

FINAL REGISTRATION REPORT

Part B

Section 10

**Assessment of the relevance of metabolites in
groundwater**

Detailed summary of the risk assessment

Product code: GLOB2007bF

Product name: Observer Pro

Chemical active substances:

Zoxamide, 67.5 g/L

Propamocarb-HCl, 450 g/L

Central Zone

Zonal Rapporteur Member State: Poland

CORE ASSESSMENT

Applicant: Globachem NV

Submission date: November 2023

MS Finalisation date: 31/10/2024

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Version history

When	What
November 2023	Initial dossier submission by applicant for approval of new product
March 2024	Dossier sent for evaluation
July 2024	zRMS finalised evaluation
October 2024	zRMS finalised evaluation after commenting period

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

10 Relevance of metabolites in groundwater

zRMS Comments:	<p>Based on PEC_{gw} assessment for metabolites submitted in Section B8, only for the RH-141455 metabolite the trigger value of 0.1 µg/L was exceeded.</p> <p>The max PEC_{gw} = 4.652 µg/L, as the worst case, in Jokioinen scenario was considered below.</p> <p>The assessment of RH-141455 metabolite according to the stepwise procedure of the EC guidance document SANCO/221/2000 –rev.11 (21 October 2021) was performed by Applicant and accepted.</p> <p>According to the EFSA Scientific Report (2006) 78, 1-80, propamocarb-HCl has no metabolites in groundwater.</p>
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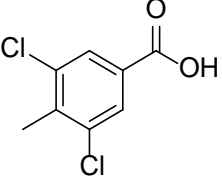
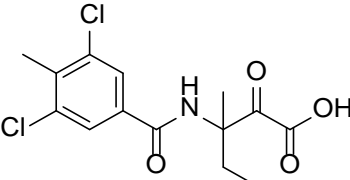
10.1 General information

Zoxamide:

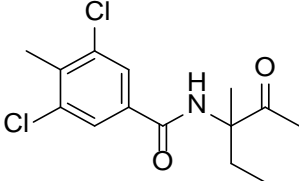
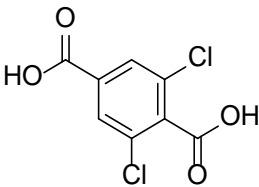
The metabolite RH-141455 is predicted to occur in groundwater at concentrations above 0.1 µg/L (see Part B Section 8). Assessment of the relevance of this metabolite according to the stepwise procedure of the EC guidance document SANCO/221/2000 –rev.10 is therefore required.

General information on the 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 assessment	
Zoxamide RH-117281	3,5-dichloro-4-methylbenzoic acid RH-24549		Max PEC _{gw} Based on:	<0.001 µg/L FOCUS PELMO 6.6.4, FOCUS PEARL 5.5.5 All scenarios
Zoxamide RH-117281	(3 <i>RS</i>)-3-(3,5-Dichloro-4-methylbenzamido)-3-methyl-2-oxopentanoic acid RH-163353		Max PEC _{gw} Based on:	<0.001 µg/L FOCUS PELMO 6.6.4, FOCUS PEARL 5.5.5 All scenarios

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Name of active substance	Metabolite name and code	Structural/molecular formula	Trigger for relevance assessment	
Zoxamide RH-117281	(<i>RS</i>)-3,5-dichloro-4-methyl-N-(3-methyl-2-oxopentan-3-yl)benzamide RH-127450		Max PEC _{gw} Based on:	<0.001 µg/L FOCUS PELMO 6.6.4, FOCUS PEARL 5.5.5 All scenarios
Zoxamide RH-117281	2,6-dichloroterephthalic acid RH-141455		Max PEC _{gw} Based on:	4.652 µg/L FOCUS PEARL 5.5.5, Jokioinen

10.2 Relevance assessment of RH-141455

Summary:

The relevance of the groundwater metabolite RH-141455 has already been assessed and the assessment agreed at EU level (SANTE/10052/2018 Rev.2, 23 March 2018), 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 PEC_{gw} calculated for the GAP and groundwater scenarios considered in this dRR). RH-141455 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.

Table 10.2-1: Summary of the relevance assessment for RH-141455

	Assessment step		Result of assessment	
	STEP 1		Metabolite of no concern?	Yes No
Quantification of groundwater contamination	STEP 2		Max PEC _{gw}	4.652 µg/L
			Based on	FOCUS PEARL 5.5.5, Jokioinen
Hazard assessment	STEP 3	Stage 1	Biological activity comparable to the parent?	No fungicidal activity

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		Stage 2	Genotoxic properties of metabolite	Non- unlikely to be genotoxic
		Stage 3	Toxic properties of metabolite;	None Less toxic than the parent compound
			Classification of parent	Not classified Skin Sens. 1, H317 (CLP)
			Classification of metabolite	Not classified , less toxic than the parent compound
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)		0.03% of ADI adult 0.09% of ADI child 0.14% of ADI infant
				ADI based on

10.2.1 STEP 1: Exclusion of degradation products of no concern

Sanco/221/2000 –rev. 10 11 allows the exclusion of metabolites from consideration if they satisfy certain criteria that would allow the conclusion to be made that they are of no concern. These criteria are as follows:

- it is CO₂ or an inorganic compound, not containing a heavy metal; or,
- it is an organic compound of aliphatic structure, with a chain length of 4 or less, which consists only of C, H, N or O atoms and which has no "alerting structures" such as epoxide, nitrosamine, nitrile or other functional groups of known toxicological concern.
- it is a substance, which is known to be of no toxicological or ecotoxicological concern, and which is naturally occurring at much higher concentrations in the respective compartment.

RH-141455 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 RH-141455 were performed (see Part B, Section 8, chapter 8.8). The uses for which concentrations of RH-141455 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

As predicted concentrations of RH-141455 exceed 0.1 µg/l, a hazard assessment is required to demonstrate that the compound:

- has a lower biological activity than the parent no fungicidal activity,
- is not unlikely to be genotoxic and
- is not defined as toxic has lower toxicity than the parent compound zoxamide.

10.2.3.1 STEP 3, Stage 1: screening for biological activity

RH-141455 lacks the haloketone toxophore (chemical group responsible for the main toxicity) and was found to have no fungicidal activity (SANTE/10052/2018 Rev.2, 23 March 2018).

10.2.3.2 STEP 3, Stage 2: screening for genotoxicity

RH-141455:

Rat metabolism study: Greater than 96 % radioactivity excreted from faeces and urine was identified to be unchanged RH-141455.

Acute oral toxicity in mice: LD50: > 5000 mg/kg bw

In vitro micronucleus test in human lymphocytes: negative

In vitro mutation test in mouse lymphoma L5178Y cells: negative

Ames test: negative

The EFSA expert meeting concluded that RH-141455 is unlikely to be genotoxic and is less toxic than the parent compound zoxamide, which already shows a low toxic profile (SANTE/10052/2018 Rev.2, 23 March 2018).

10.2.3.3 STEP 3, Stage 3: screening for toxicity

At the Pesticide Peer Review meeting, experts concluded that, if the approach of the Thresholds of Toxicological Concern (TTC) is used, RH-141455 would be of class Kramer 3 (i.e. exposure threshold would be 1.5 µg/Kg b.w) (SANTE/10052/2018 Rev.2, 23 March 2018).

Using the maximum PEC_{gw} obtained in the risk assessment of GLOB2007bF (4.652 µg/L), the estimated exposure would be 0.15507 µg/Kg b.w, which is an order of magnitude lower than the appropriate TTC.

Since RH-141455 is considered less toxic than zoxamide, following a conservative approach, the ADI of zoxamide could be used to assess the consumer risk for RH-141455 (SANTE/10052/2018 Rev.2, 23 March 2018). Doing so, the predicted intake of RH-141455 from drinking water would result 0.15507 µg/Kg (i.e. 0.03% of the ADI for a 60 kg person). This means that RH-141455 would have to be significantly more toxic than zoxamide to pose any risk to the consumers via drinking water.

10.2.4 STEP 4: Exposure assessment – threshold of concern approach

The potential exposure to RH-141455 is > 0.75 µg/L but <10 µg/L. A further assessment in Step 5 is required.

10.2.5 STEP 5: Refined risk assessment

RH-141455 has a PEC_{gw} between 0.75 µg/L and 10 µg/L. A refined assessment of the potential toxicological significance including the selected ADI is presented here.

The consumer risk assessment demonstrates an acceptable risk. The estimated safety margin including potential exposure via other routes besides drinking water for RH-141455 are 0.14 % of ADI (infant), 0.09 % of ADI (child), 0.03 % of ADI (adult).

Justification for the selected ADI:

Since RH-141455 is considered less toxic than zoxamide, following a conservative approach, the ADI of zoxamide (0.5 mg/kg bw/day) could be used to assess the consumer risk for RH-141455 (SANTE/10052/2018 Rev. 2 - 23 March 2018).

Calculation of risk (% ADI) for 5-kg bottle-fed infant (consuming 0.75 l/day):

Assuming a 5 kg infant drinking 0.75 litre of water per day, the drinking of water containing 4.652 µg/L will result in a daily intake of 0.6978 µg RH-141455/kg bw/d. This represents only 0.14% of the ADI.

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

Assuming a 10 kg child drinking 1 litre of water per day, the drinking of water containing 4.652 µg/L will result in a daily intake of 0.4652 µg RH-141455/kg bw/d. This represents only 0.09% of the ADI.

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

Assuming a 60 kg adult drinking 2 litres of water per day, the drinking of water containing 4.652 µg/L will result in a daily intake of 0.15507 µg RH-141455/kg bw/d. This represents only 0.03% of the ADI.

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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 (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
Please refer to Part B Section 6.					

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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
KCP XX	Author	YYYY	Title Company Report N Source GLP/non GLP/GEP/non GEP Published/Unpublished	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
KCP XX	Author	YYYY	Title Company Report N Source GLP/non GLP/GEP/non GEP Published/Unpublished	Y/N	Owner