FINAL REGISTRATION REPORT

Part B

Section 10

Assessment of the relevance of metabolites in groundwater

Detailed summary of the risk assessment

Product code: **M-100SC-OR2-C**

Product name(s): **JUZAN EXTRA 100 SC**

Chemical active substance:

mesotrione, 100 g/l

Central Zone

Zonal Rapporteur Member State: Poland

CORE ASSESSMENT

(authorization)

Applicant: CIECH Sarzyna S.A.

Submission date: 05/2022

MS Finalisation date: 12.2022; 05.2023

Version history

When	What
May 2022	First submission of product authorization.
December 2022	Assessment by expert
May 2023	The final version of RR after commenting period

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10 Relevance of metabolites in groundwater

10.1 General information

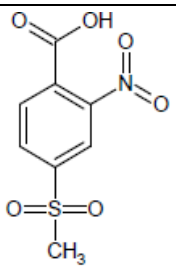
The metabolite listed below is predicted to occur in groundwater at concentrations above 0.1 µg/L (see dRR B section 8). Assessment of the relevance of this metabolite according to the stepwise procedure of the EC guidance document SANCO/221/2000 –rev.10 is therefore required.
General information on the metabolite is provided in Table 10.1-1.

The PEC_{GW} of the mesotrione metabolite AMBA (2-amino-4-(methylsulfonyl) benzoic acid) was < 0.1 µg/L in the relevant application patterns (please see dRR Part B, Section 8, chapter 8.8.2 and Table 10.1-1 below). Therefore, no assessment is required for this metabolite.

The mesotrione metabolite MNBA (4-(methylsulfonyl)-2-nitrobenzoic acid) is predicted to occur in groundwater at concentrations above 0.1 µg/L. Assessment of the relevance of this metabolite according to the stepwise procedure of the EC guidance document SANCO/221/2000 –rev.10 is therefore required.

General information on the metabolite 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	
Mesotrione	MNBA		Max PEC_{gw} Based on:	Maize 0.131 µg/L FOCUS model PELMO/ Hamburg

10.2 Relevance assessment of MNBA

The relevance of the groundwater metabolite MNBA has already been assessed and the assessment agreed at EU level (please refer to EFSA (2016)).
This metabolite is not considered relevant according to the criteria laid down in the EC guidance document SANCO/221/2000 –rev.11.

Table 10.2-1: Summary of the relevance assessment for MNBA

	Assessment step	Result of assessment	
	STEP 1	Metabolite of no concern?	No

Quantification of groundwater contamination	STEP 2		Max PEC_{gw}	0.131 µg/L
			Based on	FOCUS model PELMO/ Hamburg
Hazard assessment	STEP 3	Stage 1	Biological activity comparable to the parent?	No (EFSA, 2016)
		Stage 2	Genotoxic properties of metabolite	Non genotoxic (EFSA, 2016)
		Stage 3	Toxic properties of metabolite;	Not toxic (EFSA, 2016)
			Classification of parent	STOT RE 2; H373 (eyes, nervous system) Repr. 2; H361d (EFSA 2016; 15th ATP to CLP)
			Classification of metabolite	based on the proposed classification by the peer review as Repr. 2 (EFSA 2016; page 16)
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 MNBA were performed (see Part B, Section 8, chapter 8.8.2). The uses for which concentrations of MNBA were considered to exceed 0.1 µg/L are listed in Table 10.2-1. Details are given in Part B, Section 8, chapter 8.8.2.

10.2.3 STEP 3: Hazard assessment – identification of relevant metabolites

Step 3 of the guidance document (SANCO/221/2000) involves assessment of biological activity, genotoxicity and toxicity of a major metabolite which may potentially exceed 0.1 µg/L in groundwater.

10.2.3.1 STEP 3: Stage 1: screening for biological activity

According to the EU peer review for Mesotrione the metabolite does not have pesticidal activity.

10.2.3.2 STEP 3: Stage 2: screening for genotoxicity

MNBA was screened for genotoxic activity by the studies listed in Table 10.2-2 below. All studies have been previously reviewed under Regulation (EC) No 1107/2009; from these studies, it can be concluded that MNBA is not genotoxic in vitro or in vivo. Hence, MNBA is considered not relevant in this step of the assessment and it is considered further in Step 3, Stage 3.

Table 10.2-2: Summary of genotoxicity studies with MNBA

Study	Result	Details	Reference
Bacterial reverse mutation	Not genotoxic	TA1535, TA1537, TA98, TA100, WP2uvrA, WP2 pKM 101	Callander (1996)[a]
In vitro cytogenetics	Not genotoxic	Human lymphocytes	Fox (2000)[a]
Unscheduled DNA synthesis (UDS) *in vivo*	Not genotoxic	Limit dose 2000 mg/kg in the rat	Clay (2000)[a]
Rat bone marrow micronucleus test *in vivo*	Not genotoxic	Limit dose 2000 mg/kg	Fox (2000a)[a]

[a] Indicates that a study was reviewed at EU level.

10.2.3.3 STEP 3: Stage 3: screening for toxicity

As stated in the EU peer review on mesotrione, the MNBA metabolite has low toxicity than the parent mesotrione. The tyrosine disturbance is secondary to inhibition of p-hydroxyphenylpyruvate dioxygenase (HPPD). In a study of relative potency of HPPD inhibition, MNBA was several orders of magnitude less potent than mesotrione. It is considered that MNBA will not produce disturbance of tyrosine metabolism of sufficient magnitude to induce classifiable developmental effects.

According to the criteria regarding ecotoxicological effects laid out in Guidance Document on Relevant Metabolites (draft 1999), MNBA and AMBA are not relevant metabolites. The algal NOECs, EC50 for *Daphnia magna* and LC50 for fish exceed the thresholds of 1 mg/l, 100 mg/l and 100 mg/l respectively in both instances (Tables B.9.6. and B.9.7 of draft assessment report). In a study on earthworms in which metabolites were deemed to have been present, the LC50 for the parent was >2000 mg/kg. It is unlikely, therefore, that the LC50 for either metabolite would be below the threshold of 1000 mg/kg (B.9.6.2. of draft assessment report). There was no effect on soil microbial function in a study in which metabolites would have been formed (B.9.8.2. of draft assessment report).

A study in male rats showed that MNBA was metabolised in the gut to AMBA. Approximately 16% of the administered radioactivity was excreted in the urine, (~5% as MNBA and ~10% as AMBA), indicating either absorption of AMBA from the gut or absorption and subsequent metabolism of MNBA. MNBA was found to be of comparatively low acute toxicity, however this metabolite was identified as a potential skin sensitiser. No evidence of genotoxicity was seen in an Ames test, a UDS assay in the rat liver or in a mouse micronucleus assay. A significant increase in chromosomal aberrations was seen at the highest concentration tested in a cytogenetics study in human lymphocytes, however similar findings were not seen in a confirmatory assay. It is therefore considered that MNBA is not genotoxic. Increased motor activity was seen in female rats in a 28-day study with MNBA, however this finding is considered to be equivocal. No effects were seen in males. Minor effects on bodyweight and food consumption were noted in males only in a 90-day study. Mild hypertyrosinaemia was also seen in males at dose levels of 650 and 3000 ppm, however urinary phenolic acids were not increased at this dose level. No significant effects were seen on HPPD activity *in vitro*.
It can therefore be considered as a non-essential groundwater metabolite and is further evaluated in Step 4.

10.2.4 STEP 4: Exposure assessment – threshold of concern approach

MNBA was not considered relevant in the hazard assessment of Step 3.
The PEC_{GW} for this metabolite MNBA is 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.

Comment:

According to the criteria regarding ecotoxicological effects laid out in Guidance Document on Relevant Metabolites (SANCO/221/200-Rev.2 of October 1999) MNBA and AMBA are not relevant metabolites (DAR, UK Addendum, Revision 2, September 2001).

In brief, MNBA and AMBA are classified as non-relevant metabolites in view of their lack in pesticidal activity, genotoxicity, and other toxicological properties. Consequently, the metabolites MNBA and AMBA are considered to be non-relevant metabolites in groundwater.

A study in male rats showed that MNBA was metabolised in the gut to AMBA The metabolites MNBA and AMBA were considered to be not genotoxic. (Ames test, in vivo UDS test, chromosomal aberration, Micronucleus test) and have low acute and subchronic toxicity however this metabolite MNBA was identified as a potential skin sensitiser.

Rapporteur Member State: *United Kingdom*
September 2001 ,Revision 2 ; ADDENDUM TO THE DRAFT ASSESSMENT REPORT
Summary of Toxicology Evaluation
„The applicant submitted several additional studies and additional supplementary information on the toxicology of the active substance and the two metabolites MNBA and AMBA. Neither metabolites are considered to be of relevent toxicological „

Appendix 1 Lists of data considered in support of the evaluation

Tables considered not relevant can be deleted as appropriate.

MS to blacken authors of vertebrate studies in the version made available to third parties/public.

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

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
5.8.1.6/01	Callander, R.D.	1996a	MNBA: An Evaluation of Mutagenic Potential Using S.Typhimurium and E.Coli. Zeneca Central Toxicology Laboratory Report No. CTL/P/4955 GLP Not published	N	SYN
5.8.1	Fox, V	2000a	MNBA: In vitro cytogenetic assay in human lymphocytes Zeneca Central Toxicology Laboratory Report No. CTL/P/6343 GLP Not published	N	SYN
5.8.1	Clay, P	2000	MNBA: In vivo rat liver unscheduled DNA synthesis assay Zeneca Central Toxicology Laboratory Report No. CTL/SR1028 GLP Not published	N	SYN
5.8.1	Fox, V	2000b	MNBA: Rat bone marrow micronucleus test Zeneca Central Toxicology Laboratory Report No. CTL/SR1043 GLP Not published	N	SYN
5.8.1.1/01	Robinson, P.	1996	2-Nitro-4-Methylsulfonyl Benzoic Acid: Acute Oral Toxicity to the Rat. Zeneca Central Toxicology Laboratory Report No. CTL/P/5210 GLP Not published	N	SYN
5.8.1.7/01	Milburn, G.M.	1998	MNBA: 28 Day Oral Toxicity Study in Rats. Zeneca Central Toxicology Laboratory Report No. CTL/P/5578 GLP Not published	N	SYN
5.8.1	Rattray, N.J	2000	MNBA: 90 day dietary toxicity study in rats Zeneca Central Toxicology Laboratory Report No. CTL/PR1155 GLP Not published	N	SYN
5.8.1.1.8/02	Elcombe, B.M.	1998b	ZA1296: Effects of MNBA, a metabolite of ZA1296 on p-hydroxy phenyl pyruvate dioxygenase (HPPD) activity. Zeneca Central Toxicology Laboratory Report No. CTL/R/1367 Non-GLP Not published	N	SYN
5.8.1	Gledhill, A.J	2000	MNBA: Biotransformation in the rat Zeneca Central Toxicology Laboratory Report No: CTL/P/6326 GLP Not published	N	SYN

The following tables are to be completed by MS

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:	