

REGISTRATION REPORT

Part B

Section 10

Assessment of the relevance of metabolites in groundwater

Detailed summary of the risk assessment

Product code: CA3642

Product name(s): JOUST PRO

Chemical active substance(s):

Prothioconazole, 150 g/L

Azoxystrobin, 150 g/L

Central Zone

Zonal Rapporteur Member State: PL

CORE ASSESSMENT

New Authorisation (Art. 33)

Sponsor: Nufarm Crop Products UK Limited

Applicant: NUFARM Polska Sp. z o. o.

Submission date: 01/02/2023

Update: July 2023, September 2024

MS Finalisation date: August 2023 (initial Core Assessment)

October 2024, December 2024 (final Core Assessment)

Version history

When	What
February 2023	V 1.0 Original applicant version
July 2023	V 2.0 Addition of PEC values for Sunflower in response to comments from ZRMS (Poland).
August 2023	<p>Initial zRMS assessment</p> <p>The report in the dRR format has been prepared by the Applicant, therefore all comments, additional evaluations and conclusions of the zRMS are presented in grey commenting boxes. Minor changes are introduced directly in the text and highlighted in grey. Not agreed or not relevant information are struck through and shaded for transparency.</p>
October 2024	<p>Final report (Core Assessment updated following the commenting period)</p> <p>Additional information/assessments included by the zRMS in the report in response to comments received from the cMS and the Applicant are highlighted in yellow. Not agreed or not relevant information are struck through and shaded for transparency.</p>
December 2024	<p>Final report (Core Assessment updated following the second commenting period)</p> <p>No additional information or assessments after the commenting period.</p>

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Reviewer comments:

This part of dossier has been submitted to support registration of the plant protection product CA3642 / JOUST PRO according art. 33 of 1107/2009.

Document refers data related to the forming of metabolites in the environment (see dRR B8). dRR Part B10 has been reviewed for the purposes of ongoing registration and also checked its compliance with the current guidelines. Information has been considered as sufficient (see point 10.1) and appropriate for concluding.

10 Relevance of metabolites in groundwater

10.1 General information

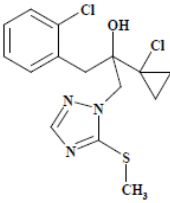
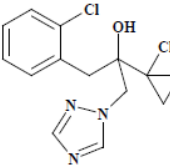
General information on the metabolites is provided in Table 10.1-1. Prothioconazole degrades in soil to form two metabolites that are present at levels >10% and are therefore potentially relevant in groundwater. The metabolites, prothioconazole-S-methyl and prothioconazole-desthio, were predicted to occur in groundwater at concentrations below 0.1 µg/L in all FOCUS scenarios for all uses in the GAP, according to the models FOCUS-PEARL (v5.5.5), FOCUS-PELMO (v6.6.4) and FOCUS-MACRO (v5.5.4). Please see dRR Part B, Section 8.8 (Environmental fate and behaviour) for a full summary of the modelling. Therefore, no further assessment of the relevance of these metabolites is required, and groundwater risks are acceptable.

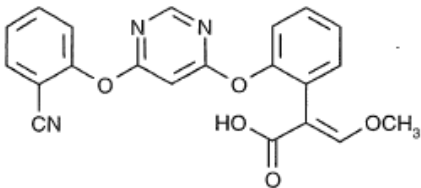
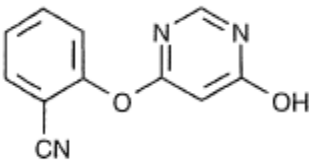
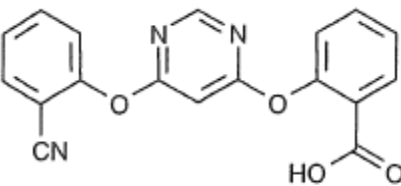
The azoxystrobin metabolite R234886 is predicted to occur in groundwater at concentrations above 0.1 µg/L (see dRR Part B Section 8). Assessment of the relevance of this metabolite according to the stepwise procedure of the EC guidance document SANCO/221/2000–rev.11 is therefore required, and is summarised in data point 10.2 below.

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 dRR Part B, Section 8.8 (Environmental fate and behaviour).

Azoxystrobin forms two other soil metabolites via photolysis, R401553 and R402173. These metabolites were predicted to occur in groundwater at concentrations below 0.1 µg/L in all FOCUS scenarios for all uses in the GAP, according to the models FOCUS-PEARL (v5.5.5), FOCUS-PELMO (v6.6.4) and FOCUS-MACRO (v5.5.4). Please see dRR Part B, Section 8.8 (Environmental fate and behaviour) for a full summary of the modelling. Therefore, no further assessment of the relevance of these metabolites is required, and groundwater risks are acceptable.

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	
Prothioconazole	Prothioconazole-S-methyl		Max PEC _{gw} Based on:	<0.1 µg/L All crops and scenarios
	Prothioconazole-desthio		Max PEC _{gw} Based on:	<0.1 µg/L All crops and scenarios

Name of active substance	Metabolite name and code	Structural/molecular formula	Trigger for relevance assessment	
Azoxystrobin	R234886 (M 02)		Max PEC _{gw} Based on:	1.524 µg/L Sunflower, alkaline soils, Hamburg scenario
	R401553 (M 28)		Max PEC _{gw} Based on:	<0.1 µg/L All crops and scenarios
	R402173 (M 30)		Max PEC _{gw} Based on:	<0.1 µg/L All crops and scenarios

10.2 Relevance assessment of R234886

Summary:

The relevance of the azoxystrobin groundwater metabolite R234886 has already been assessed and the assessment agreed at EU level (first RAR, Azoxystrobin – Volume 3, Annex B.6.8.1.3: Toxicology and Metabolism, May 2009 and EFSA Journal 2010; 8(4):1542). The assessment from the DAR is reproduced below. 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.11. 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

	Assessment step		Result of assessment	
	STEP 1		Metabolite of no concern?	No
Quantification of groundwater contamination	STEP 2		Max PEC _{gw}	1.524 µg/L
			Based on	Use on sunflower, alkaline soils, Hamburg scenario, PEARL model
Hazard assessment	STEP 3	Stage 1	Biological activity comparable to the parent?	No (R234886 showed no significant biological activity)
		Stage 2	Genotoxic properties of metabolite	Non-genotoxic
		Stage 3	Toxic properties of metabolite;	Acute oral LD ₅₀ > 5000 mg/kg bw (female rat)
			Classification of parent	Acute Tox. 3, H331
			Classification of metabolite	None
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)	<5% of ADI assuming a PEC _{gw} of 22 µg/L*
				ADI* based on

* Azoxystrobin RAR, Vol 3, Annex B.6, May 2009

10.2.1 STEP 1: Exclusion of degradation products of no concern

R234886 has been deemed not relevant at EU Level. ~~please refer to the summary in Section 10.2 above.~~
The step 1 assessment from the DAR (2009, Volume 3, Annex B.6.8.1.3) is reproduced below:

R234886 is O-demethyl-azoxystrobin. It contains two benzene rings, a pyrimidine ring, a nitrile group and a methoxy group. It cannot be excluded at Step 1.

10.2.2 STEP 2: Quantification of potential groundwater contamination

FOCUS modelling indicates levels of R234886 are in excess of 0.1 µg/L in multiple scenarios, with a maximum PEC_{gw} of 1.524 µg/L in the Hamburg scenario for sunflower crops.
~~R234886 has been deemed not relevant at EU Level, please refer to the summary in Section 10.2 above.~~

10.2.3 STEP 3: Hazard assessment – identification of relevant metabolites

10.2.3.1 STEP 3, Stage 1: screening for biological activity

R234886 has been deemed not relevant at EU Level. ~~please refer to the summary in Section 10.2 above.~~
The step 3, stage 1 assessment from the DAR (2009, Volume 3, Annex B.6.8.1.3) is reproduced below:

The notifier has presented a study (Grayson & Schneider 2008 - TMJ/5077B) comparing the fungicidal activity of azoxystrobin and R234886. The test organisms were Phytophthora infestans (late blight – test crop potato); Puccinia recondita (brown rust – test crop wheat); Cercospora arachidicola (early leaf spot – test crop peanut); & Alternaria solani (early blight – test crop tomato).

Azoxystrobin gave good control (>60% control at 2ppm) against *Phytophthora infestans*, *Puccinia recondita* & *Alternaria solani*; R234886 gave zero control against these species at 2 - 6ppm. Against *Cercospora arachidocola* azoxystrobin surprisingly gave minimal control (<10%) and R234886 gave 3.1% control – the commercial control of difenoconazole gave >90% control at 0.6 ppm.

These results show R234886 has no significant fungicidal activity against the four species tested.

10.2.3.2 STEP 3, Stage 2: screening for genotoxicity

R234886 has been deemed not relevant at EU Level. ~~please refer to the summary in Section 10.2 above.~~
The step 3, stage 2 assessment from the DAR (2009, Volume 3, Annex B.6.8.1.3) is reproduced below:

R234886 was found to be negative in an adequately performed Ames test (See B.6.8.1.2).

R234886 per se has not been tested in mammalian cell assays for gene mutation or chromosome aberrations. However, significant levels (ca 25 – 30% of a 100 mg/kg bw dose of azoxystrobin) of the glucuronide conjugate of R234886 were detected in the bile of rats. To form the glucuronide, R234886 would have been produced prior to conjugation. There is therefore the potential for R234886 to have been present in in vitro genotoxicity studies with azoxystrobin in the presence of metabolic activating systems (S9) (see B.6.4.1). It is also highly likely that R234886 would be produced in the target tissue of the rat liver in vivo UDS assay with azoxystrobin, which gave negative results (see B. 6.4.2.2).

It is debatable whether R234886 would have reached the bone marrow in the in vivo mouse micronucleus assay as it would probably have been conjugated and excreted in bile. However, direct oral or intra-peritoneal dosing of animals with R234886 is also unlikely to result in significant exposure of the bone marrow as it would be transported to the liver via the portal vein, conjugated and excreted in the bile resulting in limited systemic availability.

It is also of note that administration of azoxystrobin did not result in an increase in liver or bile duct tumours in rats or mice. Given the high levels of R234886 likely to be produced in the liver (ca 25% of the azoxystrobin dose), if R234886 had significant genotoxic potential in vivo it would be expected to give rise to liver or bile-duct tumours.

Although only one in vitro genotoxicity assay has been performed with R234886, other information on its in situ production in rats following dosing with azoxystrobin indicates that R234886 is unlikely to have significant genotoxic potential in vivo.

10.2.3.3 STEP 3, Stage 3: screening for toxicity

R234886 has been deemed not relevant at EU Level. ~~please refer to the summary in Section 10.2 above.~~
The step 3, stage 3 assessment from the DAR (2009, Volume 3, Annex B.6.8.1.3) is reproduced below:

In a range of studies, Azoxystrobin was not carcinogenic, teratogenic or toxic to reproduction, neither was it genotoxic in two in vivo assays. There is no indication of a trigger for classification for these endpoints.

Azoxystrobin is currently classified as “Toxic by inhalation – T; R23”. This classification arises from a study using very fine particles (MMAD <2µm) – see B.6.2.3.1. A similar study with particles of MMAD ca 15µm resulted in no classification being required.

The RMS considers that performing an acute inhalation study on R234886 would be contrary to Directive 86/609/EEC on the protection of experimental animals. An inhalation classification has no relevance to a non-volatile groundwater metabolite. There is no obvious scenario giving rise to an exposure to fine aerosols, atmospheres or vapours of R234886 that would be respirable and reach the lower respiratory

tract. Even if such a scenario did occur, the risk of damage to lung cells by the (fresh) groundwater is going to far outweigh the presence of 22 parts per billion R234886.

An acute oral toxicity study with R234886 showed it to be non-toxic to female rats, with an LD₅₀ of >5000 mg/kg bw (see B.6.8.1.1).

R234886 is formed to a significant extent (ca 25%) following administration of azoxystrobin and its structure is very similar to azoxystrobin. It is considered that the overt toxicity of R234886 will be adequately evaluated in the studies with azoxystrobin. The only end-point mentioned in Stage 3, Step 3 of the Guidance document (Sanco /221/2000 Rev 10) is that of inhalation toxicity of azoxystrobin, which is considered completely irrelevant to the evaluation of R234886.

It is concluded that R234886 is not relevant at Stage 3 Step 3.

10.2.4 STEP 4: Exposure assessment – threshold of concern approach

R234886 has been deemed not relevant at EU Level, please refer to the summary in Section 10.2 above.

Predicted levels of R234886 in groundwater are >0.75 µg/L therefore a refined risk assessment is required at Step 5.

10.2.5 STEP 5: Refined risk assessment

R234886 has been deemed not relevant at EU Level. please refer to the summary in Section 10.2 above.

The step 5 assessment from the DAR (2009, Volume 3, Annex B.6.8.1.3) is reproduced below:

R234886 is structurally very closely related to azoxystrobin. R234886 will be formed to a significant extent in the liver of rats exposed to azoxystrobin (ca 25 – 30% of the administered dose is found as the glucuronide of R234886). If one assumes that all the toxicity of azoxystrobin is due to R234886 an ADI for R234886 could be set based on that of azoxystrobin, corrected for the proportion of glucuronide formed and the relative molecular weights:

$$0.2 \text{ mg/kg bw/d} \times 25\% \times (403 / 568) \times (389 / 403) = 0.034 \text{ mg/kg bw/d}$$

Adjustment (October 2024): the azoxystrobin ADI was set to 0.2 mg/kg/d in EFSA 2010; 8(4):1542, while the DAR evaluation used an ADI of 0.1 mg/kg/d. The calculation has above therefore been updated with the latest ADI.

Predicted maximum levels of R234886 in groundwater (and hence drinking water) are <22 µg/L. Exposure to R234886 of a 60 kg person consuming 2 litres of drinking water per day containing 22 µg R234886/litre would be:

$$2\text{L} \times 0.022 \text{ mg/L} / 60 \text{ kg} = 0.00073 \text{ mg/kg bw/day} (<5\% \text{ of the ADI})$$

Adjustment (October 2024): for the maximum PEC_{gw} of 1.524 µg/L from use of CA3642, exposure would be **0.000508 mg/kg bw/d**, which is **0.15% of the ADI**

This evaluation assumes that the person will be exposed to water containing the maximum predicted level of R234886 on every day of their life. A more appropriate comparison for peak levels in groundwater would be the acute reference dose. However, azoxystrobin does not exhibit significant acute systemic toxicity and no acute reference dose is proposed.

Conclusion

The maximum predicted exposure from R234886 in groundwater is less than 5% of the ADI derived for R234886. Therefore R234886 is considered not relevant to human risk assessment from its presence in groundwater at up to 22 µg/L.

The consumer exposure is summarised below for adults, children and infants – using the water

consumption model for Children and Infants in the EFSA Scientific Opinion on Dietary Reference Values for water (EFSA Journal 2010; 8(3):1459). In all cases, exposure via drinking water is <1% of the ADI, even when assuming constant exposure at the worst-case PEC_{gw} and assuming that all azoxystrobin toxicity is caused by R234886. The risk is therefore acceptable to all consumers.

Table 10.2-2: Consumer exposure assessment for R234886

Consumer	PEC_{gw} (µg/L)	Body weight (kg)	Water consumption (L)	Exposure (mg/kg bw/d)	% ADI*
Adult	1.524	60	2	0.0000508	0.15 %
Child	1.524	10	1	0.0001524	0.45 %
Infant	1.524	5	0.75	0.0002286	0.67 %

* ADI = 0.034 mg/kg bw/d

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
KCA 5.8.1/01	Straube, E.	2005	Azoxystrobin metabolite R234886: Acute Oral Toxicity Study in The Rat (Up and Down Procedure) Report No. A12284 Syngenta Crop Protection AG, Basel, Switzerland GLP Unpublished	Y	Syngenta
KCA 5.8.1/02	Callander, R.	2005	Azoxystrobin metabolite R234886: Bacterial Mutation Assay in S. Typhimurium and E. Coli Report No. YV7083-REG Central Toxicology Laboratory (CTL), Cheshire, UK GLP Unpublished	N	Syngenta

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
-	-	-	-	-	-