.s./ha (Tier 2)
Child	1	10	0.832 ~~0.745~~	1.342 ~~1.202~~	1.34 ~~1.20~~	0.13 ~~0.12~~	2.60 ~~2.40~~	FOCUS PELMO and Porto/ winter cereals (pre-emergence), 1x244.2 g a.s./ha (Tier 2)
Infant	0.75	5	0.832 ~~0.745~~	1.342 ~~1.202~~	1.01 ~~0.90~~	0.20 ~~0.18~~	4.00 ~~3.61~~	FOCUS PELMO and Porto/ winter cereals (pre-emergence), 1x244.2 g a.s./ha (Tier 2)

Molar mass flufenacet 363.3 g/mol
Molar mass FOE oxalate 225.22 g/mol

Risk assessment: Combined consumer exposure through food of plant origin and drinking water
For reason of simplification, the worst-case assumption is made that plant residues consist to 100% of FOE

oxalate. The portion of the TRR and residue level for the individual metabolite which is evident from the different metabolism studies is not considered in this approach. Calculated intakes are also not limited to the supported use in/on cereals.

For the exposure calculations (IEDI calculation) median residue values from all the authorized uses of flufenacet and reported in the framework of the MRL review (EFSA 2012 - Table 4-1) are used (please refer to Section B7 point 7.2.8.1).
The calculation table according to EFSA PRIMo rev.3.1 is included in Appendix 3 of Section 7.
The highest long-term intake (IEDI) resulted in 35% of the ADI for the NL toddler diet (cf. Table 10.2-3 below).
Table 10.2-3 provides the results from summation of potential intakes by means of food of plant origin and drinking water for all EFSA PRIMo (rev 3.1) diets and consumer groups.

In order to simplify the approach, the calculation is performed for all PRIMo diets and based on conservative assumptions for intake of water as follows:

- For all PRIMo diets relevant to adults the ADI exhaustion is calculated taking into account the contribution of 2 L/day for a person of 60 kg
- For all PRIMo diets relevant to children with body weights ≥ 10 kg the ADI exhaustion is calculated taking into account the contribution of 1 L/day and 10 kg body weight
- For all PRIMo diets relevant to infants with body weights between 5 and 10 kg the ADI exhaustion is calculated taking into account the contribution of 0.75 L/day and 5 kg body weight (only relevant to UK infant and FR infant).

Table 10.2-3: Chronic exposure assessment: Upper limit consumer exposure estimate for FOE oxalate

PRIMo diet	Body weight [kg]	TMDI [1)] contribution of plant commodities for FOE oxalate (% of ADI)	FOE oxalate (M01)	
			Contribution of water (% of ADI)	total intakes (% of ADI)[1)]
Calculation of risk for 60-kg adult (consuming 2.0 L/day)				
DE general	76.4	10	0.9 ~~0.8~~	10.9 ~~10.8~~
DE women 14–50 years	67.5	10	0.9 ~~0.8~~	10.9 ~~10.8~~
DK adults	75.1	7	0.9 ~~0.8~~	7.9 ~~7.8~~
ES adults	68.5	9	0.9 ~~0.8~~	9.9 ~~9.8~~
FI adults	77.1	4	0.9 ~~0.8~~	4.9 ~~4.8~~
FR adult	66.4	8	0.9 ~~0.8~~	8.9 ~~8.8~~
IE adult	75.2	10	0.9 ~~0.8~~	10.9 ~~10.8~~
IT adult	66.5	7	0.9 ~~0.8~~	7.9 ~~7.8~~
LT adult	70	10	0.9 ~~0.8~~	10.9 ~~10.8~~
NL general population	65.8	11	0.9 ~~0.8~~	11.9 ~~11.8~~
PL general population	62.8	5	0.9 ~~0.8~~	5.9 ~~5.8~~
PT general population	60	12	0.9 ~~0.8~~	12.9 ~~12.8~~
RO general	60	19	0.9 ~~0.8~~	19.9 ~~19.8~~
SE general population	60	18	0.9 ~~0.8~~	18.9 ~~18.8~~
UK adults	76	6	0.9 ~~0.8~~	6.9 ~~6.8~~

UK vegetarian	66.7	6	0.9 0.8	6.9 6.8
GEMS/Food G06	60	20	0.9 0.8	20.9 20.8
GEMS/Food G07	60	19	0.9 0.8	19.9 19.8
GEMS/Food G08	60	19	0.9 0.8	19.9 19.8
GEMS/Food G10	60	20	0.9 0.8	20.9 20.8
GEMS/Food G11	60	19	0.9 0.8	19.9 19.8
GEMS/Food G15	60	19	0.9 0.8	19.9 19.8
Calculation of risk for 10-kg child (consuming 1.0 L/day)				
DE children	16.15	18	2.6 2.4	20.6 20.4
DK children	21.8	23	2.6 2.4	25.6 25.4
ES children	34.5	16	2.6 2.4	18.6 18.4
FR toddler	13.6	17	2.6 2.4	19.6 19.4
FR child 3 to < 15 years	18.9	19	2.6 2.4	21.6 21.4
FI child 3 years	15.2	10	2.6 2.4	12.6 12.4
FI child 6 years	22.4	8	2.6 2.4	10.6 10.4
IE child	20.0	4	2.6 2.4	6.6 6.4
IT toddler	41.6	10	2.6 2.4	12.6 12.4
NL children	18.4	19	2.6 2.4	21.6 21.4
NL toddler	10.2	35	2.6 2.4	37.6 37.4
UK toddlers	14.6	16	2.6 2.4	18.6 18.4
Calculation of risk for 5-kg bottle-fed infant (consuming 0.75 L/day)				
UK infant	8.7	20	4.0 3.6	24.0 23.6
FR infant	9.1	9	4.0 3.6	13.0 12.6

[1)] With the worst case assumption that plant residues consist to 100% of the respective metabolite

Conclusion

From the dietary exposure calculations above it can be concluded that possible intakes of FOE oxalate by means of drinking water and food of plant origin do not present a consumer health concern. The calculations are based on several worst-case assumptions, such as

- For the reason of simplification, it is assumed that for the chronic exposure calculation all flufenacet derived residues of plant origin consists of FOE oxalate.
- All commodities consumed contain residues of the flufenacet metabolite at the level of the median residue level (STMR) for flufenacet. However, actually the residue definition for enforcement covers all metabolites containing the common fluorophenyl-isopropyl moiety. The distribution of individual metabolites according to the findings in the metabolism studies is not taken into account. Although no flufenacet derived residues can be expected in food of animal origin the MRLs (set at LOQ) have been used in the IEDI calculation for animal commodities as well.
- Intake calculations are based on all crops that may be consumed and for which flufenacet uses

are authorised. Calculations are not limited to potential residues that might be present in the supported crops (small grain cereals).
- No decrease of residues during storage and processing.
- Use of the upper limit groundwater concentrations for FOE oxalate of 0.832 µg/L ~~0.745 µg/L~~ although in many scenarios this concentration will be never reached.

The calculations demonstrate a maximum ADI (of flufenacet) usage of 24.0% ~~23.6%~~ for infants, 37.6% ~~37.4%~~ for children and 20.9% ~~20.8%~~ for adults. The consumer risk assessment shows an acceptable risk for FOE oxalate. The calculations indicate that the intended use of FFA SC 508.8 G does not pose a risk to consumers as a result of exposure to this metabolite.

10.3 Relevance assessment of FOE sulfonic acid (M02)

Summary:
The relevance of the groundwater metabolite FOE sulfonic acid (M02) has already been assessed and the assessment agreed at EU level (see Addendum to DAR (Monograph), January 2003), but the relevance assessment is not applicable for the GAP and groundwater scenarios considered in this dRR (i.e., the conclusions made at the EU-level are not valid with regard to the PECgw calculated for the GAP and groundwater scenarios considered in this dRR). Therefore, the assessment and conclusions are presented here. FOE sulfonic acid is not considered relevant according to the criteria laid down in the EC guidance document SANCO/221/2000 –rev.10. A summary of the relevance assessment is given in Table Table 10.3-1 and the corresponding studies are listed in the corresponding sections.

Studies supporting PEC_{gw} data are evaluated in Section 8 (Environmental fate and behaviour), the genotoxicity studies are evaluated in Section 6 (Mammalian Toxicology). Input data for the refined risk assessment in Step 5 taking into account food as an additional source of possible intake by consumers are reported in Section 7 (Metabolism and residues). The dietary risk assessment for flufenacet is based on the "common moiety" residue definition for commodities of plant origin covering all metabolites which include the common fluorophenyl-acetamide moiety. All metabolites which own this common chemical fragment (*i.e.* also FOE sulfonic acid) are captured by the same dietary risk assessment relative to food of plant origin. The data on biological activity are evaluated in Appendix 2 of this Section.

Table 10.3-1: Summary of the relevance assessment for FOE sulfonic acid

	Assessment step		**Result of assessment**	
	STEP 1		Metabolite of no concern?	no
Quantification of groundwater contamination	STEP 2		Max PEC_{gw}	5.241 µg/L
			Based on	Modelling data FOCUS PEARL & PELMO and Jokioinen/ winter cereals (pre-emergence), 1x244.2 g a.s./ha (Tier 2)
Hazard assessment	STEP 3	Stage 1	Biological activity comparable to the parent?	No biological activity
		Stage 2	Genotoxic properties of metabolite	*In vivo* not genotoxic
		Stage 3	Toxic properties of metabolite;	Likely to be less toxic than parent compound
			Classification of parent	Acute toxicity Cat 4, H302 Skin sensi. Cat 1, H317 STOT RE Cat 2, H373
			Classification of metabolite	Metabolite does not require classification
Consumer health risk assessment	STEP 4		Estimated consumer exposure via drinking water and other sources; threshold of concern approach	Not applicable (> 0.75 µg/L)
	STEP 5		Refined risk assessment	acceptable
			Predicted exposure (% of ADI)	Adult: By drinking water 4.6% ADI All intake sources 24.6 % of ADI* Child: By drinking water 13.8% ADI All intake sources 48.8 % of ADI* Infant: By drinking water 20.8% ADI All intake sources 40.8% of ADI*
			ADI based on	Flufenacet ADI of 0.005 mg/kg bw/day based on LOAEL of 1.2 mg/kg bw/day from the 2-year rat study with an AF of 250. (Review Report (7469/VI/98-Final – 3rd July 2003)

*Assuming that all flufenacet derived residues consist to 100% of the respective metabolite

10.3.1 STEP 1: Exclusion of degradation products of no concern

The major degradation product of flufenacet, FOE sulfonic acid, contains a phenyl ring and is therefore not an aliphatic compound. Hence, FOE sulfonic acid does not meet the criteria for products of no concern as defined in step 1 of the guidance and therefore needs further assessment.

10.3.2 STEP 2: Quantification of potential groundwater contamination

PEC_{gw} calculations after leaching from soil for FOE sulfonic acid were performed (see Part B, Section 8, chapter 8.8). The uses for which concentrations of FOE sulfonic acid were considered to exceed 0.1 µg/L are listed in Table 10.3-1. Details are given in Part B, Section 8, chapter 8.8.

10.3.3 STEP 3: Hazard assessment – identification of relevant metabolites

10.3.3.1 STEP 3, Stage 1: screening for biological activity

FOE sulfonic acid (code WAK6222) does not have comparable biological target activity to the parent compound as shown in biological screening data. FOE sulfonic acid was tested for its biological activity in direct comparison studies under highly sensitive screening conditions. In these tests, it did not show any significant herbicidal activity, *i.e.* the observed activity was always less than 50% compared to the parent active substance flufenacet. Since the activity threshold of 50% as given in Guidance Document SANCO/221/2000 rev. 10 was not exceeded, the metabolite is considered to be non-relevant and is further evaluated in Stage 2.
Full summaries of biological screening studies on the metabolite that have not been previously considered within an EU peer review process are described in detail in Appendix 2.

10.3.3.2 STEP 3, Stage 2: screening for genotoxicity

The genotoxic potential of FOE-sulfonic acid was investigated in bacteria and mammalian cells *in vitro*, and in two *in vivo* tests in rats and mice. FOE-sulfonic acid resulted negative in the genotoxicity tests in bacteria and mammalian cells *in vitro* (bacterial reverse mutation, mammalian cell gene mutation). The *in vitro* chromosome aberration test resulted negative in the presence of metabolic activation but showed a positive response in the absence of metabolic activation at cytotoxic concentrations. Due to the positive response in the *in vitro* chromosome aberration test, two *in vivo* genotoxicity tests were conducted. The micronucleus test and the unscheduled DNA synthesis (UDS) assay both showed clear negative results. These results confirm that the aberrations observed under extreme *in vitro* conditions are not reflecting chemical-specific genotoxicity. Overall, it can be concluded that FOE-sulfonic acid is considered to be non-genotoxic. FOE sulfonic acid is considered not relevant and is further evaluated in Stage 3. The genotoxicity studies not yet reviewed on EU level are evaluated in Part B, Section 6, studies referenced in chapter 6.4.2 and Appendix 2 (A 2.11).

Study	Dose	Result	Reference
Mammalian cell gene mutation test (Chinese hamster V79 cells)	202-3230 µg/mL (+ S9 mix) 101-808 µg/mL (- S9 mix)	Negative (+/- S9 mix)	Wollny, 2009 A2.11.4 M-361158-01-1
Mammalian chromosome aberration test (Chinese hamster V79 cells)	250-3000 µg/mL (+ S9 mix) 200-1000 µg/mL (- S9 mix)	Negative (+ S9 mix) Positive (- S9 mix)	xxx, 2010* A2.11.5 M-366380-01-1
In vivo Micronucleus test (Mouse bone marrow)	500-2000 mg/kg bw (2x intraperitoneal)	Negative	xxx, 2010 A2.11.6 M-368627-01-1
In vivo Unscheduled DNA synthesis (UDS) assay (rat primary hepatocytes)	1000-2000 mg/kg bw (oral)	Negative	xxx, 2010 A2.11.8 M-397810-01-1
Mouse whole body autoradiography	1 x 500 mg/kg bw i.p.	Test substance distributed to the bone marrow	xxx 2017 A2.11.7 M-580054-01-1

* There are some deficiencies noted in this study conducted in 2010 when compared to the TG OECD 473 rev 2016. Some limitations in toxicity measure could explain the positive of this study result, especially when considered together with the results of other studies for this data point (Chromosome alteration: *In vitro* clastogenicity). For details refer our comments dRR Part B6 point A 2.11.5 (Nern, 2010). Thus, study is considered reliable, with restrictions due to the deficiencies observed. Based on WoE (refer dRR B6) ZRMS considers that results of this study has no impact on over all negative screening for genotoxicity.

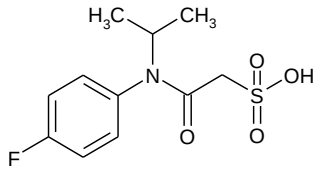
10.3.3.3 STEP 3, Stage 3: screening for toxicity

The parent flufenacet to FOE sulfonic acid is not classified as acutely or chronically toxic or very toxic, is not classified for reproductive toxicity and is not classified as a carcinogen in category 1 or 2 according to CLP 1272/2008).
Quantitative Structure Analysis Relationship (QSAR) analysis (Derek Nexus: 3.0.1, Nexus: 1.5.0) revealed for FOE sulfonic acid, as well as for the parent compound flufenacet an equivocal alert for nephrotoxicity in mammals, due to the presence of a halogenated benzene sub-structure contained in the metabolite and flufenacet.

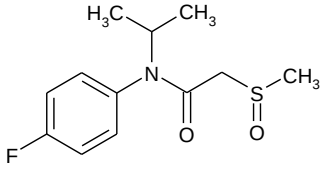
Further structural analysis (Toxtree-v.2.5.0) revealed that this metabolite belongs to Cramer class III.
An acute oral study in rat with FOE-sulfonic acid (M02) revealed low acute toxicity with a LD_{50} >2000 mg/kg bw (M-004749-01-1, Krötlinger, 1998, see Evaluation table of flufenacet (7468/VI/98-rev.10(27.12.2001)).

Furthermore, the metabolite FOE-sulfonic acid is formed in rats. In the rat metabolism study performed with the parent compound flufenacet, FOE-sulfonic acid was detected in significant, but relatively low amounts of 0.5% of the dose in urine of male and female rats (M-002247-01-1, Krolski, Jett, Bosnak and Sahali, 1995, see Monograph of flufenacet).

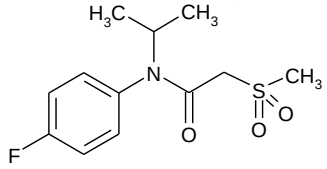
However, two structurally very similar metabolites with oxidised sulphur (M06 and M07), differing only in an additional thiomethyl group, were formed in the rat (the proposed metabolic pathway of flufenacet in rats is depicted in Appendix 3 at the end of this document). These metabolites were found in the urine and accounted in total for 4 - 6% of the applied dose. A further similar metabolite (M15), which is dealkylated at the amide-N, was found in the urine with 3 - 16%. All four metabolites have a similar and very high polarity and thus are all excreted very fast mainly via urine.



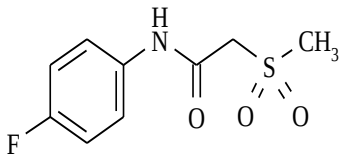
FOE-sulfonic acid (M02)



FOE-methylsulfoxide (M06)



FOE-methylsulfone (M07)



FOE-des-i-propyl methylsulfone (M15)

The metabolites FOE-sulfonic acid (M02), FOE-methylsulfoxide (M06), FOE-methylsulfone (M07), and FOE-des-i-propyl methylsulfone (M15) account in total for 8 % to 21 % of the applied dose. Thus, it can be assumed that the oxidised sulphur structure of FOE-sulfonic acid (M02) was adequately co-tested in acute and repeated dose toxicity studies conducted with the parent compound flufenacet.

Repeated dose toxicity studies with FOE-sulfonic acid itself were not performed. However, in a bioavailability study conducted in rats (M-042251-01-1, Kroetlinger and Schmidt, 2000, see evaluation table of flufenacet (7468/VI/98-rev.10(27.12.2001)) the relative oral versus intravenous bioavailability, plasma AUC profiles and urine recovery showed a very low (9.5% of the dose) oral absorption of FOE-sulfonic acid. Together with a fast-renal excretion this resulted in very low systemic exposure. Comparing absorption of FOE sulfonic acid to the parent compound for which an absorption rate of 75-89% (low dose 1 mg/kg; m/f) of the applied rate was determined in the rat ADME study, the bioavailability of the metabolite is considerably less.

Based on the study results as well as on metabolic and structural considerations the metabolite FOE-sulfonic acid was considered to be of no toxicological relevance during the EU peer review. Thus, it was concluded that the metabolite FOE-sulfonic acid from a regulatory perspective can be qualified to be 'non-relevant' according to Step 3 of this assessment (please refer to the evaluation table Doc. 7468/VI/98 rev. 10 (27.12.2001)). Taking also into account the new genotox data this evaluation is still valid with regard to the current guideline SANCO 221/2000 rev 10 (25 February 2003).

Overall, FOE-sulfonic acid is considered to be less toxic to humans than flufenacet. Further toxicity data for this metabolite are not considered to be necessary. As a worst-case assumption, the ADI of the parent compound (0.005 mg/kg bw/day) is proposed to be used for the assessment of consumer exposure via ground- or drinking water to FOE-sulfonic acid.

FOE sulfonic acid is not considered relevant and is further evaluated in Step 4.

10.3.4 STEP 4: Exposure assessment – threshold of concern approach

FOE sulfonic acid was not considered relevant in the hazard assessment of Step 3.
The PEC_{gw} for FOE sulfonic acid was > 0.75 µg/L. In addition, FOE sulfonic acid was identified as a main plant metabolite. A further assessment in Step 5 is required. Further calculations are presented in Step 5.

10.3.5 STEP 5: Refined risk assessment

FOE sulfonic acid has a PEC_{gw} between 0.75 µg/L and 10 µg/L and thus the threshold of concern approach in Step 4 is not applicable. A refined assessment of the potential toxicological significance including the selected ADI is presented here.
The metabolism of the parent compound flufenacet in plants is briefly outlined above in chapter 10.2.5.
Based on the findings from plant metabolism studies, the residue definition in plants was defined as

flufenacet (sum of all compounds containing the N fluorophenyl-N-isopropyl moiety expressed as flufenacet equivalent). It covers all the metabolites derived from the fluorophenyl-acetamide moiety, *i.e.* including FOE sulfonic acid (M02) and is suitable for both pre- and post-emergence uses. This definition is established for both risk assessment and post-registration control. The toxicological properties of the metabolites are considered to be covered by the toxicological studies conducted with the parent compound (EFSA Journal 2012;10(4):2689).

A justification of an acceptable daily intake (ADI) for FOE sulfonic acid derived from toxicological and metabolism studies is given in chapter 10.3.3.3 above. The ADI of the parent compound (0.005 mg/kg) is considered as an adequate reference value for the assessment of consumer exposure to FOE sulfonic acid. EFSA concluded in their Reasoned Opinion on the review of existing MRLs (EFSA Journal 2012;10(4):2689): *"However, since none of the metabolites* [containing the N fluorophenyl-N-isopropyl moiety] *raised any particular concern it is considered acceptable to apply the toxicological reference values of the parent compound for the time being."*

Since plant residues may be determined by means of a common moiety method which is based on the conversion of the metabolites to a common chemical fragment (4-fluorophenyl-N-isopropyl benzamine) the metabolite cannot be measured individually in plant field samples.

Risk assessment: Consumer exposure via ground-or drinking water
The exposure assessments for FOE sulfonic acid contained in groundwater are performed using the highest groundwater concentrations predicted by modelling for the use in/on winter cereals at a rate of 0.2442 kg a.s,/ha (5.241 µg/L in FOCUS PEARL & PELMO and Jokioinen, Tier 2).
Because the groundwater concentrations are compared to a toxicological reference value expressed as flufenacet, also the concentration of the metabolite contained in drinking water must be expressed as parent equivalent.

The following amounts for FOE sulfonic acid by means of intake from drinking water and the corresponding ADI usages are calculated: Per capita consumption data for water were taken as suggested by WHO/FAO (2009).

Table 10.3-2: Upper limit intake of FOE sulfonic acid via drinking water

	Consumption (L)	Body weight (kg)	(Upper limit) gw conc (µg/L) expressed as metabolite	Upper limit gw conc (µg/L) expressed as parent	Intake (µg/ person/ day) expressed as parent	µg/kg bw/day expressed as parent	% ADI (5 µg/kg bw/day)	GAP/Model/ Scenario
Adult	2	60	5.241	6.92	13.83	0.23	4.6	FOCUS PEARL & PELMO and Jokioinen/ winter cereals (pre-emergence), 1x244.2 g a.s./ha (Tier 2)
Child	1	10	5.241	6.92	6.92	0.69	13.8	FOCUS PEARL & PELMO and Jokioinen/ winter cereals (pre-emergence), 1x244.2 g a.s./ha (Tier 2)
Infant	0.75	5	5.241	6.92	5.19	1.04	20.8	FOCUS PEARL & PELMO and Jokioinen/ winter cereals (pre-emergence), 1x244.2 g a.s./ha (Tier 2)

Molar mass flufenacet 363.3 g/mol
Molar mass FOE sulfonic acid 275.3 g/mol

Relative to the proportion of intake by drinking water the WHO guidelines for drinking water quality (GDWQ, 2009) state the following:
*For threshold chemicals, the TDI (*tolerable daily intake*)/ADI* (acceptable daily intake) *covers total intake from all sources. It is, therefore, necessary to allocate a proportion of the TDI/ADI to drinking-water to derive a guideline value. In general, the primary sources of exposure are food and water. Where sufficient data are available on the exposure from sources other than drinking-water to provide an accurate assessment of actual exposure from different sources, consideration of the proportion of the TDI/ADI available for drinking-water should be taken into account so that a more appropriate allocation can be made to drinking-water. In the absence of adequate exposure data, the normal allocation to drinking-water is 20%. This value is a change from the previous allocation of 10% used in the first, second and third editions of the GDWQ, which was found to be excessively conservative, and will be incorporated in new guidelines and existing guidelines as they are revised.*

Predicted upper limit estimates on concentrations in drinking water are available and considered for dietary risk assessment involving food and drinking water (see below). The overall risk assessment is based on adequate exposure data and thus the usage of the ADI by drinking water alone is considered acceptable.

Risk assessment: Combined consumer exposure through food of plant origin and drinking water

For reason of simplification, the worst-case assumption is made that plant residues consist to 100% of FOE sulfonic acid. The portion of the TRR for the individual metabolites which is evident from the different metabolism studies is not considered in this approach.
The same principles for the dietary risk assessment and the same input data apply as described above for FOE oxalate.

The input values (median residue levels) are reported in section 7, chapter 7.2.8.1. The calculation table

according to EFSA PRIMo rev.3.1 is included in Appendix 3 of Section 7.
The highest IEDI (international estimated dietary intake) resulted in 35% of the ADI for the NL toddler diet (cf. Table 10.3-3 below).

Table 10.3-3 provides the results from summation of potential intakes by means of food of plant origin and drinking water for all EFSA PRIMo (rev 3.1) diets and consumer groups.

In order to simplify the approach, the calculation is performed for all PRIMo diets and based on conservative assumptions for intake of water as follows:

- For all PRIMo diets relevant to adults the ADI exhaustion is calculated taking into account the contribution of 2 L/day for a person of 60 kg
- For all PRIMo diets relevant to children with body weights ≥ 10 kg the ADI exhaustion is calculated taking into account the contribution of 1 L/day and 10 kg body weight
- For all PRIMo diets relevant to infants with body weights between 5 and 10 kg the ADI exhaustion is calculated taking into account the contribution of 0.75 L/day and 5 kg body weight (only relevant to UK infant and FR infant).

Table 10.3-3: Chronic exposure assessment: Upper limit consumer exposure estimate for FOE sulfonic acid

PRIMo diet	Body weight [kg]	TMDI[1)] contribution of plant commodities for FOE oxalate (% of ADI)	FOE oxalate (M01)	
			Contribution of water (% of ADI)	total intakes (% of ADI)[1)]
Calculation of risk for 60-kg adult (consuming 2.0 L/day)				
DE general	76.4	10	4.6	14.6
DE women 14–50 years	67.5	10	4.6	14.6
DK adults	75.1	7	4.6	11.6
ES adults	68.5	9	4.6	13.6
FI adults	77.1	4	4.6	8.6
FR adult	66.4	8	4.6	12.6
IE adult	75.2	10	4.6	14.6
IT adult	66.5	7	4.6	11.6
LT adult	70	10	4.6	14.6
NL general population	65.8	11	4.6	15.6
PL general population	62.8	5	4.6	9.6
PT general population	60	12	4.6	16.6
RO general	60	19	4.6	23.6
SE general population	60	18	4.6	22.6
UK adults	76	6	4.6	10.6
UK vegetarian	66.7	6	4.6	10.6
GEMS/Food G06	**60**	**20**	**4.6**	**24.6**
GEMS/Food G07	60	19	4.6	23.6
GEMS/Food G08	60	19	4.6	23.6
GEMS/Food G10	**60**	**20**	**4.6**	**24.6**
GEMS/Food G11	60	19	4.6	23.6
GEMS/Food G15	60	19	4.6	23.6
Calculation of risk for 10-kg child (consuming 1.0 L/day)				
DE children	16.15	18	13.8	31.8
DK children	21.8	23	13.8	36.8
ES children	34.5	16	13.8	29.8
FR toddler	13.6	17	13.8	30.8
FR child 3 to < 15 years	18.9	19	13.8	32.8
FI child 3 years	15.2	10	13.8	23.8
FI child 6 years	22.4	8	13.8	21.8
IE child	20.0	4	13.8	17.8
IT toddler	41.6	10	13.8	23.8
NL children	18.4	19	13.8	32.8
NL toddler	**10.2**	**35**	**13.8**	**48.8**
UK toddlers	14.6	16	13.8	29.8
Calculation of risk for 5-kg bottle-fed infant (consuming 0.75 L/day)				
UK infant	**8.7**	**20**	**20.8**	**40.8**
FR infant	9.1	9	20.8	29.8

[1)] With the worst case assumption that plant residues consist to 100% of the respective metabolite

Conclusion

From the dietary exposure calculations above it can be concluded that possible intakes of FOE sulfonic acid

by means of drinking water and food of plant origin do not present a consumer health concern. The calculations are based on several worst-case assumptions, such as

- For the reason of simplification, it is assumed that for the chronic exposure calculation all residues of plant origin consist of FOE sulfonic acid.
- All commodities consumed contain residues of the flufenacet metabolite at the level of the median residue level for flufenacet. However, actually the residue definition for enforcement covers all metabolites containing the common fluorophenyl-isopropyl moiety. The distribution of individual metabolites according to the findings in the metabolism studies is not taken into account. Although no flufenacet derived residues can be expected in food of animal origin the MRLs have been used in the IEDI calculation for animal commodities as well.
- Intake calculations are based on all crops that may be consumed and for which flufenacet uses are authorised. Calculations are not limited to potential residues that might be present in the supported crops (small grain cereals).
- No decrease of residues during storage and processing.
- Use of the upper limit groundwater concentrations for FOE sulfonic acid of 5.241 µg/L although in many scenarios this concentration will be never reached.

The calculations demonstrate an ADI (of flufenacet) usage of 40.8% for infants, 48.8% for children and 24.6% for adults. The consumer risk assessment shows an acceptable risk for FOE sulfonic acid. The calculations indicate that the intended use of FFA SC 508.8 G does not pose a risk to consumers as a result of exposure to this metabolite.

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** **GLP or GEP status** **published or not**	**Vertebrate study Y/N**	**Owner**
KCA Section 3 / 01	Hills, M.	2009	Evaluation of the pre-emergence biological activity of FOE 5043-Oxalate (code: BCS-AB16305) a metabolite of flufenacet Report No.: PP09022, Edition Number: M-353844-01-1 Bayer CropScience AG, Frankfurt am Main, Germany GLP/GEP: No unpublished	No	Bayer
KCA Section 3 / 02	Dahmen, P.	2004	Screening and efficacy data for WAK6222 (metabolite of FOE5043) Report No.: PF-F-HB_WAK6222_01, Edition Number: M-089475-01-1 Bayer AG, Leverkusen, Germany GLP/GEP: No unpublished	No	Bayer

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

Please note that all data mentioned as part of DAR, RAR, or EFSA journals are considered as 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**
-	-	-	-	-	-

List of data submitted by the applicant and not relied on

Data point	Author(s)	Year	**Title** **Company Report No.** **Source (where different from company)** **GLP or GEP status** **Published or not**	**Vertebrate study Y/N**	**Owner**
-	-	-	-	-	-

List of data relied on not submitted by the applicant but necessary for evaluation

Data point	Author(s)	Year	Title Company Report No. Source (where different from company) GLP or GEP status Published or not	Vertebrate study Y/N	Owner
-	-	-	-	-	-

Appendix 2 Additional information

Comments of zRMS:	Results of the study and conclusions are adequate for assessment of biological activity of FOE-oxalate (BCS-AB16305). ZRMS agree with study outcome. FFA metabolite M01, does not show biological activity (pre-emergence). Study accepted.

FOE oxalate (M01)

Reference:	**KCA Section 3/01**
Title:	Evaluation of the pre-emergence biological activity of FOE 5043-Oxalate (code: BCS-AB16305) a metabolite of flufenacet
Report:	Hills, M.; 2009; PP09022; M-353844-01-1
Authority registration No:	
Guideline(s):	not specified
Deviations:	not specified
GLP/GEP:	no
Acceptability:	Yes
Duplication (if vertebrate study):	Not aplicable

The study was designed to determine the biological activity of FOE -Oxalate (code BCS-AB16305, Batch SES 10565-3-1), a metabolite of flufenacet. The study was conducted under standardized glasshouse conditions using a WP05 formulation of the metabolite in comparison with a WP05 formulation of the parent flufenacet (FOE 5043, substance code AE F133402).

Materials and Methods:

- **Test material**	- **Dose rates (kg a.s./ha)**				
- FOE -Oxalate (metabolite of flufenacet) coded BCS-AB16305 (batch SES 10564-3-1) - formulated as WP05	- 0.372	- 0.310	- 0.155	- 0.077	- 0.037
- Flufenacet coded FOE 5043 (AE F133402; Batch ID: 488) formulated as a WP05.	- 0.600	- 0.500	- 0.250	- 0.125	- 0.060

The plant species tested were selected as those which have a relatively high sensitivity to flufenacet.

Plant species	Assigned number
Triticum aestivum (TRZAW)	1
Zea mays var vulgaris (ZEAMA)	2
Glycine max (GLXMA)	3
Alopecurus myosuroides (ALOMY)	4
Apera spica-venti (APESV)	5
Digitaria sanguinalis (DIGSA)	6
Echinochloa crus-galli (ECHCG)	7
Panicum miliaceum (PANMI)	8
Setaria viridis (SETVI)	9
Sorghum halepense (SORHA)	10
Amaranthus retroflexus (AMARE)	11
Ambrosia artemisiifolia (AMBEL)	12
Chenopodium album (CHEAL)	13
Galium aparine (GALAP)	14

The results of the visual assessments are presented as means from two replicates. Flufenacet demonstrated excellent control of all of the 11 weed species tested and some severe damage to wheat and corn crops with some degree of selectivity on soybeans.
The metabolite FOE-oxalate (BCS-AB16305) showed no biological activity on any of the 14 tested plant species.

Species name	kg a.s/ha	1	2	3	4	5	6	7	8	9	10	11	12	13	14	MEAN
Observed injury (%) of plants, 28 days after application																
flufenacet	**0.600**	96	63	20	100	100	100	100	100	100	100	100	96	96	98	99
	0.500	95	40	20	99	100	100	100	100	100	100	100	93	95	98	99
	0.250	93	20	20	98	100	100	100	99	100	100	98	75	95	96	96
	0.125	73	15	25	97	99	99	100	97	99	97	75	50	85	92	90
	0.060	65	0	0	97	99	99	99	97	90	97	55	18	75	85	83
FOE oxa-late	**0.372**	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	0.310	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	0.155	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	0.077	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	0.037	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Conclusions on the biological activity of FOE oxalate (M01):
In a direct comparison study, it could be shown that FOE oxalate (BCS-AB16305), a metabolite of flufenacet, had no pre-emergence biological activity when tested on a range of weeds and crops under highly sensitive screening conditions.

Comments of zRMS:	Results of the study and conclusions are adequate for assessment of biological activity of FOE sulfonic acid (WAK6222). ZRMS agree with study outcome. FFA metabolite M02, does not show biological activity (pre-emergence). Study accepted.

FOE sulfonic acid (M02)

Reference:	**KCA Section 3/02**
Title:	Screening and efficacy data for WAK6222 (metabolite of FOE5043)
Report:	Dahmen, P.; 2004; PF-F-HB_WAK6222_01; M-089475-01-1
Authority registration No:	
Guideline(s):	--
Deviations:	--
GLP/GEP:	no
Acceptability:	Yes
Duplication (if vertebrate study):	Not aplicable

This pre-emergence test was conducted to determine differences in the biological activity of flufenacet and its metabolite WAK6222 (FOE sulfonic acid).

Materials and Methods:
WAK6222 (Fraction 0-0), a.s. (purity 100%), metabolite of FOE5043.

Plants used for pre-emergence treatments were sown, sprayed with the test material and then directly placed under the specified growing conditions. The final evaluation was performed 21 days after treatment initiation.
For the metabolite the same application rates as for the parent compound were used, corrected for the molecular mass of FOE-sulfonic acid.
Evaluation of phytotoxicity was done by visual observations using a rating scale of 0 to 100%, where 100% represented complete destruction of above ground parts and 0% represented no visual damage (normal growth) as compared to untreated plants.

9 monocotyledonous and 5 dicotyledonous plant species were tested, including 11 target species and three crops:

Plant species	
Monocotyledonous	**Dicotyledonous**
Triticum aestivum (TRZAW)	*Glycine max* (GLXMA)
Zea mays (ZEAMX)	*Amaranthus retroflexus* (AMARE)
Alopecurus myosuroides (ALOMY)	*Ambrosia elatior* (AMBEL)
Apera spica-venti (APESV)	*Chenopodium album* (CHEAL)
Digitaria sanguinalis (DIGSA)	*Gallium aparine* (GALAP)
Echinochloa crus-galli (ECHCG)	
Panicum miliaceum (PANMI)	
Setaria viridis (SETVI)	
Sorghum halepense (SORHA)	

Results:

FOE5043 (flufenacet)	H2	Results (% injury) at different application rates				
Pre-emergence (g a.s./ha)						
Test species	**Code**	**600**	**500**	**250**	**125**	**60**
Monocotyledonae						
Triticum aestivum	TRZAW	5	0	0	0	0
Zea mays	ZEAMX	5	0	0	0	0
Alopecurus myosuroides	ALOMY	100	100	100	100	100
Alpera spica-venti	APESV	100	100	100	100	100
Digitaria sanguinalis	DIGSA	100	100	100	100	100
Echinochloa crus-galli	ECHCG	100	100	100	100	0
Panicum miliaceum L.	PANMI	100	100	99	99	99
Setaria viridis	SETVI	100	100	100	100	100
Sorghum halepense	SORHA	100	100	100	100	100
Dicotyledonae						
Glycine max	GLXMA	0	0	0	0	0
Amaranthus retroflexus	AMARE	100	100	100	90	20
Ambrosia elatior	AMBEL	95	90	70	40	40
Chenopodium album	CHEAL	99	99	95	60	40
Gallium aparine	GALAP	99	95	95	95	20

WAK6222 (FOE sulfonic acid)	H2	Results (% injury) at different application rates				
Pre-emergence (g a.s./ha)						
Test species	**Code**	**455**	**379**	**189**	**95**	**45**
Monocotyledonae						
Triticum aestivum	TRZAW	0	0	0	0	0
Zea mays	ZEAMX	0	0	0	0	0
Alopecurus myosuroides	ALOMY	0	0	0	0	0
Alpera spica-venti	APESV	0	0	0	0	0
Digitaria sanguinalis	DIGSA	0	0	0	0	0
Echinochloa crus-galli	ECHCG	0	0	0	0	0
Panicum miliaceum L.	PANMI	0	0	0	0	0
Setaria viridis	SETVI	0	0	0	0	0
Sorghum halepense	SORHA	0	0	0	0	0
Dicotyledonae						
Glycine max	GLXMA	0	0	0	0	0
Amaranthus retroflexus	AMARE	0	0	0	0	0
Ambrosia elatior	AMBEL	0	0	0	0	0
Chenopodium album	CHEAL	0	0	0	0	0
Gallium aparine	GALAP	0	0	0	0	0

Conclusion on the biological activity of FOE sulfonic acid (M02):

At none of the tested rates any phytotoxic effects were observed. Based on these results it is concluded that FOE sulfonic acid has no herbicidal activity.

Appendix 3 Additional information provided by the applicant

Metabolic pathway of flufenacet in the rat