

REGISTRATION REPORT

Part B

Section 10

Assessment of the relevance of metabolites in groundwater

Detailed summary of the risk assessment

Product code: A22773A

Product name: ORONDIS EVO

Chemical active substances:

Azoxystrobin, 250 g/L

Oxathiapiprolin, 12 g/L

Interzonal

Zonal Rapporteur Member State: Poland

CORE ASSESSMENT

(New authorisation)

Applicant: Syngenta

Submission date: November 2021

MS Finalisation date: June 2022, updated October 2022

(initial Core Assessment)

June 2023 (final Core Assessment)

Version history

When	What
November 2021	Applicant submission
June 2022, updated October 2022	Initial assessment by the izRMS 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 .
January 2023	Final report (Core Assessment updated following the commenting period) 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.

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Reviewer summary:

This part of dossier has been submitted to support registration of the plant protection product ORONDIS EVO (product code A22773A an a SC formulation containing 250 g/L azoxystrobin and 12 g/L oxathiapiprolin) according art. 33 of 1107/2009.

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 and appropriate for concluding.

- azoxystrobin ground water metabolite R234886 which was predicted to occur in groundwater at concentrations above 0.1 µg/L during the PRAPeR 71 meeting has been recognized by the experts as not toxicologically relevant; Toxicological relevance NO, Rat, oral LD₅₀ > 5000 mg/kg bw; negative in an *in vitro* bacterial mutation test; covered by the toxicological assessment of azoxystrobin; reference values of azoxystrobin apply; (for details refer *EFSA Conclusion on the peer review of the pesticide risk assessment of the active substance azoxystrobin. EFSA Journal 2010; 8(4):15421542*),
- oxathiapiprolin ground water metabolite IN-E8S72 which was predicted to occur in groundwater at concentrations above 0.1 µg/L was concluded not toxicologically relevant, (for details refer *EFSA 2016. Conclusion on the peer review of the pesticide risk assessment of the active substance oxathiapiprolin. EFSA Journal 2016; 14(7):4504, 19 pp*).

Document refers data related to the forming of metabolites in the environment summarized below (for details refer dRR B8):

- For uses that are relevant in CEU zone, the PEC_{GW} values were calculated based on EU agreed K_{FOC} values for azoxystrobin and respective metabolites.
For SEU uses, the K_{FOC} values used in modelling for azoxystrobin and its respective metabolites were calculated based on the geometric mean.

CEU and SEU zones

The results of FOCUS groundwater calculation for azoxystrobin indicated that PEC_{gw} values do not exceed the regulatory trigger of 0.1 µg/L at 1 m depth in any of the scenarios.

The maximum PEC_{GW} of R401553 and R402173 were below 0.1 µg/L in all scenarios.

Uses proposed for CEU zone

The sorption of metabolites R234886 is pH dependent. Therefore, the simulations were performed at Tier 1 using PUF=0 and specific K_{foC} values for acidic and alkaline soils. The maximum Tier 1 PEC_{GW} was 5.11 µg/L. Further simulations were performed for metabolite R234886 at Tier 2 using PUF=0.5. The maximum Tier 2 PEC_{GW} was 4.73 µg/L.

Uses proposed for SEU zone

The sorption of metabolites R234886 is pH dependent. Therefore, the simulations were performed using specific K_{foC} values for acidic and alkaline soils. The PUF of 0.5 was considered. The maximum PEC_{GW} for two crop cycle per year for the single application of 250 g a.s./ha was 7.43 µg/L.

The maximum PEC_{GW} for four application per year for the twofold application of 250 g a.s./ha were 13.2 µg/L (Hamburg scenario) and 7.57 µg/L (Kremsmünster scenario).

According to WORKING DOCUMENT ON THE WORK-SHARING OF THE SOUTHERN ZONE MEMBER STATES UNDER REGULATION EC 1107/2009, Rev. 7.1 of 06.08.2018, the Hamburg scenario is relevant (e.g. for Spain). For several Southern Member States the national data requirements are not given. Thus, the relevance of Hamburg scenario need to be consider at SMS level.

- For uses that are relevant in CEU zone, the PEC_{GW} values below are calculated based on EU agreed K_{FOC} values for oxathiapiprolin and respective metabolites.
For SEU uses, the K_{FOC} values used in modelling oxathiapiprolin and its respective metabolites were calculated based on the geometric mean.
The results of FOCUS groundwater calculation for oxathiapiprolin, indicated that PEC_{gw} values do not exceed the regulatory trigger of 0.1 µg/L at 1 m depth in any of the scenarios.
The maximum PEC_{GW} of IN-RDT31, IN-RAB06 and IN-QPS10 were below 0.1 µg/L in all scenarios.
However, PEC_{gw} for metabolite IN-E8S72 exceed this threshold. The maximum PEC_{GW} were 1.55 µg/L and 3.11 µg/L for CEU (two applications per year) and SEU (four applications per year), respectively.

10 Relevance of metabolites in groundwater

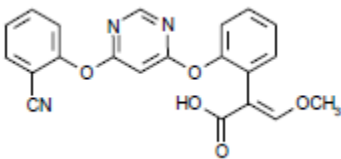
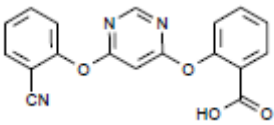
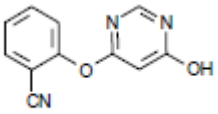
10.1 General information

The PEC_{GW} of the azoxystrobin metabolites R402173 and R401553 were $< 0.1 \mu\text{g/L}$ in the relevant application patterns (please see A22773A, Part B, Section 8.8.2 and Table 10.1-1 below). No assessment is thus required for these metabolites. Nevertheless, the azoxystrobin metabolite R234886 is predicted to occur in groundwater at concentrations above $0.1 \mu\text{g/L}$ (see please see **A22773A, Part B, Section 8.8.2**). 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.

The PEC_{GW} of the oxathiapiprolin metabolites IN-RDT31, IN-RAB06 and IN-QPS10 were $< 0.1 \mu\text{g/L}$ in the relevant application patterns (please see A22773A, Part B, Section 8.8.2 and Table 10.1-2 below). No assessment is thus required for these metabolites. Nevertheless, the oxathiapiprolin metabolite IN-E8S72 is predicted to occur in groundwater at concentrations above $0.1 \mu\text{g/L}$ (see please see **A22773A, Part B, Section 8.8.2**). 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.

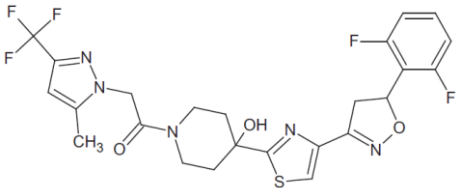
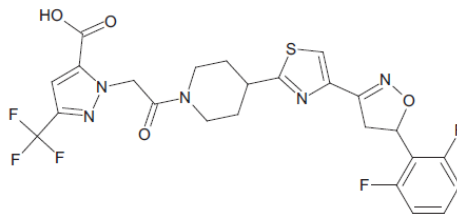
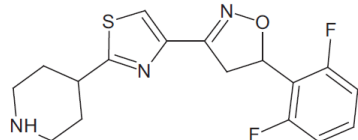
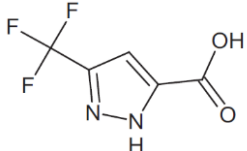
General information on the metabolites are provided in Table 10.1-1 and Table 10.1-2. The impact of the relevance assessment on whether a particular GAP use leads to acceptable risk or not is presented in the summary of the cGAP evaluation in Part B, Section 8 (Environmental fate and behaviour).

Table 10.1-1: General information on the azoxystrobin metabolites

Name of active substance	Metabolite name and code	Structural/molecular formula	Trigger for relevance assessment	
Azoxystrobin	R234886		Max PEC_{GW} Based on:	$7.57 * \mu\text{g/L}$ FOCUS-PEARL (v4.4.4), application to cabbage, $2 \times 250 \text{ g a.s./ha}$, BBCH 11-49, Kremsmünster scenario
	R402173		Max PEC_{GW} Based on:	$0.084 \mu\text{g/L}$ FOCUS-PELMO (v5.5.3), application to cabbage, $2 \times 250 \text{ g a.s./ha}$, BBCH 11-49, Porto scenario
	R401553		Max PEC_{GW} Based on:	$0.002 \mu\text{g/L}$ FOCUS-PEARL (v4.4.4), application to cabbage, $2 \times 250 \text{ g a.s./ha}$, BBCH 11-49, Hamburg scenario

* The value of $13.2 \mu\text{g/L}$ in Hamburg scenario was disregarded because, as explained in section B8, Hamburg is scenario not relevant for countries where 2 applications in 2 crop cycles (total of 4 application per year) are the intended GAP

Table 10.1-2: General information on the oxathiapiroline metabolites

Name of active substance	Metabolite name and code	Structural/molecular formula	Trigger for relevance assessment	
Oxathiapiroline	IN-RDT31		Max PEC _{gw} Based on:	< 0.001 µg/L All models, all uses and all scenarios
Oxathiapiroline	IN-RAB06		Max PEC _{gw} Based on:	< 0.001 µg/L All models, all uses and all scenarios
Oxathiapiroline	IN-QPS10		Max PEC _{gw} Based on:	< 0.001 µg/L All models, all uses and all scenarios
Oxathiapiroline	IN-E8S72		Max PEC _{gw} Based on:	3.11 µg/L FOCUS PEARL v4.4.4 / application to cabbage, 2 × 12 g a.s./ha, BBCH 11-49, Hamburg scenario

10.2 Relevance assessment of the azoxystrobin metabolite R234886

Summary:

The relevance of the groundwater metabolite R234886 has already been assessed and the assessment agreed at EU level (see **Azoxystrobin**, **EFSA Journal 2010; 8(4):15421542**), 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). Metabolite 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

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}	7.57 *µg/L
			Based on	FOCUS-PEARL (v4.4.4), application to cabbage, 2 × 250 g a.s./ha, BBCH 11-49, Kremsmünster scenario
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;	Acute oral toxicity: > 5000 mg/kg bw Acute dermal toxicity: > 2000 mg/kg bw
			Classification of parent	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/)
	STEP 5		Refined risk assessment	acceptable
			Predicted exposure (% of ADI)	Adult: < 1 % of ADI ^a Child: < 1 % of ADI ^b Infant: < 1 % of ADI ^c
			ADI based on	The ADI for R234886 was derived from a 2-year rat study and using a safety factor of 100. The ADI for R234886 is 0.2 mg/kg bw/day

^a ADI utilisation (%) = [PEC_{gw} (µg/L) × water consumption (L/day) × 100] / [bw (kg) × 1000 × ADI (mg/kg bw/day)]

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

^b ADI utilisation (%) = [PEC_{gw} (µg/L) × water consumption (L/day) × 100] / [bw (kg) × 1000 × ADI (mg/kg bw/day)]

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

^c ADI utilisation (%) = [PEC_{gw} (µg/L) × water consumption (L/day) × 100] / [bw (kg) × 1000 × ADI (mg/kg bw/day)]

Calculation of risk (% ADI) for 5-kg adult (consuming 0.75 L/day)

* The value of 13.2 µg/L in Hamburg scenario was disregarded because, as explained in section B8, Hamburg is scenario not relevant for countries where 2 applications in 2 crop cycles (total of 4 application per year) are the intended GAP

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.

It cannot be excluded as a product of no concern as R234886 is not:

- CO₂ or an inorganic compound, not containing a heavy metal;
 - 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;
 - a substance which is known to be of no toxicological or ecotoxicological concern, and which is naturally occurring at much higher concentrations in the respective compartment;
- 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 considering the proposed use of

A22773A on various crops. The groundwater concentration of R234886 was predicted to exceed 0.1 µg/L in a number of FOCUS scenarios and the maximum concentration is 7.57 µg/L. Details are given in Part B, Section 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 study on biological activity performed on R234886 has been previously reviewed under Council Directive 91/414/EEC (EFSA Journal (2010) 8(4), 1542).

Based on evidence from a fungicide screen, R234886 did not show any fungicidal activity when applied at rates known to be effective for parent azoxystrobin. Therefore R234886 is not considered to be biologically active.

Furthermore the available data indicate that R234886 is considerably less ecotoxic than the parent azoxystrobin, confirming the difference in activity between the two substances.

10.2.3.2 STEP 3, Stage 2: screening for genotoxicity

A study on genotoxicity performed on R234886 has been previously reviewed under Council Directive 91/414/EEC (EFSA Journal (2010) 8(4), 1542).

The mutagenic potential of R234886 was evaluated in a bacterial mutagenicity assay over a range of concentrations using four strains of *Salmonella typhimurium* (TA1535, TA1537, TA98 and TA100) and two strains of *Escherichia coli* (WP2 (pKM101) and WP2 *uvrA* (pKM101)) in the presence and absence of a rat liver-derived metabolic activation system (S9-mix).

Under the conditions of this assay, R234886 gave a negative, i.e. non-mutagenic, response in *S.typhimurium* strains TA1535, TA1537, TA98 and TA100 and *E.coli* strains WP2 (pKM101) and WP2 *uvrA* (pKM101) in both the presence and absence of S9-mix.

Further, R234886 is the acid metabolite of azoxystrobin and has been identified in the plasma of rats and rabbits following administration of parent azoxystrobin. The glucuronide conjugate of R234886 (metabolite V) is found at high levels, i.e. up to 29% of the dose in bile, in rats dosed with parent azoxystrobin (Azoxystrobin DAR Volume 3, Annex B.6).

Gene mutation tests with mammalian cells and chromosome aberration tests have not been conducted with R234886 because there was deemed to be adequate exposure to R234886 in the *in vivo* genotoxicity studies conducted with parent azoxystrobin. Azoxystrobin was found to be negative in the established *in vivo* assays for chromosomal damage (i.e. clastogenicity) and for interaction with the DNA (UDS test for DNA damage and repair) and furthermore, chronic studies have not shown any evidence of carcinogenicity in mouse and rat.

Based on evidence from a bacterial mutagenicity study with R234886 and *in vivo* genotoxicity tests with the parent azoxystrobin, it is concluded that metabolite R234886 is not genotoxic and further testing is not required.

10.2.3.3 STEP 3, Stage 3: screening for toxicity

Extensive toxicity testing of the active substance has been carried out and the results are described in detail in the EFSA Journal 2010; 8 (4): 1542.

The toxicity of azoxystrobin and R234886 has been evaluated in acute oral toxicity tests. The results of these studies indicate that neither azoxystrobin nor R234886 exhibits any toxicity at doses up to 5000 mg/kg bw. Toxicity tests with azoxystrobin are considered representative of the potential effects of R234886 because R234886 is the acid metabolite of azoxystrobin and has been identified in the plasma of rats and rabbits following administration of parent azoxystrobin. The glucuronide conjugate of R234886 (metabolite V) is found at high levels, i.e. up to 29% of the dose in bile, in rats dosed with parent azoxystrobin (Azoxystrobin DAR Volume 3, Annex B.6). The toxicological properties of azoxystrobin have been thoroughly evaluated and azoxystrobin has been shown to have low acute toxicity, is not genotoxic in vivo and showed no evidence of carcinogenicity in either the rat or mouse when dosed for up to two years. Furthermore, azoxystrobin is not teratogenic or reprotoxic and does not exhibit evidence of neurotoxicity in any of the toxicity studies conducted. Therefore, the active substance does neither fulfil the criteria for classification and labelling for reproductive or developmental toxicity nor for carcinogenicity.

The parent compound azoxystrobin is not classified for reproductive toxicity, mutagenicity or carcinogenic properties, *i.e.* is not classified with either the signal word Danger or Warning, the pictogram GHS08, or with the hazard phrases; H340, H341, H350, H351, H360, H361 or H362. Consequently toxicity testing with R234886 is not required based on these criteria.

The active substance azoxystrobin fulfils the criteria for classification and labelling as ‘toxic’ with regard to inhalation toxicity (GHS06, Signal word; Danger, H331), however for groundwater metabolites inhalation toxicity is of limited relevance.

In the case of R234886 it has to be considered that this metabolite occurs not only in groundwater, but is also generated in mammalian metabolism in a considerable fraction. Therefore, EFSA decided during the Peer Review process for the active substance, that non-relevance of the metabolite R234886 can be demonstrated based on the available data. In the EFSA conclusion on the pesticides peer review of the active substance azoxystrobin, the metabolite R234886 is classified as not relevant for groundwater (see EFSA Journal 2010; 8(4):1542). Furthermore, data from ecotoxicity tests also indicate that R234886 is considerably less toxic to aquatic and soil organisms than the parent azoxystrobin.

10.2.4 STEP 4: Exposure assessment – threshold of concern approach

The potential exposure to R234886 is > 0.75 µg/L but < 10 µg/L. A further assessment in Step 5 is required.

10.2.5 STEP 5: Refined risk assessment

Acute oral toxicity tests in the rat indicate that R234886 does not exhibit greater toxicity than the parent azoxystrobin. Furthermore, the occurrence of R234886 as a rat metabolite in studies with technical azoxystrobin indicates that the toxicity of R234886 can be addressed by data for azoxystrobin. Therefore, the worst-case chronic endpoint for azoxystrobin will be used for the purposes of addressing the risk of R234886 to humans as a result of groundwater contamination. The worst-case NOAEL for azoxystrobin is 18 mg a.s./kg bw/day based on the data from the 2-year rat study (EFSA Journal 2010; 8 (4): 1542). Using this endpoint and a safety factor of 100, an acceptable daily intake (ADI) for R234886 is 0.2 mg/kg bw/day. Therefore, on the basis that exposure through drinking water should not account for more than 10% of the ADI, and assuming an average water intake of 2 L/day by a 60 kg person, the acceptable safe drinking water concentration for R234886 is 0.6 mg/L.

Table 10.2-2: Refined risk assessment – Derivation of acceptable daily intake (ADI)

Metabolite	Chronic Endpoint	Safety Factor	ADI (mg/kg bw/day)
R234886	2-year rat study: 18 mg a.s./kg bw/day	100	0.2 mg/kg bw/day

The maximum predicted groundwater concentration of R234886 following applications of azoxystrobin is

4.73 µg/L. This concentration is over 100-fold lower than the acceptable safe concentration of 0.6 mg/L and equates to <1% of the ADI.

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

Maximum residue in ground water (µg/L)	Water consumption (L/day)	Individual body weight (kg)	TMDI (mg/kg bw/day)	% of ADI
7.57	0.75	5	0.001136	<1%

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

Maximum residue in ground water (µg/L)	Water consumption (L/day)	Individual body weight (kg)	TMDI (mg/kg bw/day)	% of ADI
7.57	1.0	10	0.000311	<1%

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

Maximum residue in ground water (µg/L)	Water consumption (L/day)	Individual body weight (kg)	TMDI (mg/kg bw/day)	% of ADI
7.57	2	60	0.000104	<1%

In conclusion, levels of exposure of R234886 which has the potential to exceed 0.75 µg/L in groundwater at 1m depth, are far below the established ADI and do not present a risk to human health.

10.3 Relevance assessment of the oxathiapiprolin metabolite IN-E8S72

Summary:

The relevance of the groundwater metabolite IN-E8S72 has already been assessed and the assessment agreed at EU level (see **Oxathiapiprolin, EFSA Journal 2016;14(7):4504**), 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). IN-E8S72 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 10.3-1 and the corresponding studies are listed in the corresponding sections.

Table 10.3-1: Summary of the relevance assessment for IN-E8S72

	Assessment step		Result of assessment	
	STEP 1		Metabolite of no concern?	no
Quantification of groundwater contamination	STEP 2		Max PEC _{gw}	3.11 µg/L
			Based on	FOCUS PEARL v4.4.4 / application to cabbage, 2 × 12 g a.s./ha, BBCH 11-49, Hamburg scenario
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;	none
			Classification of parent	none
			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)	Adult: < 0.1 % of ADI ^a Child: < 0.1 % of ADI ^b Infant: < 0.1 % of ADI ^c
			ADI based on	The ADI for IN-E8S72 was derived from the 28-day toxicity studies in the rat study and using a safety factor of 1000. The ADI for IN-E8S72 is 1.157 mg/kg bw/day.

^a ADI utilisation (%) = [PEC_{gw} (µg/L) × water consumption (L/day) × 100] / [bw (kg) × 1000 × ADI (mg/kg bw/day)]

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

^b ADI utilisation (%) = [PEC_{gw} (µg/L) × water consumption (L/day) × 100] / [bw (kg) × 1000 × ADI (mg/kg bw/day)]

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

^c ADI utilisation (%) = [PEC_{gw} (µg/L) × water consumption (L/day) × 100] / [bw (kg) × 1000 × ADI (mg/kg bw/day)]

Calculation of risk (% ADI) for 5-kg adult (consuming 0.75 L/day)

10.3.1 STEP 1: Exclusion of degradation products of no concern

The relevance of the groundwater metabolite **IN-E8S72** has already been assessed and the assessment agreed at EU level. Therefore only summary of the relevance assessment is given in Table 10.3-1.

10.3.2 STEP 2: Quantification of potential groundwater contamination

The relevance of the groundwater metabolite IN-E8S72 has already been assessed and the assessment agreed at EU level. Therefore only summary of the relevance assessment is given in Table 10.3-1.

10.3.3 STEP 3: Hazard assessment – identification of relevant metabolites

10.3.3.1 STEP 3, Stage 1: screening for biological activity

The relevance of the groundwater metabolite **IN-E8S72** has already been assessed and the assessment agreed at EU level. Therefore only summary of the relevance assessment is given in Table 10.3-1.

10.3.3.2 STEP 3, Stage 2: screening for genotoxicity

The relevance of the groundwater metabolite **IN-E8S72** has already been assessed and the assessment agreed at EU level. Therefore ~~only~~ summary of the relevance assessment is given in Table 10.3-1.

The following table summarises the studies conducted with metabolite IN-E8S72, which have been evaluated in the Oxathiapiprolin DAR (**Oxathiapiprolin Volume 3 – Annex B.6 (AS) 2015**).

Table 10.3-2: Summary of the results of toxicity studies for IN-E8S72

Type of test, species (Guideline)	Result	Acceptability	Reference*
Ames test (OECD 471)	Non-genotoxic	Yes	DuPont-35559*
Gene mutation test in mammalian cells	Positive	Yes	DuPont-35560*
<i>In vitro</i> chromosome aberration	Non-genotoxic	Yes	DuPont-35561*
<i>In vivo</i> micronucleus	Non-genotoxic	Yes	DuPont-36720*
28-day feeding study in rats	NOAEL 1157 mg/kg bw/day	Yes	DuPont-35562*

* indicates that a study was reviewed at EU level

10.3.3.3 STEP 3, Stage 3: screening for toxicity

The relevance of the groundwater metabolite **IN-E8S72** has already been assessed and the assessment agreed at EU level. Therefore only summary of the relevance assessment is given in Table 10.3-1.

10.3.4 STEP 4: Exposure assessment – threshold of concern approach

The potential exposure to **IN-E8S72** is > 0.75 µg/L but < 10 µg/L. A further assessment in Step 5 is required.

10.3.5 STEP 5: Refined risk assessment

Table 10.3-3: Refined risk assessment – Derivation of acceptable daily intake (ADI)

Metabolite	Chronic Endpoint ^a	Safety Factor	ADI (mg/kg bw/day)
IN-E8S72	28-day toxicity rat study: 1157 mg a.s./kg bw/day	1000	1.157 mg a.s./kg bw/day

^a according to EFSA (2016)

The maximum predicted groundwater concentration of IN-E8S72 following applications of oxathiapiprolin is 3.11 µg/L. This concentration is over 1000-fold lower than the acceptable safe concentration of 3.5 mg/L and equates to <1% of the ADI.

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

Maximum residue in ground water (µg/L)	Water consumption (L/day)	Individual body weight (kg)	TMDI (mg/kg bw/day)	% of ADI
3.11	0.75	5	0.0004665	<1%

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

Maximum residue in ground water (µg/L)	Water consumption (L/day)	Individual body weight (kg)	TMDI (mg/kg bw/day)	% of ADI
3.11	1.0	10	0.000311	<1%

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

Maximum residue in ground water (µg/L)	Water consumption (L/day)	Individual body weight (kg)	TMDI (mg/kg bw/day)	% of ADI
3.11	2	60	0.0000104	<1%

In conclusion, levels of exposure of IN-E8S72 which has the potential to exceed 0.75 µg/L in groundwater at 1m depth, are far below the established ADI and do not present a risk to human health.

Appendix 1 Lists of data considered in support of the evaluation

List of data submitted by the applicant and relied on

Please refer to Part B Sections 6 and 8.

Appendix 2 Additional information

No new studies are submitted.