

FINAL REGISTRATION REPORT

Part B

Section 10

Assessment of the relevance of metabolites in groundwater

Detailed summary of the risk assessment

Product code: FF-075

Product name(s): EUSKATEL PRO

Chemical active substance:

Prothioconazole, 200 g/L

Azoxystrobin 150 g/L

Central Zone

Zonal Rapporteur Member State: Poland

CORE ASSESSMENT

(New Product Authorization)

Applicant: Rotam Agrochemical Europe Limited

Submission date: June 2021

MS Finalisation date: February 2022; August 2022

Version history

When	What
1 June 2021	New product application in accordance with Article 33 of regulation (EC) No. 1107/2009.
February 2022	zRMS evaluation
August 2022	Final version after commenting period

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10 Relevance of metabolites in groundwater

10.1 General information

Prothioconazole

Comment of ZRMS	The metabolites of prothioconazole are predicted to occur in groundwater at concentrations below 0.001 µg/L. Thus, the assessment of the relevance of its metabolites according to the stepwise procedure (acc. to SANCO/221/2000 –rev.10) is not required.
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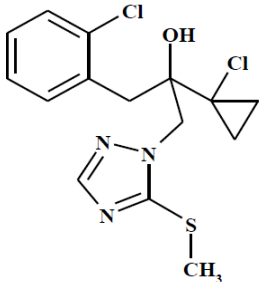
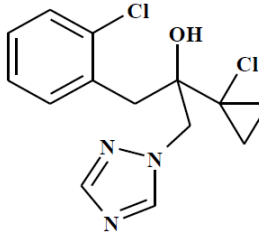
No metabolites of prothioconazole are predicted to occur in groundwater at concentrations of >0.1 µg/L, therefore, a relevance assessment is not required. Full details of the predicted environmental concentrations in groundwater (PEC_{gw}) for prothioconazole and its soil metabolites prothioconazole-S-methyl (M01) and prothioconazole-desthio (M04) are provided in Part B Section 8, Point 8.8.

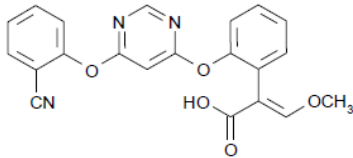
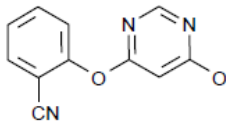
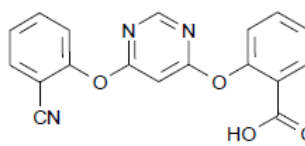
Azoxystrobin

Full details of the predicted environmental concentrations in groundwater (PEC_{gw}) for azoxystrobin and its soil metabolites R234886, R401553 and R402173 are provided in Part B Section 8, Point 8.8. The metabolite R234886 is predicted to occur in groundwater at concentrations above 0.1 µg/L (see Part B Section 8, Point 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 metabolites of prothioconazole and azoxystrobin are 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 Part B Section 8, Point 8.1 (Environmental fate and behaviour).

Table 10.1-1: General information on the metabolites of prothioconazole and azoxystrobin

Name of active substance	Metabolite name and code	Structural/molecular formula	Trigger for relevance assessment	
Prothioconazole	Prothioconazole-S-methyl (M01)		Max PEC _{gw} Based on:	<0.001 µg/L FOCUS modelling (all relevant scenarios)
	Prothioconazole-desthio (M04)		Max PEC _{gw} Based on:	<0.001 µg/L FOCUS modelling (all relevant scenarios)

Name of active substance	Metabolite name and code	Structural/molecular formula	Trigger for relevance assessment	
Azoxystrobin	R234886		Max PEC _{gw}	4.901 µg/L (Tier 2)*
			Based on:	FOCUS PEARL v 4.4.4, Châteaudun scenario for winter cereals
	R401553		Max PEC _{gw}	<0.001 µg/L
			Based on:	FOCUS modelling (all relevant scenarios)
	R402173		Max PEC _{gw}	<0.001 µg/L
			Based on:	FOCUS modelling (all relevant scenarios)

* Tier 2 simulations based on scenario specific K_{foc} values

10.2 Relevance assessment of R234886

Comments of ZRMs:	<ul style="list-style-type: none"> - According to DAR for azoxystrobin (2009), the ADI for the metabolite R234886 should be based on the value set for the parent compound, i.e. for azoxystrobin: 0.2 instead of 0.1 mg/kg bw/d (typo in Azoxystrobin – Volume 3, Annex B.6. –Toxicology and Metabolism). Therefore, the ADI value for the metabolite R234886 was recalculated and it amounts to 0.034 mg/kg bw/d; - The acute oral toxicity of metabolite R234886 is very low (rat, LD₅₀ > 5000 mg/kg bw) and the metabolite is non-genotoxic in <i>in vitro</i> bacterial mutation test. - The maximum PEC_{gw} of the metabolite R234886 amounts 4.901 µg/L. Thus, the consumer risk is required. - Taking into account the new ADI value for R234886 (0.034 mg/kg bw) and PEC_{gw} value for the metabolite the results of risk calculations for R234886 are as follows: 		
		Exposure (µg/kg b.w./d)	% ADI (parent substance)
	Adults (70 ¹ /60 ² kg b.w.)	0.00014/0.00016	0.41/0.48
	Toddlers (12 ¹ /10 ² kg b.w.)	0.00041/0.00049	1.21/1.44
	Infants (5 ^{1,2} kg b.w.)	0.00074	2.16
<p>Conclusions:</p> <p>Taking into account all toxicological data, the metabolite R234886 is considered toxicologically non-relevant. The results of the consumer risk calculations indicate</p>			

	<p>that the use of FF-075/EUSKATEL PRO according to the list of intended uses presented in GAP Table, causes no risk for health for the adults, toddlers and infants.</p> <p>¹According to EFSA Journal 2012;10(3):2579, Guidance on selected default values to be used by the EFSA Scientific Committee, Scientific Panels and Units in the absence of actual measured data.</p> <p>²WHO Guidelines for drinking-water quality: fourth edition incorporating the first addendum, 2017</p>
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Summary:

The relevance of the groundwater metabolite R234886 has already been assessed and the assessment agreed at EU level (see EFSA conclusion for Azoxystrobin, EFSA Journal 2010; 8(4):1542), 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). R234886 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 R234886 (Azoxystrobin metabolite)

	Assessment step		Result of assessment	
	STEP 1		Metabolite of no concern?	No
Quantification of groundwater contamination	STEP 2		Max PEC _{gw}	4.901 µg/L
			Based on	FOCUS PEARL v 4.4.4, Châteaudun scenario for winter cereals
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;	Azoxystrobin (the parent) was not carcinogenic, teratogenic, toxic to reproduction. It was not genotoxic. There was no indication of a trigger for classification for these endpoints. Because R234886 is formed to a significant extent (<i>ca</i> 25%) following administration and its structure is very similar to azoxystrobin, the overt toxicity for R234886 will have been adequately evaluated in the studies with the parent compound. The oral LD ₅₀ for R234886 was >5000 mg/kg and it was negative in an Ames test. Based on the weight of evidence R234886 is not considered relevant
			Classification of parent	Not classified Acute Tox.3, H331
			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 (>75%)
	STEP 5		Refined risk assessment	acceptable
			Predicted exposure (% of ADI)	0.96%
				ADI based on

* N/A: not applicable

10.2.1 STEP 1: Exclusion of degradation products of no concern

R234886 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 R234886 were performed (see Part B, Section 8, Point 8.8). The maximum PEC_{gw} for R234886 is listed in Table 10.2-1. PEC_{gw} for metabolite R234886 based on scenario specific K_{foc} values at Tier 2 were >0.1 µg/L in four of the six scenarios for winter oilseed rape ranging from <0.001 to 4.742 µg/L. For cereals, PEC_{gw} were >0.1 µg/L in six of the nine scenarios for winter cereals, ranging from <0.001 µg/L to 4.901 µg/L, and in three of the six scenarios for spring cereals, ranging from <0.001 to 4.515 µg/L. Details are given in Part B, Section 8, Point 8.8.

10.2.3 STEP 3: Hazard assessment – identification of relevant metabolites

Further evaluation not required as covered by EU evaluation.

10.2.4 STEP 4: Exposure assessment – threshold of concern approach

Further evaluation not required as covered by EU evaluation.

10.2.5 STEP 5: Refined risk assessment

Further evaluation not required as covered by EU evaluation.

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	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
10.2-2 / 01	xxxxxxx	2005	Azoxystrobin metabolite R234886: Acute Oral Toxicity Study in The Rat (Up and Down Procedure) RCC A12284 GLP, not published Syngenta File No R234886/0004	Y	Syngenta crop protection
10.2-3/ 02	Callander R.	2005	Azoxystobin Metabolite R234886: Bacterial Mutation Assay In S. Typhimurium And E.Coli Central Toxicology Laboratory (CTL), Cheshire, United Kingdom, YV7083-REG GLP, not published Syngenta File No R234886/0005	N	Syngenta crop protection

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
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