

**FINAL** REGISTRATION REPORT

**Part B**

**Section 10**

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

Detailed summary of the risk assessment

Product code: GLOB2013F

Product name(s): Observer

Chemical active substance:

Zoxamide, 450 g/L

Central Zone

Zonal Rapporteur Member State: Poland

**CORE ASSESSMENT**

Applicant: Globachem NV

Submission date: January 2024

**MS Finalisation date: 19/12/2024**

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## Version history

| When           | What  |
|----------------|---|
| January 2024   | Initial dossier submission by applicant for approval of new product |
| April 2024     | Dossier sent for evaluation   |
| September 2024 | zRMS finalised evaluation   |
| December 2024  | zRMS finalised evaluation after commenting period                   |

## Table of Contents

|                   |   |          |
|-------------------|---|----------|
| <b>10</b>         | <b>Relevance of metabolites in groundwater .....</b>                    | <b>4</b> |
| 10.1              | General information .....   | 4        |
| 10.2              | Relevance assessment of RH-141455 .....                                 | 5        |
| 10.2.1            | STEP 1: Exclusion of degradation products of no concern .....           | 6        |
| 10.2.2            | STEP 2: Quantification of potential groundwater contamination.....      | 6        |
| 10.2.3            | STEP 3: Hazard assessment – identification of relevant metabolites..... | 7        |
| 10.2.3.1          | STEP 3, Stage 1: screening for biological activity .....                | 7        |
| 10.2.3.2          | STEP 3, Stage 2: screening for genotoxicity .....                       | 7        |
| 10.2.3.3          | STEP 3, Stage 3: screening for toxicity .....                           | 7        |
| 10.2.4            | STEP 4: Exposure assessment – threshold of concern approach.....        | 7        |
| 10.2.5            | STEP 5: Refined risk assessment.....                                    | 8        |
| <b>Appendix 1</b> | <b>Lists of data considered in support of the evaluation .....</b>      | <b>9</b> |

GLOB2013F  
 Part B – Section 10 - Core Assessment  
 Applicant version

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

## 10 Relevance of metabolites in groundwater

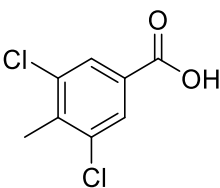
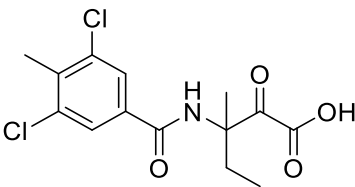
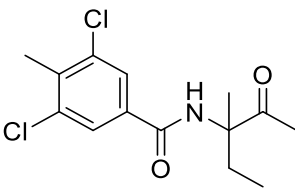
|                |   |
|----------------|---|
| zRMS Comments: | <p>The PEC<sub>gw</sub> values for metabolites of zoxamide are consistent with values presented in Section B8. The max PEC<sub>gw</sub> for RH-141455 metabolite was obtained for potatoes early application in Jokioinen scenario.</p> <p>Based on PEC<sub>gw</sub> 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<sub>gw</sub> = 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> |
|----------------|---|

### 10.1 General information

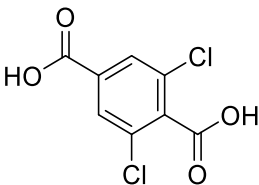
The metabolite RH-141455 is predicted to occur in groundwater at concentrations above 0.1 µg/L (see Part B Section 8). Assessment of the relevance of this metabolite according to the stepwise procedure of the EC guidance document SANCO/221/2000 –rev.10 is therefore required.

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<br>RH-117281    | 3,5-dichloro-4-methylbenzoic acid<br>RH-24549   |   | Max PEC <sub>gw</sub><br>Based on: | <0.001 µg/L<br>FOCUS<br>PELMO 6.6.4,<br>FOCUS<br>PEARL 5.5.5<br>All scenarios |
| Zoxamide<br>RH-117281    | (3 <i>RS</i> )-3-(3,5-Dichloro-4-methylbenzamido)-3-methyl-2-oxopentanoic acid<br>RH-163353 |  | Max PEC <sub>gw</sub><br>Based on: | <0.001 µg/L<br>FOCUS<br>PELMO 6.6.4,<br>FOCUS<br>PEARL 5.5.5<br>All scenarios |
| Zoxamide<br>RH-117281    | ( <i>RS</i> )-3,5-dichloro-4-methyl-N-(3-methyl-2-oxopentan-3-yl)benzamide<br>RH-127450     |   | Max PEC <sub>gw</sub><br>Based on: | <0.001 µg/L<br>FOCUS<br>PELMO 6.6.4,<br>FOCUS<br>PEARL 5.5.5                  |

GLOB2013F  
 Part B – Section 10 - Core Assessment  
 Applicant version

| Name of active substance | Metabolite name and code                       | Structural/molecular formula  | Trigger for relevance assessment       |   |
|--------------------------|--|---|--|---|
|                          |  |   |  | All scenarios   |
| Zoxamide<br>RH-117281    | 2,6-dichloroterephthalic acid<br><br>RH-141455 |  | Max PEC <sub>gw</sub><br><br>Based on: | 4.652 µg/L (potato)<br><br>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<sub>gw</sub> 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?                     | <del>Yes</del> No            |
| Quantification of groundwater contamination | STEP 2          |         | Max PEC <sub>gw</sub>                         | 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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 Part B – Section 10 - Core Assessment  
 Applicant version

|                                 |        |                               |   |   |
|---------------------------------|--------|-------------------------------|---|---|
|                                 |        | Stage 2                       | Genotoxic properties of metabolite  | <del>Non-genotoxic</del><br>Unlikely to be genotoxic            |
|                                 |        | Stage 3                       | Toxic properties of metabolite;   | <del>None</del> Less toxic than the parent compound             |
|                                 |        |                               | Classification of parent  | <del>Not classified</del> Skin Sens. 1, H317 (CLP)              |
|                                 |        |                               | Classification of metabolite  | Not classified  |
| 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<br>0.09% of ADI child<br>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 CO<sub>2</sub> 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<sub>gw</sub> 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<sub>gw</sub> 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<br>Company Report No.<br>Source (where different from company)<br>GLP or GEP status<br>Published or not | Vertebrate study<br>Y/N | Owner |
|--------------------|-----------|------|---|-------------------------|-------|
| No data submitted. |           |      |   |                         |       |

### 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<br>Company Report No.<br>Source (where different from company)<br>GLP or GEP status<br>Published or not | Vertebrate study<br>Y/N | Owner |
|-----------------------------------|-----------|------|---|-------------------------|-------|
| Please refer to Part B Section 6. |           |      |   |                         |       |