FINAL REGISTRATION REPORT

Part B

Section 10

Assessment of the relevance of metabolites in groundwater

Detailed summary of the risk assessment

Product code: **MT-565SG-OR2-C**

Product name(s): **HAKSAR TOP 565 SG**

Chemical active substance:

MCPA, 550 g/kg
Tribenuron methyl, 15 g/kg

Central Zone

Zonal Rapporteur Member State: Poland

CORE ASSESSMENT

(authorization)

Applicant: CIECH Sarzyna S.A.

Submission date: 01/2021

MS Finalisation date: 06/12/2021

Version history

When	What
January 2021	First submission of product authorization.
02/2021	Dossier sent for evaluation to Merit Mark (PL)
08/2021	zRMS finalised evaluation
December 2021	Final RR

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Evaluator comments:
The text highlighted in grey was provided by the evaluator.

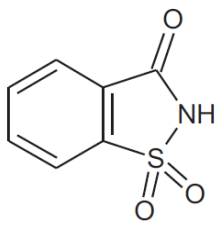
10 Relevance of metabolites in groundwater

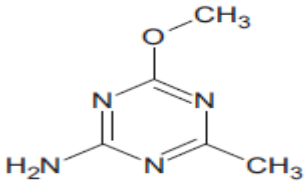
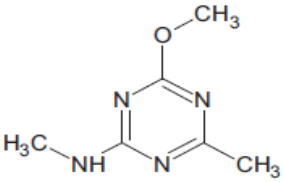
Evaluator's Comments:	The submitted PECgw values for metabolites of active substance are in accordance with PELMO and PEARL PECgw assessment (Section 8). All PECgw values are above the trigger value of 0.1 µg/L and represents the worst case (winter/spring cereals, spring application every year) with exception for metabolite IN-00581 (winter cereals, autumn application every third year). According to EFSA conclusions on Tribenuron-methyl (2017) for the metabolites IN-A4098 and IN-L5296 a genotoxic potential could not be excluded. In the EFSA Scientific Opinion of the Scientific Panel on Plant Protection Products and their Residues (PPR Panel) on the genotoxic potential of triazine amine (metabolite common to several sulfonylurea active substances) (EFSA Journal 2020;18(3):6053) was stated: "*There is no concern for the potential of triazine amine to induce gene mutations and clastogenicity; however, the potential to induce aneugenicity was not adequately investigated. For a conclusion, an in vitro micronucleus assay performed with triazine amine would be needed*." The submitted by Applicant results of *in vitro* micronucleus assay (Antonik, J., 2015) and *in vitro* mammalian cell gene mutation test (Smagur, J., 2015) support the lack of genotoxic potential of the metabolite IN-A4098 in regards to the mammalian cells. The Applicant submitted also studies for IN-L5296 - bacterial reversion mutation test (De la Torre S., 2019), *in vitro* chromosome aberrations test using Chinese Hamster Ovary cells (CHO) (Peroche A., 2019) and *in vitro* mammalian cell gene mutation test (Savineau C., 2019) (De la Torre S., 2019; Peroche, A., 2019 and Savineau, C., 2019) supporting the lack of genotoxic potential of this metabolite. These studies were evaluated and accepted during evaluation of the product TOSCANA TOP 75 WG (Product code T-75WG-OR2C). For metabolite IN-00581 the ADI value of 3.8mg/kg/ bw per day was agreed (EFSA, 2017). Taking above into consideration and the assessment of the relevance of metabolites IN-A00581, IN-A4098 and IN-L5296 performed by Applicant according to the stepwise procedure of the EC guidance document SANCO/221/2000 –rev.10 the metabolites are not considered to be relevant for the purposes of this registration report.

10.1 General information

The metabolites listed below are predicted to occur in groundwater at concentrations above 0.1 µg/L (see dRR B section 8). 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.

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

Name of active substance	Metabolite name and code	Structural/molecular formula	Trigger for relevance assessment	
tribenuron-methyl	IN-00581		Max PEC_{gw} Based on:	0.304µg/L FOCUS model PELMO/ Hamburg, winter cereals 15 g a.s./ha in autumn Tier 2, every third year, pH > 7

Name of active substance	Metabolite name and code	Structural/molecular formula	Trigger for relevance assessment	
tribenuron-methyl	IN-A4098		Max PEC_{gw} Based on:	0.631 µg/L FOCUS model PEARL /Hamburg, spring cereals 15 g a.s./ha in spring Tier 2, every year, pH > 7
tribenuron-methyl	IN-L5296		Max PEC_{gw} Based on:	0.118 µg/L FOCUS model PELMO/ Hamburg, winter cereals 15 g a.s./ha in spring Tier 2, every year, pH > 7

10.2 Relevance assessment of IN-00581

The relevance of the groundwater metabolite IN-00581 has already been assessed and the assessment agreed at EU level (please refer to EFSA conclusions for Tribenuron (2017)).
The relevance assessment is applicable as well for the GAP and groundwater scenarios considered in this dRR .
This metabolite is not considered relevant according to the criteria laid down in the EC guidance document SANCO/221/2000 –rev.10.

Table 10.2-1: Summary of the relevance assessment for IN-00581

	Assessment step		Result of assessment	
	STEP 1		Metabolite of no concern?	~~yes~~ no
Quantification of groundwater contamination	STEP 2		Max PEC_{gw}	0.304µg/L
			Based on	FOCUS model PELMO/Hamburg
Hazard assessment	STEP 3	Stage 1	Biological activity comparable to the parent?	No (EFSA, 2017)
		Stage 2	Genotoxic properties of metabolite	Non genotoxic (EFSA, 2017)
		Stage 3	Toxic properties of metabolite;	ADI 3.8 mg/kg day (EFSA, 2017)
			Classification of parent	Skin Sens. 1, H317 STOT RE CAT 2 H373 (equivalent to Xn in EU) (EFSA 2017) Regulation (EC) No 1272/2008 as amended (Commission Delegated Regulation (EU) 2020/1182
			Classification of metabolite	None (EFSA 2017)
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	n.a.

		Predicted exposure (% of ADI)	n.a.
		ADI based on	n.a.

10.2.1 STEP 1: Exclusion of degradation products of no concern

The metabolite 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 this were performed (see Part B, Section 8). The uses for which concentrations were considered to exceed 0.1 µg/L is cereals.

10.2.3 STEP 3: Hazard assessment – identification of relevant metabolites

According to the EFSA conclusions for Tribenuron (page 19) the metabolite does not have pesticidal activity and it is considered of no toxicological relevance.

10.2.4 STEP 4: Exposure assessment – threshold of concern approach

IN-00581 was not considered relevant in the hazard assessment of Step 3. The PEC_{GW} for this metabolite is well below < 0.75 µg/L and does not exceed the toxicological threshold of concern as defined in EC guidance document SANCO/221/2000 –rev.10.

10.3 Relevance assessment of IN-A4098

The relevance of the groundwater metabolite IN-A4098 has not been finalized during the evaluation done for the a.i. Tribenuron during the AIR process.

New genotoxicity studies are presented by the applicant in Section 6.

Table 10.34-1: Summary of the relevance assessment for IN-A4098

	Assessment step		**Result of assessment**	
	STEP 1		Metabolite of no concern?	no
Quantification of groundwater contamination	STEP 2		Max PEC_{gw}	0.631 µg/L
			Based on	FOCUS model PEARL/Hamburg scenario
Hazard assessment	STEP 3	Stage 1	Biological activity comparable to the parent?	No (EFSA, 2017)

		Stage 2	Genotoxic properties of metabolite	Non genotoxic (~~EFSA, 2017 and~~ dRR Part B section 6)
		Stage 3	Toxic properties of metabolite;	LD50 ~~>~~ 1000 mg /kg bw LOAEL 3.6 mg/kg bw rats (EFSA 2017)
			Classification of parent	Skin Sens. 1, H317 STOT RE CAT 2 H373 (equivalent to Xn in EU) (EFSA 2017) Regulation (EC) No 1272/2008 as amended (Commission Delegated Regulation (EU) 2020/1182
			Classification of metabolite	None (EFSA 2017)
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	n.a.
			Predicted exposure (% of ADI)	n.a.
			ADI based on	n.a.

10.3.1 STEP 1: Exclusion of degradation products of no concern

The metabolite 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 this were performed (see Part B, Section 8). The uses for which concentrations were considered to exceed 0.1 µg/L cereals.

10.3.3 STEP 3: Hazard assessment – identification of relevant metabolites

10.3.3.1 STEP 3, Stage 1: screening for biological activity

According to the EFSA conclusions for Tribenuron (page 18) the metabolite does not have pesticidal activity.

10.3.3.2 STEP 3, Stage 2: screening for genotoxicity

According to EFSA conclusions on Tribenuron (2018~~7~~)~~,~~ for the metabolite IN-A4098 ~~is negative for genotoxicity in gen mutation to bacteria as well as in chromosome damage~~ a genotoxic potential could not be excluded. In the EFSA Scientific Opinion of the Scientific Panel on Plant Protection Products and their Residues (PPR Panel) on the genotoxic potential of triazine amine (metabolite common to several sulfonylurea active substances) (EFSA Journal 2020;18(3):6053) was stated: "*There is no concern for the potential of triazine amine to induce gene mutations and clastogenicity; however, the potential to induce aneugenicity was not adequately investigated. For a conclusion, an in vitro micronucleus assay performed with triazine amine would be needed*."

~~Additionally to this information,~~ tThe applicant submitted 2 negative studies on mammalian gene mutation. The results of *in vitro* micronucleus assay (Antonik, J., 2015) and *in vitro* mammalian cell gene mutation test (Smagur, J., 2015) support the lack of genotoxic potential of the metabolite IN-A4098 in regards to the mammalian cells.

The studies are summarised on the Section 6 and confirm the lack of genotoxicity.

10.3.3.3 STEP 3, Stage 3: screening for toxicity

According to EFSA conclusions on Tribenuron (2017), the metabolite IN-A4098 is not classified. Therefore it does not fullfill the criteria for relevant (EU toxic or very toxic).

The active ingredient is neither fulfilling any of the criteria by which metabolites would be automatically considered as relevant (STOT. RE. Cat 2 eq. to Xn in EU).

10.3.4 STEP 4: Exposure assessment – threshold of concern approach

IN-A4098 was not considered relevant in the hazard assessment of Step 3.

The PEC_{GW} for IN-A4098 is well below the trigger of 0.75 µg/L and hence the metabolite is not considered to exceed the toxicological threshold of concern as defined in EC guidance document SANCO/221/2000 –rev.10.

10.4 Relevance assessment of IN-L5296

The relevance of the groundwater metabolite IN-L5296 has not been finalized during the evaluation done for the a.i. Tribenuron during the AIR process.

New genotoxicity studies are presented by the applicant in Section 6

Table 10.47-1: Summary of the relevance assessment for IN-L5296

	Assessment step		**Result of assessment**	
	STEP 1		Metabolite of no concern?	no
Quantification of groundwater contamination	STEP 2		Max PEC_{gw}	0.118 µg/L
			Based on	FOCUS model PELMO/ Hamburg scenario
Hazard assessment	STEP 3	Stage 1	Biological activity comparable to the parent?	No pesticidal activity (EFSA 2017)
		Stage 2	Genotoxic properties of metabolite	Non genotoxic (~~EFSA 2017~~, dRR Part B Section 6)
		Stage 3	Toxic properties of metabolite;	LD50 394 mg/kg bw NOAEL 8 mg/kg bw per day (EFSA 2017)
			Classification of parent	Skin Sens. 1, H317 STOT RE CAT 2 H373 (equivalent to Xn in EU) (EFSA 2017) Regulation (EC) No 1272/2008 as amended (Commission Delegated Regulation (EU) 2020/1182
			Classification of metabolite	H302 (eq. to Xn in EU) (EFSA 2017)
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	n.a.
			Predicted exposure (% of ADI)	n.a.
			ADI based on	n.a.

10.4.1 STEP 1: Exclusion of degradation products of no concern

IN-L5296 does not meet the criteria for products of no concern as defined in step 1 of the guidance and therefore needs further assessment.

10.4.2 STEP 2: Quantification of potential groundwater contamination

PEC_{gw} calculations after leaching from soil for IN-L5296 were performed (see Part B, Section 8). The uses for which concentrations were considered to exceed 0.1 µg/L is cereals.

10.4.3 STEP 3: Hazard assessment – identification of relevant metabolites

10.4.3.1 STEP 3, Stage 1: screening for biological activity

According to the EFSA conclusions for Tribenuron (page 18) the metabolite does not have pesticidal activity.

10.4.3.2 STEP 3, Stage 2: screening for genotoxicity

According to EFSA conclusions on Tribenuron (2017; Appendix A page 15), the metabolite IN-L5296 is negative for genotoxicity in all the studies (bone marrow exposure not demonstrated). However, a genotoxic potential of metabolite IN-L5296 could not be excluded.
Additionally to this information, the applicant submitted 3 negative studies on bacterial and mammal gene mutation as well as on chromosome damage - bacterial reversion mutation test (De la Torre S., 2019), *in vitro* chromosome aberrations test using Chinese Hamster Ovary cells (CHO) (Peroche A., 2019) and *in vitro* mammalian cell gene mutation test (Savineau C., 2019) supporting the lack of genotoxic potential of this metabolite.

The studies are summarised on the Section 6 and confirm the lack of genotoxicity.

10.4.3.3 STEP 3, Stage 3: screening for toxicity

According to EFSA conclusions on Tribenuron (2017), the metabolite IN-L5296 is classified as Harmful if swallowed (H302) which is equivalent to EU Xn, R22. Therefore it does not fullfill the criteria for relevant (EU toxic or very toxic).
The active ingredient is neither fulfilling any of the criteria by which metabolites would be automatically considered as relevant (STOT. RE. Cat 2 eq. to Xn in EU).

10.4.4 STEP 4: Exposure assessment – threshold of concern approach

IN-L5296 was not considered relevant in the hazard assessment of Step 3.

The PEC_{gw} for IN-L5296 is well below the trigger of 0.75 µg/L and hence the metabolite is not considered to exceed the toxicological threshold of concern as defined in EC guidance document SANCO/221/2000 –rev.10.