REGISTRATION REPORT

Part B

Section 10

Assessment of the relevance of metabolites in groundwater

Detailed summary of the risk assessment

Product code: A23109A

Product name: ORONDIS VIP

Chemical active substance:

Metalaxyl-M, 174.4 g/L
Oxathiapiprolin 30.0 g/L

Interzonal

Zonal Rapporteur Member State: Poland

CORE ASSESSMENT

(New authorisation)

Applicant: Syngenta

Submission date: June 2022

MS Finalisation date: March 2023 (initial Core Assessment)

November 2023 (final Core Assessment)

Version history

When	What
June 2022	Applicant submission
March 2023	Initial assessment by the zRMS 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.
November 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. Not agreed or not relevant information are ~~struck through~~ and shaded for transparency.

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Reviewer summary:

This part of dossier has been submitted to support registration of the plant protection product ORONDIS VIP (product code A23109A a dispersible concentrate (DC) containing 174.4 g/L metalaxyl-M and 30 g/L oxathiapiprolin) 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 and appropriate for concluding

1) Notifier submit additional genotoxicity studies to evaluate (for details refer dRR Section B6 point A 2.11) clastogenic and aneugenic potential of CGA62826 (A 2.11.1); NOA409045 (A 2.11.2); Metalaxyl-M (A 2.11.3); CGA226048(A 2.11.4). Studies outcome allow to conclude that there was no evidence of clastogenicity nor aneugenicity of the tested substance.

- Metalaxyl-M ground water metabolites which was predicted to occur in groundwater at concentrations above 0.1 µg/L (refer Table 10.1 1) SYN546520 and CGA67868 was found to be toxicologically non-relevant up to stage 3 of step 3 according the GD on the assessment of the relevance of metabolites (for details refer *EFSA 2015. Conclusion on the peer review of the pesticide risk assessment of the active substance metalaxyl-M. EFSA Journal 2015;13(3):3999*)

- Metalaxyl-M ground water metabolite NOA409045 was found to be toxicologically relevant due to the positive results obtained in an *in vitro* clastogenic, however in the follow-up *in vivo* test Dunton, J (2015) *NOA409045 – Oral (Gavage) Mouse Micronucleus Test* it was observed that there was no evidence of clastogenicity or aneugenicity following oral (gavage) administration of NOA409045 up to the regulatory test guideline maximum dose level of 2000 mg/kg/day in male mice. Therefore, NOA409045 is considered to be neither clastogenic nor aneugenic in the mouse bone marrow micronucleus assay. (for details refer dRR Section B6 point A 2.11.2). Note: The relevance of the groundwater metabolite NOA409045 was already assessed at EU level by the Metalaxyl-M zRMS Belgium (co-RMS Greece) under Article 7 and an updated RAR has been made available for commenting at MS level in May 2021. The updated RAR concluded that the groundwater metabolite NOA409045 is considered not relevant according to the criteria laid down in the EC guidance document SANCO/221/2000 –rev.11.

2) Regarding oxathiapiprolin ground water metabolite IN-E8S72 which was predicted to occur in groundwater at concentrations above 0.1 µg/L it 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*).

10 Relevance of metabolites in groundwater

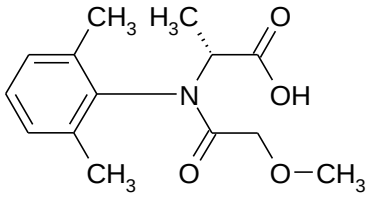
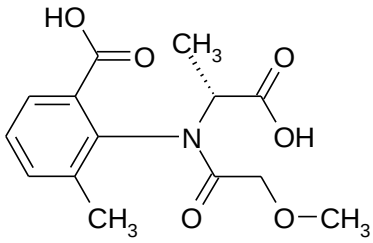
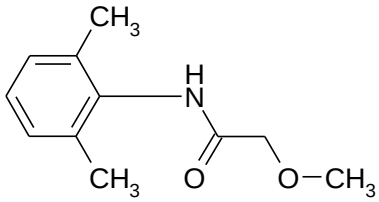
10.1 General information

The PEC_{GW} of the metalaxyl-M metabolites NOA409045, SYN546520 and CGA67868 are predicted to occur in groundwater at concentrations above 0.1 µg/L (see A23109A 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.11 is therefore required.

The PEC_{GW} of the oxathiapiprolin metabolites IN-RDT31, IN-RAB06 and IN-QPS10 were < 0.1 µg/L in the relevant application patterns (please see A23109A, 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 µg/L (see please see A23109A, Part B, Section 8.8.2). 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.

General information on the metabolites is 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 chapter 8.1 of the dRR Part B, Section 8 (environmental fate and behaviour).

Table 10.1-1: General information on the metabolite

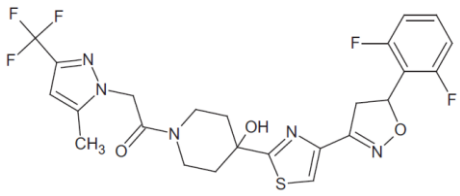
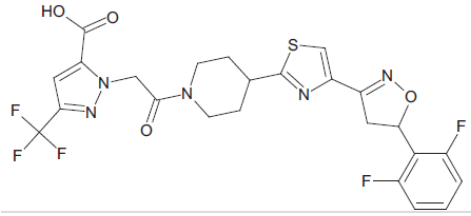
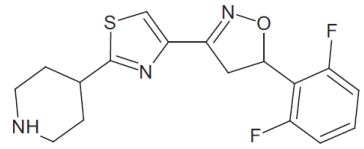
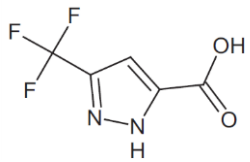
Name of active substance	Metabolite name and code	Structural/molecular formula	Trigger for relevance assessment	
Metalaxyl-M	(R)-2-[(2,6-Dimethyl-phenyl)- methoxyacetyl-amino]-propionic acid NOA409045		Max PEC_{GW} Based on:	~~6.666 µg/L Modelling result using FOCUS PEARL v5.5.5 / Cabbage 2 x 87.2 g a.s./ha. One application in each of two crop cycles, BBCH 12, Hamburg scenario in CEU.~~ 9.163 µg/L Modelling result using FOCUS PEARL v5.5.5 / Cabbage 2 x 87.2 g a.s./ha. Second crop cycle, BBCH 12, Hamburg scenario in CEU.
Metalaxyl-M	2-[(1-Carboxy-ethyl)-(2-methoxy-acetyl)- amino]-3-methyl-benzoic acid SYN546520		Max PEC_{GW} Based on:	Tier 1: 19.099 µg/L Tier 2: 4.149 µg/L Modelling result using FOCUS PEARL v5.5.5 / Cabbage 2 x 87.2 g a.s./ha. Two applications in one crop cycle, BBCH 12, Jokioinen scenario in SEU.
Metalaxyl-M	N-(2,6-Dimethyl-phenyl)-2-methoxy-acetamide CGA67868		Max PEC_{GW} Based on:	~~0.194 µg/L Modelling result using FOCUS PEARL v5.5.5 / Cabbage 2 x 87.2 g a.s./ha BBCH 12, One application in each of two crop cycles, BBCH 12, Hamburg scenario, CEU.~~ 0.267 µg/L Modelling result using FOCUS PEARL v5.5.5 / Cabbage 2 x 87.2 g a.s./ha. Second crop cycle, BBCH 12, Hamburg scenario, CEU.

The codenames for R-enantiomer parent metalaxyl-M and respective metabolites, and racemic parent metalaxyl and its metabolites are given below.

Enantiomer composition	Parent	Acid metabolite	Diacid metabolite	Amide metabolite
R-enantiomer	Metalaxyl-M, CGA329351	NOA409045	SYN546520	CGA67868[a]
Racemate (R/S)	Metalaxyl, CGA48988	CGA62826	CGA108906[b]	CGA67868[a]

[a] Non-chiral CGA67868 is formed from both metalaxyl-M and metalaxyl
[b] CGA108906 was used historically as a reference material in metalaxyl-M dosed studies. More recently the R-enantiomer SYN546520 was synthesised and utilized in sorption and rate of degradation studies

Table 10.1-2: General information on the oxathiapiprolin metabolites

Name of active substance	Metabolite name and code	Structural/molecular formula	Trigger for relevance assessment	
Oxathiapiprolin	IN-RDT31		Max PEC_{gw} Based on:	< 0.001 µg/L All models and all scenarios
Oxathiapiprolin	IN-RAB06		Max PEC_{gw} Based on:	< 0.001 µg/L All models and all scenarios
Oxathiapiprolin	IN-QPS10		Max PEC_{gw} Based on:	< 0.001 µg/L All models and all scenarios
Oxathiapiprolin	IN-E8S72		Max PEC_{gw} Based on:	~~1.939 µg/L Modelling result using FOCUS PEARL v5.5.5 / Cabbage 2 x 15 g a.s./ha BBCH 12, One application in each of two crop cycles, BBCH 12, Hamburg scenario, SEU.~~ 1.941 µg/L Modelling result using FOCUS PEARL v5.5.5 / Cabbage 2 x 15 g a.s./ha BBCH 12, Second crop cycle, BBCH 12, Hamburg scenario, SEU

10.2 Relevance assessment of metalaxyl-M metabolite NOA409045

Summary:

NOA409045 was designated as relevant in the review report (SANTE/11112/2019) based on the '*high potential to exceed the parametric drinking water limit of 0.1 µg/L in groundwater as represented by the 80th percentile annual average concentration moving below 1m depth, in geoclimatic situations represented by 20 out of 21 crop FOCUS scenario combinations for the representative uses assessed*'.

During the A1R review process a data gap was identified with regards to the clastogenic potential of NOA409045 (R enantiomer). An *in vitro* cytogenicity study (for chromosome aberration) was performed with NOA409045 (test material was 91% NOA409045 & 8% NOA436575 (S enantiomer)). The study was positive. As a result of this study the Metalaxyl-M EFSA Conclusions (**EFSA Journal 2015; 13(3):3999**) concluded that NOA409045 was considered toxicologically relevant due to positive results obtained in an *in vitro* clastogenicity test.

Syngenta needed to synthesise NOA409045 material for *in vivo* testing. Questions were also raised as to whether the positive result *in vitro* on 91% NOA409045 could have been caused by the 8% S enantiomer. Whilst waiting for the synthesis of a purer batch of NOA409045 an *in vivo* mouse micronucleus assay was conducted with CGA62826 (containing 50% NOA436575(S) and 50% NOA409045(R)) and a negative result was obtained. Thus demonstrating a higher concentration of NOA436575(S) in the test material did not give a positive result *in vivo*. In addition, as soon as a purer sample of NOA409045 (97% purity) was available for testing, an *in vivo* mouse micronucleus study was conducted and also reported negative for clastogenicity and aneugenicity. Overall, *in vivo* mouse micronucleus assays for CGA62826 and NOA409045 were performed and were found to be negative, thus overriding the positive *in vitro* cytogenicity study (for chromosome aberration).

For other endpoints data on the racemic mix, CGA62826 is relied upon to support the relevant enantiomer NOA409045 (R enantiomer) as is the case for the parent molecule, Metalaxyl-M (R enantiomer) and Metalaxyl (racemic mix). However, conservatively, where an endpoint has been derived for risk assessment the study endpoint has been corrected for exposure to the R enantiomer only.

With the available *in vivo* mouse micronucleus assays, the groundwater metabolite NOA409045 is therefore not considered as relevant according to the criteria laid down in the EC guidance document SANCO/221/2000 –rev.11. A summary of the relevance assessment for NOA409045 is given in Table 10.2-1:
. Studies supporting PEC_{GW} data are evaluated in Section 8 (Environmental fate and behaviour), the genotoxicity studies are evaluated in Part B, Section 6.

The relevance of the groundwater metabolite NOA409045 was already assessed at EU level by the Metalaxyl-M zRMS Belgium (co-RMS Greece) under Article 7 and an updated RAR has been made available for commenting at MS level in May 2021. The updated RAR concluded that the ground-water metabolite NOA409045 is considered not relevant according to the criteria laid down in the EC guidance document SANCO/221/2000 –rev.11.

Table 10.2-1: Summary of the relevance assessment for NOA409045

	Assessment step		Result of assessment	
	STEP 1		Metabolite of no concern?	No
Quantification of groundwater contamination	STEP 2		Max PEC_{GW}	~~6.660~~ 9.163 µg/L
			Based on	Modelling result using FOCUS PEARL v5.5.5 / Cabbage 2 x 87.2 g a.s./ha One application in each of two crop cycles, BBCH 12, Hamburg scenario (Chapter 8.8.2, Part B Section 8)
Hazard assessment	STEP 3	Stage 1	Biological activity comparable to the parent?	No
		Stage 2	Genotoxic properties of metabolites CGA62826 and NOA409045	Non-genotoxic, confirmed in *in vivo* micronucleus assays with both

				CGA62826 and NOA409045
		Stage 3	Toxic properties of metabolite (CGA62826)	Acute oral tox >2000 mg/kg Acute dermal tox >2000 mg/kg 28 day (gavage): NOAEL = 1000 mg/kg/day
			Classification of parent	H302 H318
			Classification of metabolite	Less toxic than the parent compound. No classification for reproductive toxicity or carcinogenic properties
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 infant)	0.27%
			ADI based on	0.5 mg/kg bw/day (28 day sub-chronic (oral), NOAEL = 1000 mg/kg bw/day

10.2.1 STEP 1: Exclusion of degradation products of no concern

NOA409045 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 it is not:

- CO_2 or an inorganic compound, not containing a heavy metal;
- an organic compound of aliphatic structure, with a chain length of four 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 NOA409045 were performed (see Part B, Section 8, chapter 8.8). The scenario for which concentrations of NOA409045 showed the highest PEC_{GW} exceeding 0.1 µg/L is listed in Table 10.2-1: . Details are given in Part B, Section 8, chapter 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 biological activity of CGA62826, a racemate of NOA409045 has been assessed for fungal targets by Nuninger and Zeun (1999), study previously EU reviewed.

Metalaxyl and metalaxyl-M are equivalent in terms of toxicity and therefore it is appropriate that the activity of NOA409045 can be deduced from the studies performed with the racemate CGA62826.

From these studies it can be concluded that the fungicidal activity of NOA409045 is less than 20% of the activity of the parent molecule. NOA409045 is therefore considered not to be biologically active.

10.2.3.2 STEP 3, Stage 2: screening for genotoxicity

CGA62826 (racemate of NOA409045) was screened for genotoxic activity by the studies listed in Ta-

ble 10.2-2 below. All studies, except Dunton (2014, 2015), have been previously reviewed under Regulation (EC) No 91/414. From these studies, it can be concluded that NOA409045 is not genotoxic *in vitro* or *in vivo*.
The Dunton studies have not been previously reviewed and full summaries are provided in Part B Section 6, Appendix 2 (Other/Special Studies) of this submission.

Table 10.2-2: Summary of genotoxicity studies with CGA62826 and NOA409045

Study	Result	Details	Reference
Ames Test *S.typhimurium* and *E.coli* (CGA62826)	Not genotoxic	*S.typhimurium* TA1535, TA1537, TA98, TA100, TA 102; *E.coli* WP2uvrA, WP2 pKM 101 312.5-5000 µg/plate	Deparade (1997)[a]
In Vitro Chromosome Aberration Test in Human Lymphocytes (NOA409045)	Genotoxic	In cultured human lymphocytes, -S9/+S9 951.8-2915 µg/ml	Bohnenberger (2014)[a]
Gene mutation in mammalian Cells (CGA62826)	Not genotoxic	Mouse lymphoma L5178Y TK+, -S9/+S9, 125-2652 µg/ml	Clay (2006)[a]
Oral Gavage Mouse Micronucleus test with CGA62826	Not genotoxic	Mouse micronucleus cells treated at 500, 1000 and 2000 mg/kg/day CGA62826 Proof of exposure demonstrated	Dunton (2014)[a] New data – see Section B6 for details
Oral Gavage Mouse Micronucleus test with NOA409045	Not genotoxic	Mouse micronucleus cells treated at 500, 1000 and 2000 mg/kg/day NOA409045 Proof of exposure demonstrated	Dunton (2015)[a] New data – see Section B6 for details

[a] Indicates that a study was reviewed at EU level

NOA409045 is considered not relevant in this step of the assessment and it is considered further in Step 3, Stage 3.

10.2.3.3 STEP 3, Stage 3: screening for toxicity

The parent compound metalaxyl-M is not classified as acutely or chronically toxic or very toxic and it is neither classified for reproductive toxicity nor as a carcinogen in category T or T+, R60, R61, R62, R63, R45 or R40 (or corresponding classification in accordance with CLP 1272/2008). Metalaxyl-M is classified for health effects in accordance with CLP 1272/2008 for:

- Acute toxicity, Category 4, H302 (“harmful if swallowed”)
- Eye damage, Category 1, H318 (“Causes serious eye damage”)

Acute oral and dermal toxicity tests, in addition to a 28-day oral gavage test on rats have been performed with CGA62826 (see Table 10.2-3). Comparison of the toxicological potency of CGA62826 with that of parent metalaxyl-M shows that it has less toxicity potential than the parent and is therefore not toxicologically relevant. It is considered that the same judgement will apply to NOA409045 based on the structural similarities.

Table 10.2-3: Summary of evaluation of the toxicity studies for CGA62826

Study	Result	Reference
Rat acute oral toxicity	LD_{50} >2000 mg/kg bw	Winkler (1996)[a]
Rat acute dermal toxicity	LD_{50} >2000 mg/kg bw	Winkler (1996a)[a]
Rat 28 day oral gavage	NOAEL = 1000 mg/kg/day No ‘adverse’ effects at top dose (limit dose)	Fankhauser (1997)[a]

[a] Indicates that a study was reviewed at EU level.

NOA409045 is considered not relevant and is further evaluated in Step 4. The toxicity studies are evaluated in Part B, Section 6, studies referenced in Chapter 6.4.

10.2.4 STEP 4: Exposure assessment – threshold of concern approach

Step 4 and 5 are required for metabolites not identified as relevant in the hazard assessment of Step 3, in order to make sure that any contamination of groundwater will not lead to unacceptable exposure of consumers via drinking water.

The potential exposure to NOA409045 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

NOA409045 has a PEC_{GW} between 0.75 µg/L and 10 µg/L. A refined assessment of the potential toxicological significance including the selected ADI is presented here.

The consumer risk assessment demonstrates an acceptable risk. NOA409045 is not part of the residue definition for food commodities, i.e., consumers are only potentially exposed via drinking water. The estimated safety margin including potential exposure via other routes besides drinking water for NOA409045 are 0.27 % of ADI (infant), 0.18 % of ADI (child), <0.1 % of ADI (adult). Derivation of ADI is presented in Table 10.2 4.

Assuming that toxicity observed in racemic metalaxyl dosed studies (50:50 R/S mixture) is fully attributed to the biologically active R isomer, toxicity could reasonably be expected to be a factor of 2 higher when based on pure R-enantiomer metalaxyl-M exposure. Otherwise, if toxicity from racemic dosed studies is attributed to both R and S isomers, use of metalaxyl racemic studies to assess R-enantiomer metalaxyl-M exposure is alternatively considered to be a worst case. The same assumptions will therefore apply to the metabolites of metalaxyl and metalaxyl-M; therefore, a safety factor of 2000 is applied.

Table 10.2-4: Refined risk assessment – Derivation of acceptable daily intake (ADI)

Metabolite	Toxicity studies	SF	ADI
NOA409045	28 day subchronic (oral) NOAEL = 1000 mg/kg bw/day	2000*	0.5 mg/kg bw/day

* - 100 fold inter & intraspecies safety factor & additional 10 fold safety factor for extrapolation to chronic exposure & additional 2 fold safety factor for NOA409045 content in the test material administered (CGA62826)

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
~~6.666~~ 9.163	0.75	5	0.001000	0.27%

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
~~6.666~~ 9.163	1.0	10	0.000667	0.18%

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
~~6.666~~ 9.163	2	60	0.000222	<0.1%

10.3 Relevance assessment of the metalaxyl-M metabolite SYN546520

Summary:

The relevance of the groundwater metabolite SYN546520 has already been assessed and the assessment agreed at EU level (see **EFSA Journal 2015; 13(3):3999**), 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). SYN546520 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 10.3-1 and the corresponding studies are listed in the corresponding sections. EFSA (2015) stated that SYN546520 was considered non-relevant, as it is not expected to be more toxic than the parent metalaxyl-M and therefore the reference values of the parent would be applicable to this metabolite to perform an exposure assessment.

Table 10.3-1: Summary of the relevance assessment for SYN546520

	Assessment step		Result of assessment	
	STEP 1		Metabolite of no concern?	No
Quantification of groundwater contamination	STEP 2		Max PEC_{GW}	Tier 1: 19.099 µg/L Tier 2: 4.149 µg/L
			Based on	Modelling result using FOCUS PEARL v5.5.5 / Cabbage 2 x 87.2 g a.s./ha. Two applications in one crop cycle, BBCH 12, Jokioinen scenario in SEU. (Chapter 8.8.2, Part B Section 8)
Hazard assessment	STEP 3	Stage 1	Biological activity comparable to the parent?	No
		Stage 2	Genotoxic properties of metabolite (CGA108906)	Non-genotoxic
		Stage 3	Toxic properties of metabolite (CGA108906)	Acute oral tox >2000 mg/kg Acute dermal tox >2000 mg/kg 28 day (gavage): NOAEL = 200 mg/kg/day
			Classification of parent	H302 H318
			Classification of metabolite	No classification for reproductive toxicity or carcinogenic properties
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 infant)	2.9%, Tier 1 0.6%, Tier 2
			#ADI based on	0.1 mg/kg bw/day (28 day sub-chronic (oral), NOAEL = 1000 mg/kg bw/day

[#] - 100 fold inter & intraspecies safety factor & additional 10 fold safety factor for extrapolation to chronic exposure & additional 2 fold safety factor for SYN546520 content in the test material

10.3.1 STEP 1: Exclusion of degradation products of no concern

SYN546520 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 it is not:

- CO_2 or an inorganic compound, not containing a heavy metal;
- an organic compound of aliphatic structure, with a chain length of four 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.

10.3.2 STEP 2: Quantification of potential groundwater contamination

PEC_{GW} calculations after leaching from soil for SYN546520 were performed (see Part B, Section 8, chapter 8.8). The scenario for which concentrations of SYN546520 showed the highest PEC_{GW} exceeding 0.1 µg/L are listed in Table 10.3-1. Details are given in Part B, Section 8, chapter 8.8.

10.3.3 STEP 3: Hazard assessment – identification of relevant metabolites

10.3.3.1 STEP 3, Stage 1: screening for biological activity

The biological activity of CGA108906 (racemate of SYN546520) has been assessed for fungal targets by Nuninger and Zeun (1999), study previously EU reviewed.

Metalaxyl and metalaxyl-M are equivalent in terms of toxicity and therefore it is appropriate that the activity of SYN546520 can be deduced from the studies performed with the racemate CGA108906.

From these studies it can be concluded that the fungicidal activity of SYN546520 is less than 20% of the activity of the parent molecule. SYN546520 is therefore considered not to be biologically active.

10.3.3.2 STEP 3, Stage 2: screening for genotoxicity

CGA108906 (racemate of SYN546520) was screened for genotoxic activity by the following data package of *in vitro* genotoxicity studies: Ames test and gene mutation test with mammalian cells. CGA108906 was non- genotoxic as shown by a negative Ames test and negative gene mutation test with mammalian cells. SYN546520 is considered not relevant and is further evaluated in Stage 3. The genotoxicity studies are evaluated in Part B, Section 6, studies referenced in Chapter 6.4.

CGA108906 (racemate of SYN546520) was screened for genotoxic activity by the studies listed in Table 10.3-2 below. All studies have been previously reviewed under Regulation (EC) No 91/414. From these studies, it can be concluded that SYN546520 is not genotoxic *in vitro* or *in vivo*. Hence, SYN546520 is considered not relevant in this step of the assessment and it is considered further in Step 3, Stage 3.

Table 10.3-2: Summary of evaluation of the genotoxicity studies for SYN546520

Study	Result	Details	Reference
Ames Test *S.typhimurium* and *E.coli*	Not genotoxic	*S.typhimurium* TA1535, TA1537, TA98, TA100, TA 102; *E.coli* WP2uvrA	Ogorek (1997)[a]
In vitro cytogenetic test,	Not genotoxic	Chinese hamster V79 cells, -	Czich (2001)[a]

Study	Result	Details	Reference
Chinese hamster V79 cells		S9/+S9 750-3000 µg/ml	
In vitro cytogenetic test, Chinese hamster V79 cells	Not genotoxic	Chinese hamster V79 cells, -S9: 37-1200 µg/ml +S9: 55-2000 µg/ml	Deparade (1998)[a]
Gene mutation in mammalian Cells, Mouse lymphoma L5178Y	Not genotoxic	Mouse lymphoma L5178Y TK+, -S9/ +S9 500-2953 mg/ml	Clay (2001)[a]

[a] Indicates that a study was reviewed at EU level.

10.3.3.3 STEP 3, Stage 3: screening for toxicity

The parent compound metalaxyl-M is not classified as acutely or chronically toxic or very toxic and it is neither classified for reproductive toxicity nor as a carcinogen in category T or T+, R60, R61, R62, R63, R45 or R40 (or corresponding classification in accordance with CLP 1272/2008). Metalaxyl-M is classified for health effects in accordance with CLP 1272/2008 for:

- Acute toxicity, Category 4, H302 ("harmful if swallowed")
- Eye damage, Category 1, H318 ("Causes serious eye damage")

Toxicity studies have been performed for CGA108906, the racemate of SYN546520 (see Table 10.3-3). Comparison of the toxicological potency of CGA108906 with that of parent metalaxyl-M shows that it has less toxicity potential than the parent and is therefore not toxicologically relevant. It is considered that the same judgement will apply to SYN546520 based on the structural similarities.

Table 10.3-3: Summary of evaluation of the toxicity studies for SYN546520

Study	Result	Reference
Rat acute oral toxicity	LD_{50} > 2000 mg/kg bw	Hartmann (1994)[a]
Rat acute dermal toxicity	LD_{50} > 2000 mg/kg bw	Winkler (1996b)[a]
Rat 28 day oral gavage	NOAEL=1000 mg/kg/day (Increased heart rate in males and changes urine parameters for both sexes at top dose of 1000 mg/kg.	Gerspach (1997)[a]

[a] Indicates that a study was reviewed at EU level.

SYN546520 is considered not relevant in this step of the assessment and it is considered further in Step 4. The toxicity studies are evaluated in Part B, Section 6, studies referenced in Chapter 6.4.

10.3.4 STEP 4: Exposure assessment – threshold of concern approach

Step 4 and 5 are required for metabolites not identified as relevant in the hazard assessment of Step 3, in order to make sure that any contamination of groundwater will not lead to unacceptable exposure of consumers via drinking water.

The potential exposure to SYN546520 is >10 µg/L at Tier 1. The potential exposure to SYN546520 is >0.75 µg/L but <10 µg/L at Tier 2. A further assessment in Step 5 is required.

10.3.5 STEP 5: Refined risk assessment

SYN546520 Tier 1 has a PEC_{GW} >10 µg/L. As a higher Tier 2 PEC is available, the calculation of risk for both Tier 1 and Tier 2 are assessed. SYN546520 Tier 2 has a PEC_{GW} between 0.75 µg/L and 10 µg/L. A refined assessment of the potential toxicological significance including the selected ADI is presented here.

The consumer risk assessment demonstrates an acceptable risk. CGA108906 is not part of the residue definition for food commodities, i.e., consumers are only poten-tially exposed via drinking water. The The estimated safety margin including potential exposure via other routes besides drinking water for Tier 2 SYN546520 are 0.6 % of ADI (infant), 0.4 % of ADI (child), 0.1 % of ADI (adult). Derivation of ADI

is presented in Table 10.3-4.

Assuming that toxicity observed in racemic metalaxyl dosed studies (50:50 R/S mixture) is fully attributed to the biologically active R isomer, toxicity could reasonably be expected to be a factor of 2 higher when based on pure R-enantiomer metalaxyl-M exposure. Otherwise if toxicity from racemic dosed studies is attributed to both R and S isomers, use of metalaxyl racemic studies to assess R-enantiomer metalaxyl-M exposure is alternatively considered to be a worst case. The same assumptions will therefore apply to the metabolites of metalaxyl and metalaxyl-M; therefore a safety factor of 2000 is applied.

Table 10.3-4: Refined risk assessment – Derivation of acceptable daily intake (ADI)

Metabolite	Toxicity studies	SF	ADI
CGA108906	28 day subchronic (oral) NOAEL=1000 mg/kg bw/day	2000*	0.1 mg/kg bw/day

* 100 fold inter & intraspecies safety factor & additional 10 fold safety factor for extrapolation to chronic exposure & additional 2 fold safety factor for SYN546520 content in the test material

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
19.099, Tier 1	0.75	5	0.002865	2.9%
4.149, Tier 2	0.75	5	0.000622	0.6%

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
19.099, Tier 1	1.0	10	0.001910	1.9%
4.149, Tier 2	1.0	10	0.000415	0.4%

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
19.099, Tier 1	2	60	0.000637	0.6%
4.149, Tier 2	2	60	0.000138	0.1%

In conclusion, Tier 2 levels of exposure of SYN546520 which have 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.
In addition to the toxicology data, studies of biological activity show that the metabolite does not present an environmental or human health risk.

10.4 Relevance assessment of the metalaxyl-M metabolite CGA67868

Summary:

The relevance of the groundwater metabolite CGA67868 has already been assessed and the assessment agreed at EU level (see **EFSA Journal 2015; 13(3):3999**), 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 3 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). CGA67868 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 10.4-1 and the corresponding studies are listed in the corresponding sections.

Table 10.4-1: Summary of the relevance assessment for CGA67868

	Assessment step		Result of assessment	
	STEP 1		Metabolite of no concern?	No
Quantification of groundwater contamination	STEP 2		Max PEC_{GW}	~~0.194~~ 0.267 µg/L
			Based on	Modelling result using FOCUS PEARL v5.5.5 / Cabbage 2 x 87.2 g a.s./ha BBCH 12, One applications in each of two crop cycles, BBCH 12, Hamburg scenario in CEU. (Chapter 8.8.2, Part B Section 8)
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	NA
			Classification of parent	H302 H318
			Classification of metabolite	No classification for reproductive toxicity or carcinogenic properties
Consumer health risk assessment	STEP 4		Estimated consumer exposure via drinking water and other sources; threshold of concern approach	Acceptable (<0.75µg/L)
	STEP 5		Refined risk assessment	NA
			Predicted exposure (% of ADI)	NA
			ADI based on	NA

NA: not applicable

10.4.1 STEP 1: Exclusion of degradation products of no concern

CGA67868 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 it is not:

- CO_2 or an inorganic compound, not containing a heavy metal;
- an organic compound of aliphatic structure, with a chain length of four 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.

10.4.2 STEP 2: Quantification of potential groundwater contamination

PEC_{GW} calculations after leaching from soil for CGA67868 were performed (see Part B, Section 8, chapter 8.8). The scenario for which concentrations of CGA67868 showed the highest PEC_{GW} exceeding 0.1 µg/L are listed in Table 10.4-1. Details are given in Part B, Section 8, chapter 8.8.

10.4.3 STEP 3: Hazard assessment – identification of relevant metabolites

10.4.3.1 STEP 3, Stage 1: screening for biological activity

The biological activity of CGA67868 has been assessed for fungal targets by Oostendrop (2012), study previously EU reviewed.

From this study it can be concluded that the fungicidal activity of CGA67868 is less than 10% of the activity of the parent molecule. CGA67868 is therefore considered not to be biologically active.

10.4.3.2 STEP 3, Stage 2: screening for genotoxicity

CGA67868 (synonymous to CGA92370, which was tested) was screened for genotoxic activity by the following data package of *in vitro* genotoxicity studies (see Table 10.4-2): Reverse mutation assay, gene mutation with mammalian cells and chromosome aberration test. CGA92370 was non-genotoxic as shown by a negative reverse mutation assay, negative gene mutation test with mammalian cells and negative chromosome aberration test. CGA92370 was considered not relevant and is further evaluated in Stage 3. The genotoxicity studies are evaluated in Part B, Section 6, studies referenced in Chapter 6.4.

Table 10.4-2: Summary of evaluation of the genotoxicity studies for CGA67868

Study	Result	Details	Reference
Reverse Mutation Assay Test *S.typhimurium* and *E.coli*	Not genotoxic	*S.typhimurium* TA1535, TA1537, TA98, TA100, *E.coli* WP2uvrA	Sokolowski (2012)[a]
Gene mutation in mammalian Cells, Mouse lymphoma L5178Y	Not genotoxic	Mouse lymphoma L5178Y TK+, -S9/ +S9 125-2000 µ/ml	Wollny (2012)[a]
Chromosome Aberration Test in Human Lymphocytes	Not genotoxic	In cultured human lymphocytes, -S9/+S9 1932 µg/ml	Bohnenberger (2012)[a]

[a] Indicates that a study was reviewed at EU level.

10.4.3.3 STEP 3, Stage 3: screening for toxicity

The parent compound metalaxyl-M is not classified as acutely or chronically toxic or very toxic and it is neither classified for reproductive toxicity nor as a carcinogen in category T or T+, R60, R61, R62, R63, R45 or R40 (or corresponding classification in accordance with CLP 1272/2008). Metalaxyl-M is classified for health effects in accordance with CLP 1272/2008 for:

- Acute toxicity, Category 4, H302 (“harmful if swallowed”)
- Eye damage, Category 1, H318 (“Causes serious eye damage”)

Since parent compound metalaxyl-M is not classified as acutely or chronically toxic or very toxic, no further toxicity studies are triggered under SANCO/10597/2003 –rev. 10.1, 2012.

10.4.4 STEP 4: Exposure assessment – threshold of concern approach

The potential exposure to CGA67868 is <0.75 µg/L, therefore further assessment is not required.

10.5 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.11. A summary of the relevance assessment is given in Table 10.5-1.

Table 10.5-1: 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}	1.941~~29~~ µg/L
			Based on	Modelling result using FOCUS PEARL v5.5.5 / Cabbage 2 x 15 g a.s./ha. One application in each of two crop cycles, BBCH 12, Hamburg scenario in SEU. (Chapter 8.8.2, Part B Section 8)
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 infant)	<0.1 %
			ADI based on	The ADI for IN-E8S72was 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.

10.5.1 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 10.5-1.

10.5.2 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 10.5-1.

10.5.3 STEP 3: Hazard assessment – identification of relevant metabolites

10.5.3.1 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 10.5-1.

10.5.3.2 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 10.5-1.

10.5.3.3 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 10.5-1.

10.5.4 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.

10.5.5 STEP 5: Refined risk assessment

The relevance of the groundwater metabolite IN-E8S72 has already been assessed and the assessment agreed at EU level. The consumer risk assessment demonstrates an acceptable risk. The estimated safety margin including potential exposure via other routes besides drinking water for IN-E8S72 are <0.1 % of ADI (infant, child or adult). Derivation of ADI is presented in Table 10.5-2.

Table 10.5-2: 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)

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
1.941	0.75	5	0.000291	<0.1 %

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
1.941	1.0	10	0.000194	<0.1 %

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
1.941	2	60	0.000065	<0.1 %

In conclusion, levels of exposure of IN-E8S72 which has the potential to exceed 0.75 µg/L in groundwater at 1 m 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

Please refer to Part B Sections 6 and 8.

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
-	-	-	-	-	-

Appendix 2 Additional information

Not required.