

FINAL REGISTRATION REPORT

Part B

Section 10

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

Detailed summary of the risk assessment

Product code: CHR/F/PROTAZO 375 SC

Product name(s): CLARO 375 SC, KAJMAN 375 SC

Chemical active substance(s):

Prothioconazole, 175 g/l

Azoxystrobin, 200 g/l

Central Zone

Zonal Rapporteur Member State: Poland

CORE ASSESSMENT

Applicant: Innvigo Sp. z o.o.

Submission date: May 2020

MS Finalisation date: 28/04/2022

Version history

When	What
May 2021	Dossier sent for evaluation
December 2021	Applicant updated dRR on the zRMS request
January 2022	zRMS finalised evaluation
April 2022	Final version prepared by zRMS after Commenting period

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Evaluator comments:

The text highlighted in grey was provided by the evaluator.

10 Relevance of metabolites in groundwater

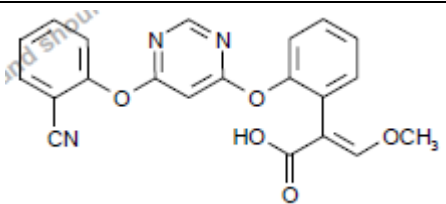
Evaluator's Comments:	Based on PEC _{gw} assessment for metabolites of azoxystrobin only the R234886 was relevant in alkaline soils. R234886 is not considered relevant according to the criteria laid down in the EC guidance document SANCO/221/2000 – rev.10. The maximum predicted exposure from R234886 in groundwater (considering max PEC _{gw} 4.4677 µg/L) is less than 5% of the ADI derived for R234886. No risk is anticipated for consumers after exposure to R234886 via drinking water.
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10.1 General information

The metabolite R234886 are predicted to occur in groundwater at concentrations above 0.1 µg/L (see dRR Part B, Section 8). Assessment of the relevance of these metabolites according to the stepwise procedure of the EC guidance document SANCO/221/2000 –rev.10 is therefore required.

General information on the metabolites 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 KCP 9.2.4 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
Azoxystrobin	R234886		Max PEC _{gw} 4.3934 4.4677 µg/L Based on: Focus PEARL 4.4.4 Hamburg Spring cereals alkaline soils

10.2 Relevance assessment of R234886

Summary:

The relevance of the groundwater metabolite R234886 has already been assessed and the assessment agreed at EU level (DAR Azoxystrobin - 2009, Vol3 – B6) , 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 **Błąd! Nie można odnaleźć źródła odwołania.** and the corresponding studies are listed in the corresponding sections.

Table 10.2-1: Summary of the relevance assessment for ASTCA according to the RAR Florasulam-2013, Vol3 – B6

	Assessment step	Result of assessment	
Identification of groundwater contamination	STEP 1	Metabolite of no concern?	Yes
	STEP 2	Max PEC _{gw}	4.3934 4.4677 µg/L

			Based on	FOCUS PEARL, 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;	Not toxic or very toxic (T or T+)
			Classification of parent	not currently classified as toxic or very toxic
			Classification of metabolite	not currently classified as toxic or very toxic
Consumer health risk assessment	STEP 4		Estimated consumer exposure via drinking water and other sources; threshold of concern approach	No acceptable(PEC _{gw} >0.75 µg/L)
	STEP 5	Refined risk assessment		Not required
		Predicted exposure (% of ADI)		<5% of ADI
				ADI based on

* N/A: not applicable

Step 1

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

Step 2

FOCUS modelling indicates levels of R234886 are in excess of 0.1 µg/L in multiple scenarios.

Step 3

Stage 1

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 arachidocola* (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.

Stage 2

R234886 was found to be negative in an adequately performed Ames test.

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) 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

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*.

Stage 3

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 end-points. Azoxystrobin is currently classified as „Toxic by inhalation – T; R23“. This classification arises from a study using very fine particles (MMAD <2µm) . 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. 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.

Stage 4

Predicted levels of R234886 in groundwater are >0.75 µg/person/day therefore a refined risk assessment is required.

Stage 5

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 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:

$$0.1 \text{ mg/kg bw} * 25\% * (403/568) *(389/403) = 0.017 \text{ mg/kg bw.}$$

Predicted maximum levels of R234886 in groundwater (and hence drinking water) are 4.3934 µg/L.
Exposure to R234886 for:

- a) infant – 5 kg person consuming 0.75 liter of drinking water per day containing 4.3934 µg R234886/L:

$$(0.75\text{L} * 0.0043934 \text{ mg}) / 5 = 0.000659 \text{ mg/kg bw/day (3.88\% of the ADI)}$$

b) toodler – 10 kg person consuming 1 liter of drinking water per day containing 4.3934 µg R234886/L:

$$(1\text{L} * 0.0043934 \text{ mg/L}) / 10 \text{ kg} = 0.00043934 \text{ mg/kg bw/day (2.58\% of the ADI)}$$

c) adult – 60 kg person consuming 2 liters of drinking water per day containing 4.3934 µg R234886/L:

$$(2\text{L} * 0.0043934 \text{ mg/L}) / 60 \text{ kg} = 0.0001465 \text{ mg/kg bw/day (0.86\% of the ADI)}$$

Appendix 1 Lists of data considered in support of the evaluation

Appendix 2 Additional information