FINAL REGISTRATION REPORT

Part B

Section 10

Assessment of the relevance of metabolites in groundwater

Detailed summary of the risk assessment

Product code: CHR/H/IMA 40 SL

Product name(s):

Mazzam 40 SL

Zemax 40 SL

Chemical active substance(s):

Imazamox, 40 g/L

Central Zone

Zonal Rapporteur Member State: Poland

Co-Rapporteur Member State: Hungary, Romania, Slovakia

CORE ASSESSMENT

(authorization)

Applicant: Innvigo Sp. z o.o.

Submission date: 09.2022

MS Finalisation date: 12/07/2024

CHR/H/IMA 40 SL / Mazzam, Zemax
Part B – Section 8 – Core Assessment
Innvigo Sp. Z o. o./Poland version

Version history

When	What
January 2023	Dossier sent for evaluation
September 2023	Applicant update
November 2023	Applicant update
April 2024	zRMS evaluation of dRR
July 2024	Final version prepared by zRMS after Commenting period

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

10 Relevance of metabolites in groundwater

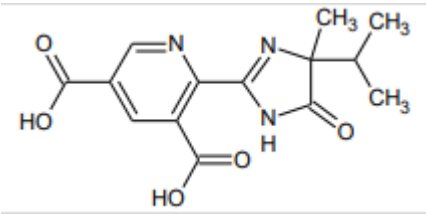
zRMS Comments:	The PECgw values for imazamox and its metabolite CL 312622 presented in Table 10.1-1 were assessed in Section 8. A risk envelope approach was taken into consideration (Tier 2 with uptake factor PUF = 0.5 for active substance and its metabolite, application every third year). The PECgw = 0.322 µg/L represents a worse case.

10.1 General information

The metabolite CL 312622 are predict predicted to occur in groundwater at concentrations above 0.1 µg/L (see PART B Section 8 of CHR/H/IMA 40 SL). 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 provided in Table 10.11. 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 KCP 9.2.4 of the dRR Part B, Section 8 (Environmental fate and behaviour).

Table 10.11: General information on the metabolite(s)

Name of active substance	Metabolite name and code	Structural/molecular formula	Trigger for relevance assessmnent	
Imazamox	CL 312622		Max PEC_{gw} Based on:	0.322 µg/L PELMO 6.6.4, Hamburg

10.2 Relevance assessment of CL 312622

zRMS Comments:	The PECgw value for metabolite submitted by the applicant is in accordance with PELMO 6.6.4, Hamburg modeling results. The maximum PECgw value for CL 312622 is above the trigger value of 0.1 - According to EFSA Scientific Report (EFSA Journal, 2016;14(4):4432), the metabolite CL 312622 is considered relevant because it cannot be excluded that it shares the developmental toxicity potential of imazamox. It leads to the critical area of concern. Available information, including toxicity studies, indicate that the metabolite has no pesticidal activity, it is of low acute oral toxicity to rats (>5000 mg/kg b.w.) and it is not genotoxic in standard *in vitro* test battery (Ames test, Gene mutation assay (HPRT), In vitro /Micronucleus tests). - Taking into account concerns presented above, the QSAR analysis was provided by the Applicant (2023, Cotterill J.V. and Jones S., In Silico Assessment of Reproductive and Developmental Toxicity of a Metabolite of Imazamox Fera Project Number: FR02225-20). Summary of the assessment of the results of QSAR analysis:

	- The concerns: the suitability of the model for predicting the assessed toxic effects and the fact that the *in silico* analysis submitted for the assessment did not show any structural alerts for the parent substance (imazamox), which has demonstrated teratogenic effect. - The following data were analysed and taken into account: • no structural alerts for the metabolite CL 312622; • comparison results of the chemical structure of imazapyr (substance without reproductive toxicity) and metabolite CL 312622 (presence of an additional carboxyl group, reducing the toxicity of the compound); • predicted NOAEL values for tested compounds; • projected PECgw values (below 0.75 µg/L) giving a predicted exposure to the metabolite in the worst case scenario (child, 5 kg) amounts to 0.0483 µg/L (0.002 % ADI for the parent substance); **Conlusions:** Toxicological data presented above indicate that the metabolite CL 312622 can be considered toxicologically non-relevant and the risk resulting from consumer exposure to this metabolite is very low.

Summary:

The relevance of the groundwater metabolite CL 312622 has already been assessed and the assessment agreed at EU level (RAR Imazamox-2015, Vol1) , and the relevance assessment is applicable as well for the GAP and groundwater scenarios considered in this dRR (i.e., the conclusions reached at Step 4 and 5 of the relevance assessment made at the EU-level are valid also with regard to the PECgw calculated for the GAP and groundwater scenarios considered in this dRR). CL 312622 is not considered relevant according to the criteria laid down in the EC guidance document SAN-CO/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.

Table 10.21: Summary of the relevance assessment for CL 312622

	Assessment step		**Result of assessment**	
	STEP 1		Metabolite of no concern?	No
Quantification of groundwater contamination	STEP 2		Max PEC_{gw}	0.322 µg/L
			Based on	FOCUS PELMO, Hamburg
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;	Not toxic or very toxic (T or T+)
			Classification of parent	not currently classified as toxic or very toxic
			Classification of metabolite	not currently classified as toxic or very toxic

Consumer health risk assessment	STEP 4	Estimated consumer exposure via drinking water and other sources; threshold of concern approach	<0.75 µg/L
	STEP 5	Refined risk assessment	Not Required
		Predicted exposure (% of ADI)	Not Required
		ADI based on	Not Required

* N/A: not applicable

10.2.1 STEP 1: Exclusion of degradation products of no concern

The major metabolites, CL 312622 contain a phenyl ring and therefore are not aliphatic compounds. Hence, these metabolites are not automatically metabolite of no concern.
Therefore an assessment has been conducted as given in the EU Guidance Document on the assessment of the relevance of metabolites in groundwater (Anonymous, 2003; Sanco/221/2000 - rev. 10, 25th February 2003).

10.2.2 STEP 2: Quantification of potential groundwater contamination

Maximum PECgw for CL312622 is 0.322 µg/L.

10.2.3 STEP 3: Hazard assessment – identification of relevant metabolites

CL 312622 is not relevant according to the hazard screening outlined in Step 3. See assessment below (point 10.2.3.1 – 10.2.3.3)

10.2.3.1 STEP 3, Stage 1: screening for biological activity

The metabolites CL 312622 potentially occurred in ground water at concentration above the limit of 0.1 µg/L. These metabolites are significantly less toxic than the parents for aquatic plants (more than 2 orders of magnitude for CL 312622). In addition, CL 312622 seem to have lost herbicidal activity Therefore, metabolite are not considered to be significantly biologically active.

10.2.3.2 STEP 3, Stage 2: screening for genotoxicity

A genotoxicity screening had to be performed according to the Sanco Guidance Document on Relevant Metabolites in Groundwater (Sanco/221/2000 –rev.10- final 25 February 2003). In addition to the Ames test and the in vitro micronucleus test a gene mutation test with mammalian cells was conducted to fulfill the criteria as outlined in this Guidance Document. Thus, the HPRT test was performed with CL 312622 to complete the package of in vitro genotoxicity studies for groundwater metabolites.

10.2.3.3 STEP 3, Stage 3: screening for toxicity

An oral acute toxicity was performed on this metabolite. The oral LD50 of AC 299263 technical was > 5000 mg/kg bw for both sexes of rats.

Taking account that:

- the imazamox classification change in December 2022 (17th ATI) - the Repr. 2 H361 was added
- the latest version of guidance Sanco/221/2000 – rev.11 21 October 2021 were stated as follow:

For parent active substances, which are classified for reproductive toxicity (any category: 1A, 1B or 2 according to Regulation (EC) No 1272/200816), it must be shown by an appropriate test or ***convincing other evidence that the metabolite does not qualify for the same classification.*** *Metabolites, which qualify for a classification of their reproductive toxicity (any category) are considered to be "relevant".*

We decided to conduct QSAR study (2023, Cotterill J.V. and Jones S., IN SILICO ASSESSMENT OF REPRODUCTIVE AND DEVELOPMENTAL TOXICITY OF A METABOLITE OF IMAZAMOX FERA PROJECT NUMBER: FR02225-20) please find below summary for this study:

On balance, the weight of evidence obtained in this study suggests that the Metabolite is unlikely to be a Reproductive toxicant (there were no Reproductive Toxicity structural alerts (from either Derek Nexus or the OECD QSAR Toolbox for any of the test compounds). The test compounds were all predicted to be non-Estrogen and non-Androgen Receptor binder in the VEGA models. There is no evidence to suggest that the Metabolite is likely to be Developmental Toxicant (there were no Developmental Toxicity structural alerts from either Derek Nexus or the OECD QSAR Toolbox) and a high NOEL/LOEL estimate of 998 mg/kg/day was obtained. However, it should be noted that there were no structural alerts for Developmental Toxicity for Imazamox either, which is known to be teratogenic in rabbits (but not in rats). Unfortunately, there were no reliable estimates obtained using QSAR models for Developmental Toxicity for any of the test compounds to add to the weight of evidence. The Developmental toxicity NOEL/LOEL estimate for the Metabolite (998 mg/kg/day) however, was higher than that of Imazamox (325 mg/kg/day; Reprotox GHS classification Repr2, H361d, suspected of damaging the unborn child) and similar to that of Imazapyr (956 mg/kg/day; no Reprotox GHS classification).

In our opinion presented results indicate that the Metabolite is of less toxicological concern (for Developmental Toxicity) than Imazamox, due to it should be considered to be " not relevant".

10.2.4 STEP 4: Exposure assessment – threshold of concern approach

Metabolite which have not been identified as being relevant according to the hazard screening outlined in Step 3, should be further tested in an exposure assessment to make sure that any contamination of groundwater will not lead to unacceptable exposure of consumers via their drinking water.

The potential exposure to metabolite CL 312622 is >below 0.75 µg/L. A further assessment in Step 5 is not required.

Conclusion:
In summary the metabolite CL 312622 is considered to be biologically, toxicologically and ecotoxicologically non relevant.

Appendix 1 Lists of data considered in support of the evaluation

List of data submitted by the applicant and relied on

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

Cross reference to the section B6 of the dRR

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
	2023, Cotterill J.V. and Jones S.,	2023	IN SILICO ASSESSMENT OF REPRODUCTIVE AND DEVELOPMENTAL TOXICITY OF A METABOLITE OF IMAZAMOX FERA PROJECT NUMBER: FR02225-20 Fera Science Ltd., non-GLP	N	PUH Chemirol Sp z o.o.

Appendix 2 Additional information