FINAL REGISTRATION REPORT

Part B

Section 10

Assessment of the relevance of metabolites in groundwater

Detailed summary of the risk assessment

Product code: SHA 2619 A

Product name(s): KONARK

Chemical active substances:

Flufenacet, 60 g/L
Pendimethalin, 300 g/L

Central Zone

Zonal Rapporteur Member State: Poland

CORE ASSESSMENT

Applicant: Sharda Cropchem España S.L.

Submission date: March 2021

MS Finalisation date: October 2021; May 2023

Version history

When	What
10/2021	Assessment by the expert
May 2023	zRMS revision after commenting phase – final version of the RR

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10 Relevance of metabolites in groundwater

10.1 General information

The metabolites of Flufenacet, Flufenacet sulfonic acid (M2) and Flufenacet oxalate (M1) are predicted to occur in groundwater at concentrations above 0.1 µg/L (see dRR section B8 Tables 8.8-4 and 8.8-5), meanwhile the only Pendimethalin metabolite M455H001 shown concentrations greater than 0.1 µg/L (see dRR section B8 Tables 8.8-9 and 8.8-10). Therefore, 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.

10.1.1 Flufenacet

All leaching simulation run with FOCUS PELMO and PEARL resulted in PEC_{GW} values highly below 0.1 µg/L for flufenacet for all FOCUS scenarios.

Like explained in the DAR of Flufenacet (Annex B.7, 1997) in the lysimeter studies (see point CP9.3.2): the levels of FOE oxalate were < 0.1 µg/L and the level of FOE sulfonic acid were 3.7 µg/L (max. value - 1st year) and 0.015 µg/L (mean value - 2nd year). It can be noted that the level of FOE sulfonic acid in the lysimeter studies are significantly lower than the values of the FOCUS models, therefore, the models can be considered as not being representative.

Therefore, a refinement has been proposed using the FOE sulfonic acid DT_{50} geomean derived from field studies.

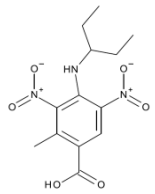
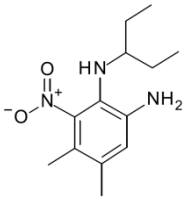
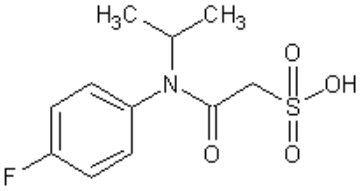
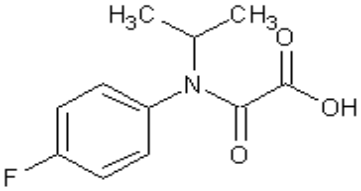
The TIER 1 refinement shown the FOE sulfonic acid maximum concentrations in winter cereals in Jokioinen scenario (5.297µg/L), for FOCUS PEARL model that is in the range of field studies.

General information on the metabolites are provided in Pendimethalin
According to the simulations, the maximum predicted concentrations in leachate water at 1m depth were high below 0.1 µg/L for Pendimethalin and its non relevant metabolites M455H001 and M455H033 with the exception in winter and spring cereals preemergence PEARL Okehampton and Hamburg scenarios respectively where non relevant metabolite M455H001 exceed the trigger value with a maximum of 0.119 µg/L. Therefore, assessment of the relevance of metabolite M455H001 according to the stepwise procedure of the EC guidance document SANCO/221/2000 –rev.10 is therefore required.
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 8.8.3.1 of the dRR Part B, Section 8 (Environmental fate and behaviour).

10.1.2 Pendimethalin

According to the simulations, the maximum predicted concentrations in leachate water at 1m depth were high below 0.1 µg/L for Pendimethalin and its non relevant metabolites M455H001 and M455H033 with the exception in winter and spring cereals preemergence PEARL Okehampton and Hamburg scenarios respectively where non relevant metabolite M455H001 exceed the trigger value with a maximum of 0.119 µg/L. Therefore, assessment of the relevance of metabolite M455H001 according to the stepwise procedure of the EC guidance document SANCO/221/2000 –rev.10 is therefore required.

Table 10.1-1: General information on the metabolites

Name of active substance	Metabolite name and code	Structural/molecular formula	Trigger for relevance assessment	
Pendimethalin	M455H001		Max PEC_{gw} 0.119 µg/L Based on: PEARL Okehampton **For Germany and Slovenia < 0.1 µg/L after TIER 1 and 2 refinements, thus no assessment is needed**	
	M455H033		<0.001 µg/L	
Flufenacet	FOE sulfonic acid code (M2)		Max PEC_{gw} 5.297 µg/L Based on: PEARL Jokioinen (winter cereals)	
	FOE oxalate code: (M1)		< 0.1 µg/L Field leaching data	Max PEC_{gw} 0.577 µg/L Based on: PELMO Hamburg winter cereals

10.2 Flufenacet metabolites

10.2.1 Relevance assessment of FOE sulfonic acid

Summary:

The predicted environmental concentrations of FOE sulfonic acid in groundwater have been assessed. Please refer to Part B, section 8, point 8.8.3 for all the details and calculations.

The FOE sulfonic acid PEC_{gw} is ranged between 5.905 to 27.736 µg/L.

According to the "*Flufenacet BD-C addendum mamtox, 2001-01*" and "*Flufenacet BD-C addendum eco-tox, 2003-04-08*" it has been demonstrated that FOE sulfonic acid:

- "*is considered of no toxicological relevance*"
- "*is clearly less toxic to non-target organisms (fish, Daphnia, algae, Lemna, earthworm, mammals) than the active ingredient*"

Table 10.2-1: 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}	5.297 µg/L
			Based on	PEARL Jokioinen winter cereals
Hazard assessment	STEP 3	Stage 1	Biological activity comparable to the parent?	No
		Stage 2	Genotoxic properties of metabolite	Non-genotoxic
		Stage 3	Toxic properties of metabolite;	FOE sulfonic acid can be considered toxicologically equivalent to the parent compound. The parent compound was not classified for toxicology and the metabolites are not defined as toxic. FOE sulfonic acid has no relevant toxicity for fish, daphnid and aquatic plants and is less toxic than flufenacet the FOE sulfonic acid is not acutely toxic to earthworms and have no significant effect on carbon and nitrogen mineralisation up to 0.75 mg/kg soil.
			Classification of parent	H302, H317, H373, H400, H410
			Classification of metabolite	-
Consumer health risk assessment	STEP 4		Estimated consumer exposure via drinking water and other sources; threshold of concern approach	not acceptable (>0.75 µg/L)
	STEP 5		Refined risk assessment	Acceptable
			Predicted exposure (% of ADI)	14% for toddler
			ADI based on	Parent (0.005 mg/kg bw per day from the EU Pesticide Database)

10.2.1.1 STEP 1: Exclusion of degradation products of no concern

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.

10.2.1.2 STEP 2: Quantification of potential groundwater contamination

The predicted environmental concentrations of FOE sulfonic acid in groundwater has been assessed. Please refer to Part B, section 8, point 8.8-3 for all the details and calculations.

The TIER 1 refinement shown the FOE sulfonic acid maximum concentrations in winter cereals in Jokioinen scenario (5.297µg/L), for FOCUS PEARL model.

According to the "*Flufenacet BD-C addendum mamtox, 2001-01*" and "*Flufenacet BD-C addendum ecotox, 2003-04-08*" it has been demonstrated that FOE sulfonic acid:

"*is considered of no toxicological relevance*"

"*is clearly less toxic to non-target organisms (fish, Daphnia, algae, Lemna, earthworm, mammals) than the active ingredient*"

10.2.1.3 STEP 3: Hazard assessment – identification of relevant metabolites

(a) STEP 3, Stage 1: screening for biological activity

According to the "*Flufenacet BD-C addendum mamtox,2001-01*" the following information on FOE sulfonic acid are available: *based firstly on the physical properties that show a high hydro solubility which suggests a low biological absorption, the solubility in water is 55 g/l at 20°C at pH 4 to 9; under same conditions, its K_{ow} is 0.0019, leading to a log K_{ow} = -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 sulfonic acid is considered of no toxicological relevance*.

(b) STEP 3, Stage 2: screening for genotoxicity

According to the "*Flufenacet BD-C addendum mamtox, 2001-01*" the following information on the genotoxicity of FOE sulfonic acid is available: *FOE sulfonic acid is considered to be non-mutagenic without and with S9 mix in the plate incorporation as well as in the pre-incubation modification of the Salmonella/microsome test*.

(c) STEP 3, Stage 3: screening for toxicity

According to the "*Flufenacet BD-C addendum mamtox, 2001-01*" the following information on the toxicity of FOE sulfonic acid is available: *the acute oral LD50 of FOE sulfonic acid is > 2000 mg/kg bw*.

10.2.1.4 STEP 4: Exposure assessment – threshold of concern approach

In agreement with the SANCO Guidance the FOE sulfonic acid is considered as non-relevant because it passes the Step 3, and the Step 4 should be done in order to be sure that that any contamination of groundwater will not lead to unacceptable exposure of consumers via their drinking water.

Since the potential exposure to FOE sulfonic acid is > 0.75, a further assessment in Step 5 is required.

10.2.1.5 STEP 5: Refined risk assessment

A refined risk assessment considering all the contributions to the diet has been performed since FOE-sulfonic acid concentrations in groundwater were predicted to be higher than the threshold of concern of 0.75 µg/L. The highest groundwater concentration of FOE sulfonic acid, below the cut off value of 10 µg/L and without refinement, given by the model was 5.297 µg/L (Jokioinen scenario in PEARL model winter cereals). Since also the ADI of the parent is used, the concentration equivalent to the parent should be used. The molecular weight of flufenacet is 363.34 g/mol and the molecular weight of FOE sulfonic acid is 275.3 g/mol. ((5.297/275.3)*363.34 = 6.99 µg/L.

Calculation of risk (% ADI) for 60 -kg adult (consuming 2.0 L/day):

$$Exposure = \frac{6.99\ [\mu g\ L^{-1}]\ x\ 2\ [L\ d^{-1}]}{60\ [kg\ bw]\ x\ 1000\ [\mu g\ mg^{-1}]} = 2.33\ x\ 10^{-4}\ [mg\ kg\ bw^{-1} d^{-1}]$$

Calculation of risk (% ADI) for 10-kg toddler (consuming 1.0 L/day):

$$Exposure = \frac{6.99\ [\mu g\ L^{-1}]\ x\ 1\ [L\ d^{-1}]}{10\ [kg\ bw]\ x\ 1000\ [\mu g\ mg^{-1}]} = 6.99\ x\ 10^{-4}\ [mg\ kg\ bw^{-1} d^{-1}]$$

Calculation of risk (% ADI) for 8 -kg infant (consuming 0.75 L/day):

$$Exposure = \frac{6.99\ [\mu g\ L^{-1}]\ x\ 0.75\ [L\ d^{-1}]}{8\ [kg\ bw]\ x\ 1000\ [\mu g\ mg^{-1}]} = 6.55\ x\ 10^{-4}\ [mg\ kg\ bw^{-1} d^{-1}]$$

	% of ADI (ADI = 0.005 mg/kg bw/day)*
Adults	4.7
Toddlers	14.0
Infants	13.1

***ADI value of Flufenacet from the EU Pesticide Database**

As shown in the above table, the highest estimated exposure via drinking water is 14.0% of the ADI, but consideration must be taken since the PECgw value was not refined.

The consumer risk assessment demonstrates an acceptable risk for the adult, child and infant after ingestion of drinking water contaminated with FOE sulfonic acid due to the agricultural uses of KORNAK.

10.3 Pendimethalin metabolites

10.3.1 Relevance assessment of M455H001

For Germany and Slovenia no relevance assessment is needed because the PECgw in all crops and scenarios after TIER 1 and 2 refinements are lower than 0.1 µg/L.

Summary:

The predicted environmental concentrations of non relevant metabolite M455H001 in groundwater have been assessed. Please refer to Part B, section 8, point 8.8.3 for all the details and calculations.

The M455H001 PEC_{gw} is ranged between <0.001 to 0.119 µg/L.

Table 10.3-1: Summary of the relevance assessment for M455H01

	Assessment step	Result of assessment	
	STEP 1	Metabolite of no concern?	no
groundw	STEP 2	Max PEC_{gw}	0.119 µg/L

			Based on	PEARL Okehampton winter cereals
Hazard assessment	STEP 3	Stage 1	Biological activity comparable to the parent?	No
		Stage 2	Genotoxic properties of metabolite	Non-genotoxic
		Stage 3	Toxic properties of metabolite;	Non-toxic
			Classification of parent	H317, H400, H410
			Classification of metabolite	-
Consumer health risk assessment	STEP 4		Estimated consumer exposure via drinking water and other sources; threshold of concern approach	Acceptable (>0.75 µg/L)
	STEP 5		Refined risk assessment	-
			Predicted exposure (% of ADI)	-
			ADI based on	Parent (0.125 mg/kg bw per day from the EU Pesticide Database)

10.3.1.1 STEP 1: Exclusion of degradation products of no concern

M455H001 does not meet the criteria for products of no concern as defined in step 1 of the guidance and therefore needs further assessment.

10.3.1.2 STEP 2: Quantification of potential groundwater contamination

According to the simulations, the maximum predicted concentrations in leachate water at 1m depth were high below 0.1 µg/L for Pendimethalin and its non relevant metabolites M455H001 and M455H033 with the exception in winter and spring cereals preemergence PEARL Okehampton and Hamburg scenarios respectively where non relevant metabolite M455H001 exceed the trigger value with a maximum of 0.119 µg/L. Therefore, assessment of the relevance of metabolite M455H001 according to the stepwise procedure of the EC guidance document SANCO/221/2000 –rev.10 is therefore required.STEP 3: Hazard assessment – identification of relevant metabolites

(a) STEP 3, Stage 1: screening for biological activity

No biological activity against organism.

(b) STEP 3, Stage 2: screening for genotoxicity

Nonetheless, M455H001 was tested for its genotoxic potential in an Ames test, a chromosome aberration test, a mouse lymphoma test and an in vivo micronucleus assay. In conclusion, M455H001 is not considered to be a relevant metabolite.

(c) STEP 3, Stage 3: screening for toxicity

No further screening for toxicity was performed.

10.3.1.3 STEP 4: Exposure assessment – threshold of concern approach

In agreement with the SANCO Guidance the M455H001 is considered as non-relevant because it passes the Step 3, and the Step 4 should be done in order to be sure that that any contamination of groundwater will not lead to unacceptable exposure of consumers via their drinking water.

Since the potential exposure to M455H001 is < 0.75, a further assessment in Step 5 is not required.

10.3.1.4 STEP 5: Refined risk assessment

Not required.

Expert comment:

According to the "Flufenacet BD-C addendum mamtox, 2001-01" and "Flufenacet BD-C addendum ecotox, 2003-04-08" it has been demonstrated that FOE sulfonic acid:

- **"is considered of no toxicological relevance"**
- **"is clearly less toxic to non-target organisms (fish, Daphnia, algae, Lemna, earth-worm, mammals) than the active ingredient"**

According (STEP 5) the consumer risk assessment demonstrates an acceptable risk for the adult, child and infant after ingestion of drinking water contaminated with FOE sulfonic acid due to the agricultural uses of KORNAK

Pendimethalin: relevance assessment of 455H001 was tested for its genotoxic potential in an Ames test, a chromosome aber-ration test, a mouse lymphoma test and an in vivo mic Since the potential exposure to M455H001 is < 0.75, a further assessment in Step 5 is not required. onucleus assay. In conclusion, M455H001 is not considered to be a relevant me-tabolite.

According to the 18th ATP (16/02/2022), pendimethalin is a developmental toxin, qualifying for Repr. 2, H361d classification. This is due to skeletal malformations (absent ribs and absent verte-bra) observed in the rabbit developmental toxicity study in the absence of maternal toxicity. Fur-thermore, in the 2-generation study the slight decrease in the number of pups (F1 and F2) at 5000 ppm should also be considered in respect to developmental toxicity

Appendix 1 Lists of data considered in support of the evaluation

List of data submitted by the applicant and relied on

Appendix 2 Additional information