DRAFT REGISTRATION REPORT

Part B

Section 10

Assessment of the relevance of metabolites in groundwater

Detailed summary of the risk assessment

Product code: A9873C

Product name(s): Wakil XL

Wakil 325

Chemical active substances:

Cymoxanil, 100 g/kg

Fludioxonil, 50 g/kg

Metalaxyl-M, 169.6 g/kg

~~Interzonal~~

~~Zonal Rapporteur Member State: France~~

Great Britain (GB)

~~CORE~~ NATIONAL ASSESSMENT

~~(Renewal of authorisation)~~

Submitted to support Article 7 amendment of approval of Metalaxyl-M in GB

Applicant: Syngenta

Submission date: 21/10/2021

MS Finalisation date: 31/01/2024

Version history

When	What
October 2021	Applicant submission to support amendment of approval under Article 7 of retained Regulation (EC) No 1107/2009
December 2023	HSE (GB) assessment added in green boxes

This is an application from Syngenta for the renewal of WAKIL XL /WAKIL 325 (A9873C) under Article 43 of Regulation (EC) No. 1107/2009 following the renewal of EU approval of the active substance Metalaxyl-M.

No equivalence assessment is required.

This application follows the data requirements for the active substance laid down in Regulation (EU) No. 544/2011 and the data requirements for the plant protection product laid down in Regulation (EU) No. 545/2011, also called 'old' data requirements. Metalaxyl-M is an 'AIR-2' substance which approval has been renewed in accordance with Regulation (EU) No 1141/2010, therefore Regulations (EU) No 283/2013 and (EU) No 284/2013 are not applicable to the renewal of authorizations for Metalaxyl-M-containing plant protection products (derogation by Commission Regulation (EU) No 2015/1475; further details in the guidance document SANTE/11509/2013 rev. 5.2).

Following the renewal of EU approval of the active substance Metalaxyl-M, the submission for the product renewal of WAKIL XL /WAKIL 325 (A9873C) was made by 01 September 2020, in accordance with Article 43 of Regulation (EC) No 1107/2009.
All data relied on are provided with this application. The reference lists at Appendix 1 of dRR Part B Sections 1-10 define the data owner and data access. Data protection is a national concern and is addressed in Part A, Appendix 4.

The guidance on Renewal of Authorization according to Art 43 (SANCO/2010/13170 rev 14) requests that within the dRR 'changes to the risk assessment are highlighted'. This is the first submission of WAKIL XL / WAKIL 325 (A9873C) in the dRR format of April 2015, consequently all of the summary text is previously unreviewed and should be considered as 'changed'. To facilitate the review, Syngenta has highlighted the summaries of reports not previously reviewed by the zRMS in yellow.

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EVALUATION, SUMMARY AND CONCLUSION BY REGULATORY AUTHORITY	
Name of authority	**HSE Chemicals Regulation Division (CRD), UK**
Reviewer's comments	The applicant, Syngenta Crop Protection AG, submitted this application to amend the conditions of approval of metalaxyl-M in accordance to Article 7 of Regulation 1107/2009 in Great Britain (GB). On the 5 May 2020 the Commission Implementing Regulation (EU) 2020/617 renewing the approval of the active substance metalaxyl-M, and restricting the use of seed treated with a plant protection product containing it to be sown only in greenhouses, was published[1]. The renewal of metalaxyl-M applies since 1 June 2020. Since this was

[1] Commission Implementing Regulation (EU) 2020/617 of 5 May 2020 renewing the approval of the active substance metalaxyl-M, and restricting the use of seeds treated with plant protection products containing it, in

before UK withdrawal from the EU, the Commission Implementing Regulation for the renewal of metalaxyl-M applies direct in GB.

Two representative formulations were considered in the renewal of approval for metalaxyl-M, 'Apron XL' (A9642C) and 'Ridomil Gold Mz'/68 WG Fubol Gold' (A9651D). For this Article 7 amendment application in GB, two different formulations have been considered. The formulation 'Vibrance SB' (A20607B) containing 14.4 g/L metalaxyl-M, 22.5 g/L fludioxonil and 15.0
g/L sedaxane to support the field seed treatment use on sugar and fodder beet, and the formulation 'Wakil XL' (A9873C) containing 169.6 g/Kg metalaxyl-M, 100 g/Kg cymoxanil and 50 g/Kg fludioxonil) to support
the field seed treatment use on peas (vining) are the basis of this Article 7 application for metalaxyl-M to GB.

The applicant has re-submitted the draft registration reports prepared for the product renewals of 'Vibrance SB' and 'Wakil XL' under Article 43 of Regulation No 1107/2009 following the renewal of approval of the active substance metalaxyl-M. The information and data submitted within these draft registration reports have been considered previously by HSE for the applications for authorisation of a new product under Article 33 of Regulation No 1107/2009. Where relevant, re-evaluation of data or information has not occurred where studies have been performed in accordance with the current requirements and the results have been deemed acceptable.

This draft registration report has been provided by the applicant, where required, comments have been inserted in green boxes by HSE or the text amended by the HSE in green (applicant's text has been struck through in green where necessary).

HSE notes that the product authorisations for 'Vibrance SB' and 'Wakil XL' were withdrawn in GB by the applicant. This was based on the approval restriction provided for in Commission Implementing Regulation (EU) 2020/617 that only the treatment of seeds intended to be sown in greenhouses may be authorised. Since all authorised GB uses of 'Vibrance SB' and 'Wakil XL' products are on seeds which are direct drilled in the field, these products do not comply with the restriction and therefore could not be renewed under Article 43 of Regulation No 1107/2009. HSE notes that no authorisation for 'Vibrance SB' or 'Wakil XL' is sought within this Article 7 amendment application. Therefore, HSE has only considered the information presented in the draft registration reports that relate to metalaxyl-M. For a future GB authorisation of these products a separate application would be required with a full evaluation of the data and information for all active substances present in the formulation.

Note that as of 1st January 2024, The Retained EU Law (Revocation and Reform) Act 2023 has taken effect and retained EU law are now known as assimilated law. As this assessment has been prepared prior to the Retained EU Law Act taking effect, assessment may still refer to "retained" regulation as opposed to "assimilated".

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10 Relevance of metabolites in groundwater

10.1 General information

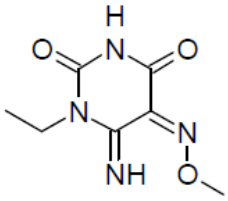
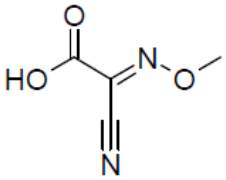
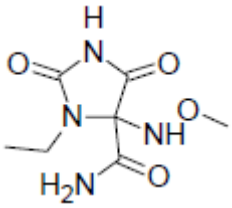
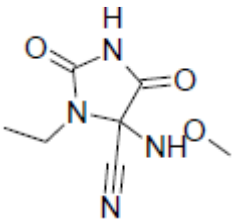
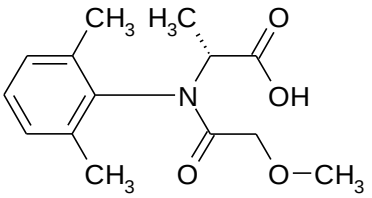
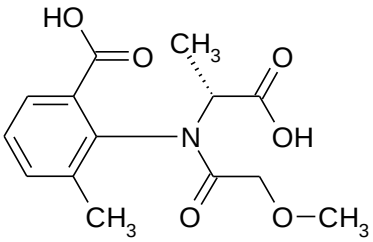
The cymoxanil metabolites IN-U3204, IN-W3595, IN-KQ960 and IN-JX915 are not predicted to occur in groundwater at concentrations above 0.1 µg/L (see A9873C Part B Section 8). Assessment of the relevance of these metabolites according to the stepwise procedure of the EC guidance document SANCO/221/2000 –rev.10 is therefore not required.

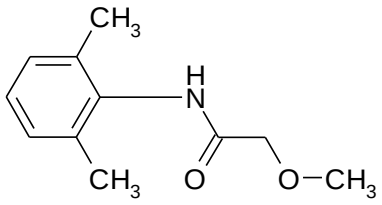
There are no relevant metabolites for fludioxonil.

The metalaxyl-M metabolites NOA409045, CGA67868 and SYN546520 are predicted to occur in groundwater at concentrations above 0.1 µg/L (see A9873C 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 is 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 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 assessmnent	
cymoxanil	1-ethyl-6-iminodihydropyrimidine-2,4,5(3H)-trione 5-(O-methyloxime) IN-U3204		Max PEC_{GW} Based on:	<0.001 µg/L All models, crops and scenarios
cymoxanil	2-cyano-2-methoxyiminoacetic acid IN-W3595		Max PEC_{GW} Based on:	<0.001 µg/L All models, crops and scenarios
cymoxanil	3-ethyl-4-(methoxyamino)-2,5-dioxoimidazolidine-4-carboxamide IN-KQ960		Max PEC_{GW} Based on:	<0.001 µg/L All models, crops and scenarios
cymoxanil	3-ethyl-4-(methoxyamino)-2,5-dioxoimidazolidine-4-carbonitrile IN-JX915		Max PEC_{GW} Based on:	<0.001 µg/L All models, crops and scenarios
metalaxyl-M	(R)-2-[(2,6-Dimethyl-phenyl)- methoxyacetyl-amino]-propionic acid NOA409045		Max PEC_{GW} Based on:	3.53 µg/L Modelling result using FOCUS PEARL v4.4.4 / Peas 1 x 78.75 g a.s./ha BBCH 00, Hamburg scenario
metalaxyl-M	2-[(1-Carboxy-ethyl)-(2-methoxy-acetyl)-amino]-3-methyl-benzoic acid SYN546520		Max PEC_{GW} Based on:	13.4 µg/L, Tier 1 2.89 µg/L, Tier 2 Modelling result using FOCUS PEARL v4.4.4 / Peas 1 x 78.75 g a.s./ha BBCH 00, Hamburg / Jokioinen scenarios

Name of active substance	Metabolite name and code	Structural/molecular formula	Trigger for relevance assessmnent	
metalaxyl-M	N-(2,6-Dimethyl-phenyl)-2-methoxy-acetamide CGA67868		Max PEC_{GW} Based on:	0.107 µg/L Modelling result using FOCUS PEARL v4.4.4 / Peas 1 x 78.75 g a.s./ha BBCH 00, Hamburg scenario

The code names 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

10.2 Relevance assessment of metalaxyl-M metabolite NOA409045

Summary:

NOA409045 was designated as relevant in the draft 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 synthezise NOA409045 material for *in vivo* testing. Questions were also raised as to whether the positive result *in vitro* on 91% NOA409045 could have been be 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.10. 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.

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}	3.53 µg/L
			Based on	Modelling result using FOCUS PEARL v4.4.4 / Peas 1 x 78.75 g a.s./ha BBCH 00, 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 racemate of NOA409045)	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)	<1%
			#ADI based on	0.5 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 NOA409045 content in the test material

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 [redacted] and [redacted] (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 Table 10.2-2 below. All studies, except [redacted] (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 [redacted] 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	[redacted] (1997)[a]
In Vitro Chromosome Aberration Test in Human Lymphocytes (NOA409045)	Genotoxic	In cultured human lymphocytes, -S9/+S9 951.8-2915 µg/ml	[redacted] (2014)[a]
Gene mutation in mammalian Cells (CGA62826)	Not genotoxic	Mouse lymphoma L5178Y TK+, -S9/+S9, 125-2652 µg/ml	[redacted] (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	[redacted] (2014) 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	[redacted] (2015) New data – see Section B6 for details

		Proof of exposure demonstrated	

[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 to 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 **Error! Reference source not found.**). 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	[redacted] (1996)[a]
Rat acute dermal toxicity	LD_{50} >2000 mg/kg bw	[redacted] (1996a)[a]
Rat 28 day oral gavage	NOAEL = 1000 mg/kg/day No 'adverse' effects at top dose (limit dose)	[redacted] (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. The estimated safety margin including potential exposure via other routes besides drinking water for NOA409045 are <1 % of ADI (infant), <1 % of ADI (child), <1 % of ADI (adult). Derivation of ADI is presented in Table 10.2-4.

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

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
3.53	0.75	5	0.00053	<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
3.53	1.0	10	0.000353	<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
3.53	2	60	0.00012	<1%

EVALUATION, SUMMARY AND CONCLUSION BY REGULATORY AUTHORITY	
Name of authority	**HSE Chemicals Regulation Division (CRD), UK**
Reviewer's comments	**NOA409045** Toxicology: The metalaxyl-M metabolite NOA409045 is predicted to occur in groundwater at concentrations above 0.1 µg/L. The groundwater level is confirmed by HSE in the dRR Part B8 Section 8.8. Assessment of the relevance of this metabolite has been performed according to the stepwise procedure of the EC guidance document SANCO 221/2000 Rev 11. The relevance of this metabolite cannot be excluded at STEP 1 (metabolite of no concern) or at STEP 2 (quantification of potential groundwater contamination). The assessment at STEP 3 - Stage 1 (screening for biological activity), Stage 2 (screening for genotoxicity) was performed during the EU review of metalaxyl-M. NOA409045 was not biologically active. A critical area of concern was raised concerning the genotoxic potential of NOA409045, based on a positive in vitro chromosome aberration assay. The available studies at renewal of the active substance were the

following: a bacterial reverse mutation assay ([redacted], 1997), a mammalian cell gene mutation assay ([redacted], 1998), a mouse lymphoma cell gene mutation assay ([redacted], 2006), all performed on the racemic mixture CGA62826. An in vitro chromosome assay performed on the R-enantiomer NOA409045 was performed ([redacted], 2014) and was concluded to be positive.

Syngenta supplied an in vivo micronucleus assays as an appropriate follow up to address the outstanding concerns regarding the clastogenic potential of NOA409045 (SANTE/11112/2019 Rev 5, 2020). The available studies are in vivo micronucleus assays conducted on NOA409045 and the racemic mixture CGA62826 (50% NOA409045 and 50% NOA436575) ([redacted] 2015b and 2014, respectively). HSE concluded the study on the racemic mixture was not required to determine the clastogenic potential of NOA409045. HSE evaluated the study on the metabolite under the Article 43 renewal evaluation of Apron XL (see dRR Part B6 Appendix 2 for details), the result of the study was negative. Therefore, the clastogenic potential of NOA409045 can be dismissed.
On this basis, HSE concludes that the genotoxic potential of metabolite NOA409045 has been fully investigated and is not relevant at Stage 2 of STEP 3.

Metalaxyl-M is not classified for carcinogenicity, reproductive toxicity, acute toxicity, or specific target organ toxicity (single or repeat exposure) in Category 1 in accordance with GB Mandatory Classification. On this basis, HSE concludes that the metabolite NOA409045 is not relevant at Stage 3 of STEP 3.

The maximum predicted level of NOA409045 in groundwater is > 0.75 µg/L (4.809 µg/L); therefore it cannot be addressed at STEP 4 (Threshold of Concern) and a refined risk assessment (STEP 5) is required. A metabolite-specific ADI of 0.5 mg/kg bw/day should be used as the reference value, as determined during the EU review; this was derived from the NOAEL of 1000 mg/kg bw/day from a 28-day study the racemic mixture CGA62826. An an uncertainty factor of 100 can be applied plus an additional factor of 10 for extrapolation from sub-acute to chronic exposure. To account for read across from a racemic mixture an additionally assessment factor of 2 is also applied (EFSA Journal 2015;13(3):3999).

<u>Conclusion</u>

Based on the information available, NOA409045 is not relevant at STEP 3 (Hazard Assessment). The relevance assessment cannot be completed at STEP 4 (Threshold of Concern). Therefore, a refined risk assessment (STEP 5) is required and the ADI of 0.5 mg/kg bw/day should be used as the reference value.

<u>Step 5: Refined risk assessment</u>

The metabolite NOA409045 of could be present in groundwater at levels requiring further consideration. Based upon worst case modelling conducted in the assessment for crop resulting in worst case PEC_{gw} estimation it is indicated that metabolite A is present above the trigger value of 0.1 µg/L in groundwater.

NOA409045 is not in the plant or animal residue definition for risk assessment; It was not considered in the food during the consumer risk assessment.

PEC_{gw} calculations after leaching from soil for metabolite A indicates that the potential exposure to metabolite NOA409045 is > 0.75 µg/L but < 10 µg/L, with maximum PEC_{gw} of 4.809 µg/L.

	In relation to the drinking water contribution, the highest intake is expected for infants (< 4 months). EFSA Guidance on pesticides in foods for infants and young children estimates the water consumption of bottle-fed infants as 1.135 L/day, equating to 227 ml/kg bw/day (EFSA 2018). Estimated intakes of NOA409045 from drinking water for the critical consumer group infants are 0.00109 mg/kg bw/day. This is 0.2 % of the established ADI (0.5 mg/kg bw/day). **As the estimated intake of NOA409045 from drinking water is ≤ 100 % of the established ADI, and dietary intakes from other sources is not expected, no further consideration is required.**

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.10. 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}	13.4 µg/L, Tier 1 2.89 µg/L, Tier 2
			Based on	Modelling result using FOCUS PEARL v4.4.4 / Peas 1 x 78.75 g a.s./ha BBCH 00, Hamburg / Jokioinen sceanrios. (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 racemate of SYN546520)	Non-genotoxic
		Stage 3	Toxic properties of metabolite (CGA108906 racemate of SYN546520)	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 (>0.75µg/L)
	STEP 5		Refined risk assessment	Acceptable
			Predicted exposure (% of ADI)	<2.5%
			#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 scenarios 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 [redacted] and [redacted] (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	[redacted] (1997)[a]
In vitro cytogenetic test, Chinese hamster V79 cells	Not genotoxic	Chinese hamster V79 cells, -S9/+S9 750-3000 µg/ml	[redacted] (2001)[a]
In vitro cytogenetic test, Chinese hamster V79 cells	Not genotoxic	Chinese hamster V79 cells, -S9: 37-1200 µg/ml +S9: 55-2000 µg/ml	[redacted] (1998)[a]
Gene mutation in mammalian Cells, Mouse lymphoma L5178Y	Not genotoxic	Mouse lymphoma L5178Y TK+, -S9/ +S9 500-2953 mg/ml	[redacted] (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 to 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	[redacted] (1994)[a]
Rat acute dermal toxicity	LD_{50} > 2000 mg/kg bw	[redacted] (1996b)[a]
Rat 28 day oral gavage	NOAEL=1000 mg/kg/day (Inreased heart rate in males and changes urine parameters for both sexes at top dose of 1000 mg/kg.	[redacted] (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. The estimated safety margin including potential exposure via other routes besides drinking water for Tier 2 SYN546520 are <1 % of ADI (infant), <1 % of ADI (child), <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
13.4, Tier 1	0.75	5	0.00201	<2.5%
2.89, Tier 2	0.75	5	0.000434	<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
13.4, Tier 1	1.0	10	0.00134	<2%
2.89, Tier 2	1.0	10	0.000289	<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
13.4, Tier 1	2	60	0.00044	<1%
2.89, Tier 2	2	60	0.000096	<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.

EVALUATION, SUMMARY AND CONCLUSION BY REGULATORY AUTHORITY	
Name of authority	**HSE Chemicals Regulation Division (CRD), UK**
Reviewer's comments	**SYN546520** Toxicology: The metalaxyl-M metabolite SYN546520 is predicted to occur in groundwater at concentrations above 0.1 µg/L. The groundwater level is confirmed by HSE in the

dRR Part B8 Section 8.8. Assessment of the relevance of this metabolite has been performed according to the stepwise procedure of the EC guidance document SANCO 221/2000 Rev 11.

The relevance of this metabolite cannot be excluded at STEP 1 (metabolite of no concern) or at STEP 2 (quantification of potential groundwater contamination). The assessment at STEP 3 - Stage 1 (screening for biological activity), Stage 2 (screening for genotoxicity) was performed during the EU review of metalaxyl-M. SYN546520 was not biologically active and was not genotoxic.

Metalaxyl-M is not classified for carcinogenicity, reproductive toxicity, acute toxicity, or specific target organ toxicity (single or repeat exposure) in Category 1 in accordance with GB Mandatory Classification. On this basis, HSE concludes that the metabolite SYN546520 is not relevant at Stage 3 of STEP 3.

The maximum predicted level of SYN546520 in groundwater is > 0.75 µg/L (14.642 µg/L); therefore it cannot be addressed at STEP 4 (Threshold of Concern) and a refined risk assessment (STEP 5) is required. A metabolite-specific ADI of 0.1 mg/kg bw/day should be used as the reference value, as determined during the EU review; this was derived from the NOAEL of 200 mg/kg bw/day from a 28-day study the racemic mixture CGA108906. An an uncertainty factor of 100 can be applied plus an additional factor of 10 for extrapolation from sub-acute to chronic exposure. To account for read across from a racemic mixture an additionally assessment factor of 2 is also applied (EFSA Journal 2015;13(3):3999).

Conclusion

Based on the information available, SYN546520 is not relevant at STEP 3 (Hazard Assessment). The relevance assessment cannot be completed at STEP 4 (Threshold of Concern). Therefore, a refined risk assessment (STEP 5) is required and the ADI of 0.1 mg/kg bw/day should be used as the reference value.

Step 5: Refined risk assessment

The metabolite SYN546520 of could be present in groundwater at levels requiring further consideration. Based upon worst case modelling conducted in the assessment for crop resulting in worst case PEC_{gw} estimation it is indicated that metabolite A is present above the trigger value of 0.1 µg/L in groundwater.

SYN546520 is not in the plant or animal residue definition for risk assessment; It was not considered in the food during the consumer risk assessment.

PEC_{gw} calculations after leaching from soil for metabolite A indicates that the potential exposure to metabolite SYN546520 is > 0.75 µg/L **and greater than** 10 µg/L, with maximum PEC_{gw} of **14.642 µg/L.**

The maximum PECgw is greater than the pragmatic limit of 10 µg/L for non-relevant GW metabolites. This is to be considered on a case by case basis, in this case, toxicology have agreed that there is no concern for a similar 2020 application for product Subdue (M20776). This is applicable to the current assessment, as the levels are similar, see DAR Vol3 Section B6 for tox agreement.

In relation to the drinking water contribution, the highest intake is expected for infants (< 4 months). EFSA Guidance on pesticides in foods for infants and young

	children estimates the water consumption of bottle-fed infants as 1.135 L/day, equating to 227 ml/kg bw/day (EFSA 2018). Estimated intakes of SYN546520 from drinking water for the critical consumer group infants are 0.00332 mg/kg bw/day. This is 3.3 % of the established ADI (0.1 mg/kg bw/day). **As the estimated intake of SYN546520 from drinking water is ≤ 100 % of the established ADI, and dietary intakes from other sources is not expected, no further consideration is required.**

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.10. 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}	0.107 µg/L
			Based on	Modelling result using FOCUS PEARL v4.4.4 / Peas 1 x 78.75 g a.s./ha BBCH 00, 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 metabolite (CGA92370 synonymous to CGA67868)	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 is 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 [redacted] (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: 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*	[redacted] (2012)[a]

		WP2uvrA	
Gene mutation in mammalian Cells, Mouse lymphoma L5178Y	Not genotoxic	Mouse lymphoma L5178Y TK+, -S9/ +S9 125-2000 µ/ml	[redacted] (2012)[a]
Chromosome Aberration Test in Human Lymphocytes	Not genotoxic	In cultured human lympho-cytes, -S9/+S9 1932 µg/ml	[redacted] (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 to 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.

EVALUATION, SUMMARY AND CONCLUSION BY REGULATORY AUTHORITY	
Name of authority	**HSE Chemicals Regulation Division (CRD), UK**
Reviewer’s comments	**CGA67868** Toxicology: The metalaxyl-m metabolite CGA67868 is predicted to occur in groundwater at concentrations above 0.1 µg/L. The groundwater level is confirmed by HSE in the dRR Part B8 Section 8.8. Assessment of the relevance of this metabolite has been performed according to the stepwise procedure of the EC guidance document SANCO 221/2000 Rev 11. The relevance of this metabolite cannot be excluded at STEP 1 (metabolite of no concern) or at STEP 2 (quantification of potential groundwater contamination). The assessment at STEP 3 - Stage 1 (screening for biological activity), Stage 2 (screening for genotoxicity) was performed during the EU review of metalaxyl-M. CGA67868 was not biologically active and was not genotoxic. The maximum predicted level of CGA67868 in groundwater is <0.75 µg/L (0.142 µg/L). Based on the information available, it may be appropriate to address this metabolite at STEP 4 (Threshold of Concern). Should a refined risk assessment (STEP 5) be required, the parent reference values should be used as determined during the EU review. The ADI of the parent metalaxyl-M is 0.08 mg/kg bw/day. Conclusion Based on the information available, CGA67868 is not relevant at STEP 3 (Hazard Assessment) and it may be acceptable to conclude on its relevance in groundwater at STEP 4 (Threshold of Concern). Should a refined risk assessment (STEP 5) be necessary, the ADI of 0.08 mg/kg bw/day should be used as the reference value.

	Residues – as the metabolite is <0.75 µg/L no further consideration is required.

Appendix 1 Lists of data considered in support of the evaluation

List of data submitted by the applicant and relied on

No new studies submitted

List of data submitted or referred to by the applicant and relied on, but already evaluated at EU peer review

No new studies submitted

List of data submitted by the applicant and not relied on

No new studies submitted

List of data relied on not submitted by the applicant but necessary for evaluation

No new studies submitted

Appendix 2 Additional information

Not applicable.

Appendix 3 Groundwater consumer risk model outputs

NOA409045

Insert level in B7 (µg/l)	4.809	
ADI	0.5	mg/kg bw/day

Water consumption (litres/kg bw)

	EU/WHO	
adult	0.033	2 litres 60 kg bw
child	0.100	1 litre 10 kg bw
infant	0.150	0.75 litre 5 kg bw
infant (EFSA Journal 2018;16(6):5286)	0.227	260 g/kg bw/day formula based on 33 g/kg bw powder and 227 ml/kg bw/day

Results (intake in µg/kg bw/day)

	EU/WHO
adult	0.16
child	0.48
infant (WHO)	0.72
infant (EFSA Journal 2018;16(6):5286)	1.09

Results (intake in mg/kg bw/day)

	EU/WHO
adult	0.00016
child	0.00048
infant (WHO)	0.00072
infant (EFSA Journal 2018;16(6):5286)	0.00109

Results (%ADI)

	EU/WHO
adult	<0.1
child	<0.1
infant (WHO)	0.1
infant (EFSA Journal 2018;16(6):5286)	0.2

SYN546520

Insert level in B7 (µg/l)	14.642	
ADI	0.1	mg/kg bw/day

Water consumption (litres/kg bw)

	EU/WHO	
adult	0.033	2 litres 60 kg bw
child	0.100	1 litre 10 kg bw
infant	0.150	0.75 litre 5 kg bw
infant (EFSA Journal 2018;16(6):5286)	0.227	260 g/kg bw/day formula based on 33 g/kg bw powder and 227 ml/kg bw/day

Results (intake in µg/kg bw/day)

	EU/WHO
adult	0.49
child	1.46
infant (WHO)	2.20
infant (EFSA Journal 2018;16(6):5286)	3.32

Results (intake in mg/kg bw/day)

	EU/WHO
adult	0.00049
child	0.00146
infant (WHO)	0.00220
infant (EFSA Journal 2018;16(6):5286)	0.00332

Results (%ADI)

	EU/WHO
adult	0.5
child	1.5
infant (WHO)	2.2
infant (EFSA Journal 2018;16(6):5286)	3.3