REGISTRATION REPORT

Part B

Section 10

Assessment of the relevance of metabolites in groundwater

Detailed summary of the risk assessment

Product code: Cymoxanil 33% + Zoxamide 33% WG

Product name(s): **Lieto 66 WG**

Chemical active substance(s):

Cymoxanil, 330 g/kg
Zoxamide, 330 g/kg

Central Zone

Rapporteur Member State: Poland

CORE ASSESSMENT

(product re-registration)

Applicant: Sipcam Oxon S.p.A.

Submission date: 30/12/2020

MS Finalisation date: September 2021

Revision date: December 2021

DATA PROTECTION CLAIM

Under Article 59 of Regulation 1107/2009/EC, the applicant claims data protection for these studies. The data protection status and corresponding justification as valid for the respective country will be confirmed in the respective PART A.

STATEMENT FOR OWNERSHIP

The summaries and evaluations contained in this review report may be based on unpublished proprietary data submitted for the purpose of the assessment undertaken by the regulatory authority that prepared it. Other registration authorities should not grant, amend, or renew a registration on the basis of the summaries and evaluation of unpublished proprietary data contained in this review report unless they have received the data on which the summaries and evaluation are based, either –

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Version history

When	What
30th December 2020	Submission of initial Version 0 by the applicant.
September 2021	Verion evaluated by zRMS PL
December 2021	Revised version, addressing the comments of MSs.

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10 Relevance of metabolites in groundwater

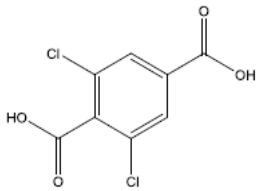
Evaluator's Comments:	The submitted PECgw value for metabolite RH-141455 of zoxamide at Tier 1 and Tier 2 were accepted. Based on PECgw assessment for metabolites of cymoxanil concentration in groundwater were below the trigger value of 0.1 µg/L.

10.1 General information

Zoxamide

The metabolite RH-141455 is predicted to occur in groundwater at concentrations above 0.1 µg/L (see dRR Part B, Section 8, chapter 8.8). 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 10.1-2. 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) - zoxamide

Name of active substance	Metabolite name and code	Structural/molecular formula	Trigger for relevance assessment	
Zoxamide	RH-141455		Max PEC_{gw} 0.622 µg/L Based on: PELMO Vine late Hamburg	**> 0.1 µg/L** *

* drinking water limit; **bold** = potentially relevant metabolite (i.e. > 0.1 µg/L)

As a result, the zoxamide metabolite RH-141455 is not appearing > 0.75 µg/L but might appear at maximum values of 0.622 µg/L (PELMO, vine late, Hamburg) and 0.458 µg/L (PELMO, potato late, Jokionen) and therefore can exceed the drinking water limit after the use of CYMOXANIL 33% + ZOXAMIDE 33% WG on potatoes or vine. It therefore will be considered further in the following assessment.

Cymoxanil

No metabolite is predicted to occur in groundwater at concentrations > 0.1 µg/L, so no further relevance evaluation is required.

10.2 Relevance assessment of RH-141455 – metabolite of zoxamide

The zoxamide metabolite RH-141455 is not appearing > 0.1 µg/L (the drinking water limit) after the use of CYMOXANIL 33% + ZOXAMIDE 33% WG on vines early. However, it is appearing > 0.1 µg/L (but < 0.75 µg/L) in EU groundwater scenarios after the use of CYMOXANIL 33% + ZOXAMIDE 33% WG on vines late and potatoes early and late therefore is considered in the following assessment.

Summary:

The relevance of the groundwater metabolite RH-141455 of the active substance zoxamide has already been assessed at EU level (see RAR 2017 and EFSA Peer Review Conclusion 2017) for different GAP uses with higher seasonal application rates. As a result, RH-141455 was regarded as not relevant according to Step 5 of the EC guidance document SANCO/221/2000 –rev.10 (see RAR 2017). However, EFSA (2017) requested further toxicological data in their Peer Review Conclusion - such as a repeated dose toxicity study for RH141455 - to set a reference value for the metabolite RH-141455. Meanwhile, this study has been performed and provided to the RMS Latvia and cMSs for interzonal evaluation. It confirms the low toxicity of RH-141455 with a NOAEL > 1000 mg/kg bw/d.

For the actual GAP uses with lower seasonal application rates of zoxamide (compared to the GAP uses defended on EU level), the max. predicted concentrations in the groundwater/drinking water are > 0.01 µg/L but < 0.75 µg/L. Thus, a Step 4 exposure assessment according to EC guidance document SANCO/221/2000 –rev.10 has been performed.

During AIR (see RAR, 2017), the ADI for zoxamide was confirmed at 0.5 mg/kg bw/day and it was concluded that it is not necessary to allocate an ARfD – as for the first EU approval of zoxamide. As a conservative approach for the risk assessment on EU level, an additional assessment factor of 10 was applied to the ADI for zoxamide to establish an ADI for the metabolite RH-141455 of 0.05 mg/kg bw/day (50 µg/kg bw/day). However, a new 90-d dietary toxicity study in rats is now available to derive an ADI (Satish Kumar, 2020; report no. U-19102). Based on the REACH guidance (Table R 8-5) [1] a factor of 200 can be applied, which leads to a more realistic ADI for RH-141455 of 5.0 mg/kg bw/d. Exposure calculations for a 5-kg bottle-fed infant, a 10-kg child and a 60-kg adult confirm no undue risks for consumers from the maximum predicted RH-141455 concentrations in the drinking water.

RH-141455 is also a metabolite which might be found in potatoes and has therefore been regarded as potentially relevant by EFSA (2017) in their Peer Review Conclusion. However, in supervised field trials with potatoes performed in accordance with actual worst-case GAP uses, residues in potato tubers were < 0.01 mg/kg (the LOQ for the analytical method). Therefore, the contribution to the dietary intake of RH-141455 via potatoes is not relevant.

As a result, RH-141455 is considered to be not 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 in the following table, the study summaries are given in the corresponding sections.

[1,2] Guidance on Information Requirements and Chemical Safety Assessment, Chapter R.8: Characterization of Dose [Concentration]-Response for Human Health, dated Nov. 2012

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}	Max PEC_{gw} 4.647 µg/L (Tier 1) 0.622 µg/L (refined)
			Based on	Tier 1: FOCUS PEARL groundwater calculations Scenario: Potatoes early, Jokionen Refined: FOCUS PELMO groundwater calculations Scenario: Vine late, 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	LD_{50} > 5000 mg/kg bw 90-d dietary NOAEL >1000 mg/kg bw/d
			Classification of parent	Not classified
			Classification of metabolite	Not classified
Consumer health risk assessment	STEP 4		Estimated consumer exposure via drinking water and other sources; threshold of concern approach g/L)	Tier 1: Acceptable. Refined: Acceptable (< 0.75 µg/L)
	STEP 5		Refined risk assessment	N/A *
			Predicted exposure (% of ADI)	N/A*
			ADI based on	N/A*

* N/A: not applicable

10.2.1 STEP 1: Exclusion of degradation products of no concern

During EU AIR for zoxamide the following information was concluded at Step 1 (see DAR 2017, Vol.1): *In soil, the major metabolites which either exceeded 10% AR on one occasion or 5% on more than 2 occasions were RH-127450 (8.1-15.1% AR), RH-24549 (5.5-33.8% AR), RH-163353 (7.9-15% AR) and RH-141455 (8% 8.4%). None of these substances meet any of the conditions set out in guidance document "Sanco/221/2000 –rev.10- final, 25 February 2003" to be considered to be degradation products of no concern. Therefore, further consideration is necessary.*

In the following it turned out that only RH-141455 bears the potential risk to appear at concentrations > 0.1 µg/L in the groundwater/drinking water. As a result, only this metabolite was further considered for a relevance assessment – as it is done here.

The metabolite RH-141455 (3,5-dichloro-4-carboxybenzoic acid) reached at maximum 8.4 % (day 14) in

a soil metabolism study performed with the parent compound zoxamide. It developed from the metabolite RH-24549 (FF = 0.5). Besides, it occurred in a surface water degradation study with zoxamide (pelagic test according to OECD guideline 309; van den Bosch, 2014) at max. amounts of 10.5 %. Thus, it can potentially reach groundwater/drinking water and is therefore addressed in the respective PEC calculations.

Besides, RH-141455 does not meet the criteria for products of no concern as defined in step 1 of the guidance EC guidance document SANCO/221/2000 –rev.10 and therefore needs further assessment. It is neither CO_2 or an inorganic compound not containing a heavy metal, nor is it an organic compound of aliphatic structure with a chain length of 4 or less, consisting 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. As a last point, it is not a substance which is known to be of no toxicological or ecotoxicological concern, and/or which is naturally occurring at much higher concentrations in the respective compartment.

10.2.2 STEP 2: Quantification of potential groundwater contamination

During EU AIR for zoxamide the following PEC calculations were considered at Step 2 (see DAR 2017, Vol.1): Predicted Environmental Concentrations in groundwater have been calculated for RH-141455 using the FOCUS groundwater scenarios and the PELMO 5.5.3 and PEARL 4.4.4. models (refer to Volume 3, CP, B.8). Potatoes and grapevines (5 applications of 180 g a.s./ha) were used for the simulations. For vines, 60% crop interception was considered for all applications. For potatoes, 60% crop interception was considered for the first, second and third application with 85% for the fourth and fifth application. Predicted environmental concentrations of RH-141455 were above the threshold value of 0.1 µg/L in all scenarios for vines using both models. The values were from 0.516 to 5.493 µg/l. For potatoes, using application every year, the PEC values were above 0.1 µg/L in all scenarios, except for the Sevilla scenario, with both models. The values were from 0.046 to 8.369 µg/L.

For the here relevant intended GAP uses of CYMOXANIL 33% + ZOXAMIDE 33% WG with an application pattern of 3 x 148.5 g/ha zoxamide (for wine grapes and potatoes) the zoxamide metabolite RH-141455 is not appearing > 0.1 µg/L (the drinking water limit) after the use of CYMOXANIL 33% + ZOXAMIDE 33% WG on vines early. However, it is appearing > 0.1 µg/L (but < 0.75 µg/L) in FOCUS groundwater scenarios after the use of CYMOXANIL 33% + ZOXAMIDE 33% WG on vines late and potatoes (see Part B, Section 8, chapter 8.8.2.1), and therefore needs further assessment.

The here relevant use for which max. concentrations of RH-141455 were considered to exceed 0.1 µg/L is listed in Table 10.2-1.

10.2.3 STEP 3: Hazard assessment – identification of relevant metabolites

10.2.3.1 STEP 3, Stage 1: screening for biological activity

The following information summarises the conclusion in 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."

The biological activity of RH-141455 does not have comparable target activity as the parent active compound as shown in biological screening data. RH-141455 is considered not relevant and is further evaluated in Stage 2.

zRMS: RH-141455 does not have biological activity comparable to parent substance zoxamide

10.2.3.2 STEP 3, Stage 2: screening for genotoxicity

The following information summarises the conclusion in the RAR (2017) on the Step 3 – Stage 2 assessment (see DAR 2017, Vol.1): *The genotoxicty of RH-141455 has been assessed in three in vitro assays refer to Volume 3, CA, B.6): In a bacterial gene mutation assay (1998), histidine-dependent TA98, TA100, TA1535, TA1537, and TA102 strains of Salmonella typhimurium were exposed to the metabolite, RH-141455 (Lot number WJZ 4091B, purity 98.74%) dissolved in dimethyl sulfoxide at concentrations of 0 (solvent control) to 5000 µg/plate in the presence and absence of an Arochlor 1245-treated rat S-9 liver fraction. In the tests with metabolic activation, 2-anthramine was used as the positive control for all strains. In the tests without metabolic activation, the positive controls used were: 2- nitrofluorene (TA98), sodium azide (TA100 and TA1535), 9-aminoacridine (TA1537), and mitomycin-c (TA102). The number of revertants was determined. The results were confirmed in an independent assay. The study was certified to be GLP compliant and satisfied the essential criteria of OECD guideline # 471. The metabolite, RH-141455 did not induce an increase in revertants compared to solvent controls. This was true for all tester strains both with and without metabolic activation. RH-141455 was not mutagenic in the Salmonella gene mutation assay under the conditions of this assay.*
In an in vitro mutation test using mouse lymphoma L5178Y, RH-141455 did not demonstrate mutagenic potential in this in vitro cell mutation assay. In an in vitro micronucleus test in cultured human lymphocytes, RH-141455 did not show any evidence of causing an increase in the induction of micronuclei. Refer to Volume 3, CA, B.6 of RAR for further details.

RH-141455 was screened for genotoxic activity by the following data package of *in vitro* genotoxicity studies: Ames test, gene mutation test with mammalian cells, and an *in vitro* mammalian cell micronucleus test. RH-141455 was non-genotoxic as shown by a negative Ames test (according to OECD 471), a negative gene mutation test with mammalian cells (according to OECD 476), and a negative *in vitro* mammalian cell micronucleus test in human lymphocytes (according to OECD 487). RH-141455 is considered not relevant and is further evaluated in Stage 3. The genotoxicity studies are evaluated in Part B, Section 6, chapter 6.4.1. For a summary of the information, please refer to the dRR Part B Section 6, chapter 6.4.1.

zRMS: As shown in Part B 6 metabolite RH-141455 is not genotoxic.

10.2.3.3 STEP 3, Stage 3: screening for toxicity

The parent zoxamide to RH-141455 is not classified on the basis of its toxicological data (see RAR 2017 and EFSA Peer Review Conclusion 2017) and with regard to its classification in accordance with CLP 1272/2008. RH-141455 might occur > 0.01 in the drinking water and has therefore further been evaluated for safety reasons and as requested by EFSA (2017).

RH-141455 (and its structurally related metabolite RH-141452) are formed by the hydrolysis of zoxamide to form the intermediate, RH-24549, which is then oxidised first to RH-141452 and then to RH-141455 (see rat metabolism in the dRR Part B Section 6, Figure 2).

Both RH-141452 and RH-141455 are rat metabolites found at low levels in urine (Swenson, R.E., Frederick, C.B., Graves, D.D. 1998a, Report No: 94R-235, ER Ref No: 24.1). RH-141452 (designated M-17 in the rat metabolism study) was isolated from rat urine by acid/base extraction, and identified by HPLC and TLC by comparison with an authentic reference standard. Analysis by LC-MS gave a molecular weight consistent with RH-141452. The identity was confirmed by derivatisation (methylation with diazomethane) followed by GC/MSD analysis. RH-141452 (M-17) was estimated to account for 0.37% of the administered dose in the low dose female group. RH-141455 was not detected by this method.

Both RH-141452 and RH-141455 were, however, found in rat urine using a non-radiolabelled residue method. Rat urine was diluted with water, acidified and extracted with ethyl acetate to separate the acidic components. After concentration and derivatization (methylation) with diazomethane, the metabolites were identified by GC/MSD and quantified using GC-ECD. Using this method, RH-141455 was found at 0.006% of dose in males and 0.004% of dose in females. RH-141452 was found at higher levels of 0.037% of dose in males and 0.034% of dose in females.
Metabolism of zoxamide to RH-141452 and RH-141455 has the effect of increasing the polarity of the residue and thereby increasing water solubility, which facilitates excretion. From the structures of RH-141452 and RH-141455, which are small molecules containing aromatic carboxylic acids, it would be predicted that these compounds would be readily excreted largely unchanged.

Rat metabolism studies have been performed with both RH-141452 and RH-141455, which confirm this expectation (Wu, D., Gu, Z., 1998a, Report No: 97RC-154, ER Ref No: 27.1 and Wu, D., Gu, Z. 1998b, Report No: 98RC-017, ER Ref No: 27.2).

Following oral administration of RH-141455 to rats, greater than 96% of radioactivity excreted in faeces (73%) and urine (11%) was identified to be unchanged parent. Some very minor metabolites were also observed in urine samples but were not identified due to their extremely low percentage of dose.

The hydrolysis of zoxamide and the subsequent oxidation steps to form RH-141452 and RH-141455 are regarded as detoxification reactions and therefore, both metabolites would be expected to be less toxic than parent zoxamide. In acute oral toxicity studies in male and female mice, the acute oral LD_{50} values of RH-141452 and RH-141455 in male and female mice were both > 5000 mg/kg bw.

In genotoxicity testing, the two related metabolites gave negative results in the *Salmonella typhimurium* gene mutation assay (Ames test). In addition, RH-141455 gave negative results in an *in vitro* micronucleus test in human lymphocytes and also in an *in vitro* mutation test using mouse lymphoma L5178Y cells.

In addition, a comparison of the toxicological profile of zoxamide and two metabolites, RH-141452 and RH-141455, has been made using OECD QSAR Toolbox version 3.4.0.17 (Pellizzaro, M. and Da Silva, M., 2017; see RAR (2017)). This analysis also indicates that both metabolites are expected to have a lower toxicity than parent zoxamide.

However, EFSA (2017) requested *"Further genotoxic data are needed for metabolites RH-141452 and RH-150721, and further repeated dose toxicity studies in order to set reference values for RH-141452, RH-141455 and RH-150721 were not available (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Section 2)."* These data were provided as far as applicable and are summarised in the dRR Part B Section 6. Full summaries of studies on the metabolite RH-141455 that have not previously been considered within an EU peer review process are additionally described in detail in Appendix 2 (A 2.11 Other/Special Studies) of the Section 6 document.

Table 10.2-2: Summary of the results of toxicity studies for RH-141455

Type of test, species (Guideline)	Result	Acceptability	Reference*
Ames (OECD 471)	non-genotoxic	Yes	Sames, J.L., Ciaccio, P.J., 1998*;

Type of test, species (Guideline)	Result	Acceptability	Reference*
			Report no. 98R-048
In vitro mutation test using mouse lymphoma L5178Y cells (OECD 476)	non-genotoxic	Yes	Woods, 2014*; Report no. FRK0049
In vitro micronucleus test in human lymphocytes (OECD 487)	non-genotoxic	Yes	Woods, 2014*; Report no. FRK0050
Acute oral mouse (OECD 401)	LD_{50} >5000 mg/kg bw	Yes	Ferguson et al., 1998*; Report no. 98R-047
14 d dietary toxicity in rats (OECD 407)	NOAEL >1000 mg/kg bw/d**	YES	Satish Kumar, 2020; Report no. U-19071
90 d dietary toxicity in rats (OECD 408) Limit test incl. 28 d recovery and plasma TK	NOAEL >1000 mg/kg bw/d ***	YES	Satish Kumar, 2020; Report no. U-19102

* indicates that a study was reviewed at EU level
** NOAEL = 15000 ppm, which is equivalent to 1123 and 1069 mg/kg body weight/day for the males and females, respectively.
***NOAEL = 16000 ppm, which is equivalent to 924 and 1119 mg/kg body weight/day for the males and females, respectively, and 1021 mg/kg body weight/day for males and females combined.

Therefore, the metabolite RH-141455 is not as toxic as is the parent compound zoxamide (which has itself a low toxicity).

zRMS: The justification provided is acceptable and metabolite RH-141455 can be considered as toxicologically non-relevant.

10.2.4 STEP 4: Exposure assessment – threshold of concern approach

RH-141455 was not considered relevant in the hazard assessment of Step 3.

The available data show that the metabolite RH-141455 does not have fungicidal activity, that it is not genotoxic, has an acute oral LD_{50} > 5000 mg/kg bw, and is therefore not more toxic than the parent zoxamide - which itself is of low toxicity.

During AIR (see RAR, 20017), the ADI for zoxamide was confirmed at 0.5 mg/kg bw/day and it was concluded that it is not necessary to allocate an ARfD – as for the first EU approval of zoxamide. As a conservative approach for the risk assessment on EU level, an additional assessment factor of 10 was applied to the ADI for zoxamide to establish an ADI for the metabolite RH-141455 of 0.05 mg/kg bw/day (50 µg/kg bw/day). See also RAR (2017) and EFSA Peer Review Conclusion (2017).

However, there is now also a 90-d dietary toxicity study in rats available to derive an ADI (Satish Kumar, 2020; report no. U-19102). Based on the REACH guidance (Table R 8-5) [2], the following ADI can be derived :

90 d NOAEL for RH-141455 : > 1 000 mg/kg bw/d

Safety factor : 100 (standard) x 2 (from 90 d study to chronic[3]) = 200

[2,2] Guidance on Information Requirements and Chemical Safety Assessment, Chapter R.8: Characterization of Dose [Concentration]-Response for Human Health, dated Nov. 2012

--> ADI = 5.0 mg/kg bw/d

zRMS PL: The proposed ADI for metabolite RH-141455 is acceptable

Assessment based on Tier 1 PEC values (considering EFSA 2017 only input values):

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

A 5-kg bottle-fed infant has a daily water consumption of 0.75 L/day. The maximum PECgw value calculated for RH-141455 is 4.647 µg/L. This would be equivalent to a daily consumption of 3.4853 µg/person/day, or 0.6971 µg/kg bw/day for a bottle-fed infant weighing 5 kg, which is considerably lower than the possible ADI for RH-141455 (i.e. 5 mg/kg bw/d).

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

A 10-kg child has a daily water consumption of 1 L/day. The maximum PECgw value calculated for RH-141455 is 4.647 µg/L. This would be equivalent to a daily consumption of 4.647 µg/person/day, or 0.4647 µg/kg bw/day for a child weighing 10 kg, which is considerably lower than the possible ADI for RH-141455 (i.e. 5 mg/kg bw/d).

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

In accordance with SANCO/221/2000 –rev. 10- final, 25 February 2003, it is assumed that an individual has a daily water consumption of 2 L/day. The maximum PECgw value calculated for RH-141455 is 4.647 µg/L. This would be equivalent to a daily consumption of 9.294 µg/person/day, or 0.1549 µg/kg bw/day for a person weighing 60 kg, which is considerably lower than the possible ADI for RH-141455 (i.e. 5 mg/kg bw/d).

Assessment based on refined PEC values (considering also results of new e-fate studies):

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

A 5-kg bottle-fed infant has a daily water consumption of 0.75 L/day. The maximum PECgw value calculated for RH-141455 is 0.622 µg/L. This would be equivalent to a daily consumption of 0.4665 µg/person/day, or 0.0933 µg/kg bw/day for a bottle-fed infant weighing 5 kg, which is considerably lower than the possible ADI for RH-141455 (i.e. 5 mg/kg bw/d).

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

A 10-kg child has a daily water consumption of 1 L/day. The maximum PECgw value calculated for RH-141455 is 0.622 µg/L. This would be equivalent to a daily consumption of 0.622 µg/person/day, or 0.0622 µg/kg bw/day for a child weighing 10 kg, which is considerably lower than the possible ADI for RH-141455 (i.e. 5 mg/kg bw/d).

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

In accordance with SANCO/221/2000 –rev. 10- final, 25 February 2003, it is assumed that an individual has a daily water consumption of 2 L/day. The maximum PECgw value calculated for RH-141455 is 0.622 µg/L. This would be equivalent to a daily consumption of 1.244 µg/person/day, or 0.02073 µg/kg bw/day for a person weighing 60 kg, which is considerably lower than the possible ADI for RH-141455 (i.e. 5 mg/kg bw/d).

RH-141455 is also a metabolite which might be found in potatoes and has been regarded as potentially

relevant by EFSA (2017) int their Peer Review Conclusion. However, in supervised field trials with potatoes performed in accordance with an actual worst-case GAP, residues in potato tubers were < 0.01 mg/kg (the LOQ for the analytical method). Therefore, the contribution to the dietary intake of RH-141455 via potatoes is not relevant.

As a conclusion, the metabolite RH-141455 is considered to be not relevant in accordance with the guidance document on the assessment of the relevance of metabolites in groundwater (SANCO/221/2000 –rev.10-final, 25 February 2003).

10.2.5 STEP 5: Refined risk assessment

Not relevant.

zRMS: The application of the formulation CYMOXANIL 33% + ZOXAMIDE 33% (Reboot 66 WG) in line with GAP does not pose a health risk for consumers of water due to potential occurrence on metabolite RH-141455 in ground water.

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	Verte-brate 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	Verte-brate study Y/N	Owner
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 GEP No published	N	GWI
KCA 5.8.1	xxx	1998	14C-RH-141,455: Rat metabolism study, Tier I testing xxx, Report No. 98RC-017, ER Ref No. 27.2 xxx, Report No. RPT00411 GLP Not published	N	GWI

Data point	Author(s)	Year	Title Company Report No. Source (where different from company) GLP or GEP status Published or not	Verte-brate study Y/N	Owner
KCA 5.8.1	xxx	1998	RH-141,455: Acute oral toxicity study in male and female mice xxx, Report No. 98R-047, September 24, 1998, ER Ref No. 27.3 GLP Not published	N	GWI
KCA 5.8.1	Sames, J.L., Ciaccio, P.J.	1998	RH-141,455: *Salmonella typhimurium* gene mutation assay (Ames test) Rohm and Haas Co., Report No. 98R-048, September 23, 1998, ER Ref No. 27.4 GLP Not published	N	GWI
KCA 5.8.1	xxx	2014	RH-141455: *In vitro* mutation test using mouse lymphoma L5178Y xxx, Report No. FRK0049, July 8, 2014 GLP Not published	N	GWI
KCA 5.8.1	Woods, I.	2014	RH-141455: *In vitro* micronucleus test in human lymphocytes Huntingdon Life Sciences Eye Research Centre, UK, Report No. FRK0050, July 8, 2014 GLP Not published	N	GWI

GWI – Gowan Crop Protection Ltd.

For cymoxanil it is referred to the references in the EU review dossier (DAR 2007) and the EFSA Peer Review Conclusion (2008).

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	Verte-brate 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	Verte-brate study Y/N	Owner

Appendix 2 Additional information

None.