REGISTRATION REPORT

Part B

Section 10

Assessment of the relevance of metabolites in groundwater

Detailed summary of the risk assessment

Product code: GWN-10616

Chemical active substances:

Zoxamide, 60 g/L

Potassium phosphonates, 755 g/L

Phosphonic acid equivalents, 500 g/L

Central Zone

Zonal Rapporteur Member State: Poland

CORE ASSESSMENT

Applicant: XXXX

Submission date: 31/10//2023

Evaluation date: 07/2024 (update 09/2024)

MS Finalisation date: 11/2024

Version history

When	What
July 2024	Version submitted by the applicant and evaluated by zRMS PL.
September 2024	Update based on RMS request of July 2024
November 2024	Version evaluated by zRMS taking into account comments received from cMSs and the applicant

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10 Relevance of metabolites in groundwater

10.1 General information

The formulated product GWN-10616 containing the active substance Zoxamide and Potassium phosphonate is intended to be applied to grapevine, pome fruit and potatoes according to GAP.

Regarding application to intended uses, only one metabolite, RH-141455, is predicted to occur in groundwater at concentrations above 0.1 µg/L (see Part B8 "Environmental Fate).
Assessment of the relevance of this metabolite according to the stepwise procedure of the EC guidance document SANCO/221/2000 – rev.11 (2021) is therefore required.

General information on the metabolite RH-141455 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 8.8 of the dRR Part B, Section 8 (Environmental fate and behaviour). Updated PEC_{gw} calculations for metabolite RH-141455 based on input parameters accepted by RMS-LV as requested by the zRMS (see Review Comments below) were performed and included.

Review Comments:

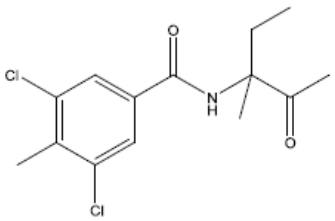
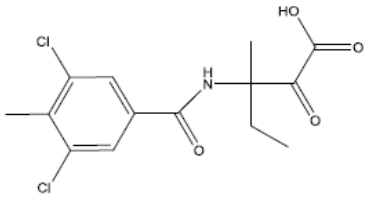
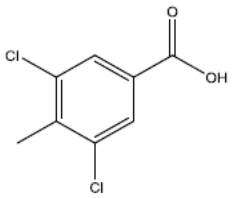
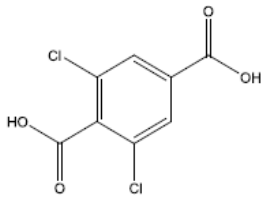
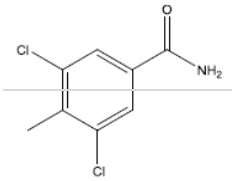
The leaching simulation run with FOCUS PELMO, FOCUS PEARL and FOCUS MACRO resulted in PEC_{GW} values below 0.1 µg/L for zoxamide metabolites: RH-127450, RH-24549, and RH-163353, for all FOCUS scenarios.

Using refined endpoints, the metabolite RH-141455 exceed the threshold of 0.1 µg/L, but below 0.75 µg/L for all application uses. Maximum simulated concentrations of RH-141455 considering refined endpoints are 0.137 µg/L Châteaudun, 0.525 µg/L Hamburg, 0.506 µg/L Jokioinen, 0.367 µg/L Kremsmünster, 0.404 µg/L Okehampton, 0.286 µg/L Piacenza, 0.095 µg/L Porto calculated by model FOCUS PEARL 5.5.5 and 0.114 µg/L Châteaudun, 0.596 µg/L Hamburg, 0.157 µg/L Jokioinen, 0.581 µg/L Kremsmünster, 0.151 µg/L Okehampton, 0.279 µg/L Piacenza and 0.131 µg/L Porto calculated by model FOCUS PELMO 6.6.4.

It should be noted that in Applicant's calculations for RH-141455 the formation fraction of 0.504 was used. Nevertheless, in RMS-LV opinion the correct ff value for the metabolite RH-141455 in Mechthildshausen soil is 1 and the correct arithmetic mean ff value is 0.629. Thus, during the comment stage the Applicant is requested to perform additional calculation for metabolite RH-141455 based on accepted by RMS-LV input parameters. These calculations are particularly required to confirm the maximum concentration of RH-141455 in groundwater below threshold of 0.75 µg/L, as assumed in the assessment of relevance of metabolites in part B10.

Additional calculations for metabolite RH-141455 based on accepted by RMS-LV input parameters were submitted by the Applicant. New PECgw values are consider to be valid. Maximum simulated concentrations of RH-141455 considering correct refined endpoints are 0.170 µg/L Châteaudun, 0.655 µg/L Hamburg, 0.632 µg/L Jokioinen, 0.235 µg/L Kremsmünster, 0.157 µg/L Okehampton, 0.356 µg/L Piacenza, 0.118 µg/L Porto calculated by model FOCUS PEARL 5.5.5 and 0.135 µg/L Châteaudun, 0.701 µg/L Hamburg, 0.636 µg/L Jokioinen, 0.338 µg/L Kremsmünster, 0.180 µg/L Okehampton 0.341 µg/L Piacenza and 0.154 µg/L Porto calculated by model FOCUS PELMO 6.6.4.

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-127450		Max PEC_{gw} Based on:	< 0.100 µg/L FOCUS PEARL 5.5.5, FOCUS PELMO 6.6.4 all scenarios
Zoxamide	RH-163353		Max PEC_{gw} Based on:	< 0.100 µg/L FOCUS PEARL 5.5.5, FOCUS PELMO 6.6.4 all scenarios
Zoxamide	RH-24549		Max PEC_{gw} Based on:	< 0.100 µg/L FOCUS PEARL 5.5.5, FOCUS PELMO 6.6.4 all scenarios
Zoxamide	RH-141455		Max PEC_{gw} Based on:	~~0.596~~ 0.701 µg/L Hamburg FOCUS PELMO 6.6.4
~~Zoxamide~~	~~RH-139432~~		~~Max PEC_{gw}~~ ~~Based on:~~	~~< 0.100 µg/L~~ ~~FOCUS PEARL 5.5.5, FOCUS PELMO 6.6.4 all scenarios~~

10.2 Relevance assessment of RH-141455

Summary:

The groundwater metabolite RH-141455 is not considered as relevant according to the criteria laid down in the EC guidance document SANCO/221/2000 –rev.11.
A summary of the relevance assessment for RH-141455 is given in

Table 10.2-1. Studies supporting PEC_{gw} data are evaluated in Section 8 (Environmental fate and behaviour), the genotoxicity studies are evaluated in Section 6 (Mammalian Toxicology). The data on biological activity are evaluated in Section 10.2.3.1.

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

	Assessment step		Result of assessment	
	STEP 1		Metabolite of no concern?	No
Quantification of groundwater contamination	STEP 2		Max PEC_{gw}	0.701 ~~0.596~~ µg/L
			Based on	FOCUS PEARL 5.5.5, FOCUS PELMO 6.6.4 Hamburg, grapevine
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;	LD_{50} > 5000 mg/kg bw ~~90-d dietary NOAEL > 1000 mg/kg bw/d~~ 90 d dietary LOAEL 924 mg/kg bw per day
			Classification of parent	Not classified Skin Sens. 1,H317
			Classification of metabolite	Not classified
Consumer health risk assessment	STEP 4		Estimated consumer exposure via drinking water and other sources; threshold of concern approach	na
	STEP 5		Refined risk assessment	na
			Predicted exposure (% of ADI)	na
			ADI based on	14-d dietary NOAEL of 368 mg/kg bw/d and uncertainty factor of 1000 ADI = 0.3 mg/kg bw/d

na: not applicable

10.2.1 STEP 1: Exclusion of degradation products of no concern

The metabolite RH-141455 does not meet the criteria for products of no concern as defined in step 1 of SANCO/221/2000 –rev.11 and therefore needs further assessment.

10.2.2 STEP 2: Quantification of potential groundwater contamination

PEC_{gw} calculations after leaching from soil for metabolite RH-141455 were performed (see Part B, Section 8, chapter 8.9). 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

10.2.3.1 STEP 3, Stage 1: screening for biological activity

The biological activity of RH-141455 does not have comparable target activity as the parent active compound as shown in biological screening data (Smith and Nelson, 1999; KCA 3.6).

The following information summarises the relevant information from the RAR (2017) on the Step 3 – Stage 1 assessment (see DAR 2017, Vol.1): "*A fungicide secondary screen under greenhouse conditions was performed for the metabolite RH-141455 and the structurally similar metabolite, RH-141452. For the screen, technical preparations of RH-141452 and RH-141455 were prepared by dissolving 30 mg of the technical metabolite in 2 mL of an acetone/methanol mixture (50:50). The solution was then further diluted to provide test solutions at two dilutions. The resulting preparations were sprayed onto test plants and one day later, plants were inoculated with the test pathogens. The effectiveness of each preparation was assessed 5 to 12 days after inoculation depending on the disease. Disease assessment was made by visual comparison of infection on the untreated and treated plant leaves. Incremental control values of 0, 50, 75, 80, 85, 90, 95, 99 and 100 percent were used to differentiate activity between treatments, doses and the untreated controls. Neither metabolite showed any fungicidal activity on a range of plant pathogens including tomato and potato late blight and grape downy mildew. Zoxamide showed high activity for the same pathogens*."

RH-141455 is therefore considered not relevant and is further evaluated in Stage 2.

10.2.3.2 STEP 3, Stage 2: screening for genotoxicity

In accordance with the EC guidance document SANCO/221/2000 –rev.11, metabolite RH-141455 was screened for genotoxic activity by the following data package of *in vitro* genotoxicity studies: an Ames test, an *in vitro* gene mutation test with mammalian cells, and an *in vitro* micronucleus test.
RH-141455 was non-genotoxic as shown by the negative Ames test (Sames and Ciaccio (1998), KCA 5.8.1), a negative gene mutation test with mammalian cells (XXXX (2014), KCA 5.8.1) and a negative *in vitro* micronucleus test (XXXX (2014), KCA 5.8.1). The toxicological data were evaluated during active ingredient renewal (AIR) on EU level (please refer to RAR, 2017 and EFSA Peer Review Conclusion, 2017).
RH-141455 is considered not relevant and is further evaluated in Stage 3.

10.2.3.3 STEP 3, Stage 3: screening for toxicity

The parent to RH-141455, Zoxamide, is not classified as acutely or chronically toxic (or corresponding classification in accordance to CLP 1272/2008).
Based on an acute oral toxicity study in mice (XXXX *et al*. (1998), KCA 5.8.1), RH-141455 was not classified as acutely toxic in accordance with CLP 1272/2008. Based on 14-day (XXXX (2020), KCP 7.4/06) and 90-day (XXXX (2020), KCP 7.4/07) dietary toxicity studies in rats, RH-141455 was considered as non-toxic after sub-chronic exposure. The toxicological data were evaluated during active ingredient renewal (AIR) on EU level (please refer to RAR, 2017 and EFSA Peer Review Conclusion, 2017) and additional studies have been provided to RMS Latvia. Full summaries of studies on the repeated dose toxicity studies on metabolite RN-141455 submitted to Latvia are described in detail in Appendix 2 in Part B, Section 6 (A 2.11 Other/Special Studies) for the sake of completeness.

RH-141455 is therefore considered not relevant, and further assessments are not required.

10.2.4 STEP 4: Exposure assessment – threshold of concern approach

~~Not relevant since RH-141455 was not considered relevant in the hazard assessment of Step 3.~~
PEC_{GW} <0.75ug/L, no further assessment required.

zRMS PL:
It is agreed that metabolite of Zoxamide RH-141455 has a lower biological activity than the parent, is not genotoxic and is not defined as toxic therefore it does not meet the criteria provided for "relevant metabolites" and "metabolites of no concern" in Guidance Document on The Assessment of The Relevance of Metabolites in Groundwater of Substances Regulated under Regulation (EC) No 1107/2009 Sanco/221/2000 – rev.11(21 October 2021.) Its concentration in the groundwaters is below an acceptable estimated upper limit for the concentration of a metabolite of 0.75 µg/L, therefore it does not pose an unacceptable risk for consumers.

10.2.5 STEP 5: Refined risk assessment

Not relevant since the max. PEC_{gw} for RH-141455 is < 0.75 µg/L.

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
KCP 7.4/06	XXXX	2020	RH-141455: 14-day oral dietary dose range finding study in Sprague Dawley rats XXXX XXXX Report No. U-19071 No GLP Not published	Y	XXXX
KCP 7.4/07	XXXX	2020	RH-141455: 90-day oral dietary toxicity study with toxicokinetics and 28-day recovery period in Sprague Dawley rats XXXX XXXX, Report No. U-19102 GLP Not published	Y	XXXX
KCA 3.6	Smith, T.and Nelson, W.J.	1999	Greenhouse fungicidal efficacy report or RH-141452 and RH-141455 Rohm and Haas Co., Report No. FUN 99-059, ER Ref No. 34.8	N	XXXX

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
			GEP Unpublished		
KCA 5.8.1	XXXX	1998	RH-141,455: acute oral toxicity study in male and female mice. Report No. 98R-165, ER Ref. No. 24.3 XXXX GLP Unpublished	Y	XXXX
KCA 5.8.1	Sames, J.L., Ciaccio, P.J.,	1998	RH-141,455: *Salmonella typhimurium* gene mutation assay (Ames test). Report No. 98R-048, ER Ref No: 27.4 Rohm and Haas Co. GLP Unpublished	N	XXXX
KCA 5.8.1	XXXX	2014	RH-141455: *In vitro* mutation test using mouse lymphoma L5178Y Study No. FRK0049 Huntingdon Life Sciences, Eye Research Centre, Suffolk, IP23 7PX, UK GLP Unpublished	N	XXXX
KCA 5.8.1	XXXX	2014	RH-141455*: In vitro* Micronucleus Test in Human Lymphocytes Study No. FRK0050 XXXX GLP Unpublished	N	XXXX

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
-	-	-	-	-	-