DRAFT REGISTRATION REPORT

Part B

Section 10

Assessment of the relevance of metabolites in groundwater

Detailed summary of the risk assessment

Product code: A20607B

Product name(s): Vibrance SB

Chemical active substances:

Fludioxonil, 22.5 g/L
Metalaxyl-M, 14.4 g/L
Sedaxane, 15 g/L

~~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

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 VIBRANCE SB (A20607B) 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 VIBRANCE SB (A20607B) 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 VIBRANCE SB (A20607B) 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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10 Relevance of metabolites in groundwater

10.1 General information

EVALUATION, SUMMARY AND CONCLUSION BY REGULATORY AUTHORITY	
Name of authority	**HSE Chemicals Regulation Division (CRD), UK**
Reviewer's comments	This Article 7 assessment only concerns the active substance metalaxyl-M, therefore the applicant's PECgw values for the other active substances, fludioxonil and sedaxane, have not been evaluated by HSE. The 80th percentile PECgw values for the proposed uses have been calculated with the FOCUS PEARL, PELMO and MACRO models. Parent and metabolite PECgw values were below the 0.1 µg/L trigger value in all scenarios. No further consideration is required. Detailed assessment of the predicted exposure of groundwater from use of 'Vibrance SB' is in dRR Part B8.

The metalaxyl-M metabolites NOA409045, SYN546520 and CGA67868 are predicted to occur in groundwater at concentrations below 0.1 µg/L (see A20607B UK Part B Section 8). Therefore, no data is required to demonstrate the non-relevance of these metabolites.

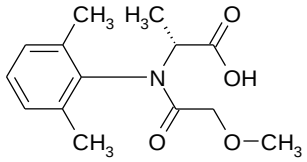
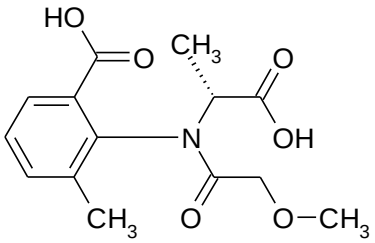
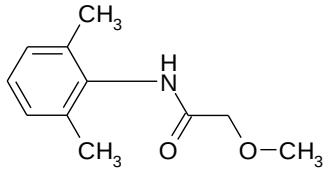
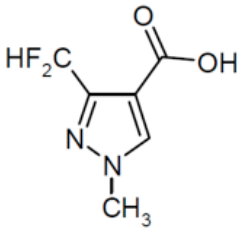
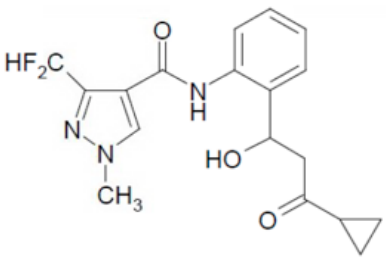
There are no relevant metabolites for fludioxonil.

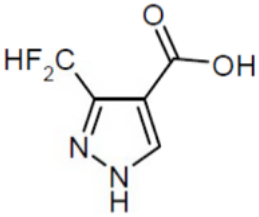
The sedaxane metabolites CSAA798670 and CSCD728931 are predicted to occur in groundwater at concentrations below 0.1 µg/L (see A20607B UK Part B Section 8). Therefore, no data is required to demonstrate the non-relevance of these metabolites

The sedaxane metabolite CSCD465008 is predicted to occur in groundwater at concentrations above 0.1 µg/L at Tier 1, but PEC_{GW} are below 0.1 µg/L at Tier 2 (see A20607B UK Part B Section 8). Based on Tier 2 results, it is justified that relevance assessment for metabolite CSCD465008 is not required. However, for completeness, an assessment of the relevance of this metabolite according to the stepwise procedure of the EC guidance document SANCO/221/2000 –rev.10 has been provided using Tier 1 PEC_{GW}.

General information on the metabolite 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 UK dRR Part B, Section 8 (Environmental fate and behaviour).

Table 10.1-1: General information on the metabolites

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:	0.012 µg/L Modelling result using FOCUS PEARL v4.4.4 / Sugar beet 0.62 g a.s./ha BBCH 00 Châteaudun scenario
Metalaxyl-M	2-[(1-Carboxy-ethyl)-(2-methoxy-acetyl)-amino]-3-methyl-benzoic acid SYN546520		Max PEC_{GW} Based on:	0.094 µg/L, Tier 1 0.020 µg/L, Tier 2 Modelling result using FOCUS PEARL v4.4.4 / Sugar beet 0.62 g a.s./ha BBCH 00 Hamburg scenario
Metalaxyl-M	N-(2,6-Dimethyl-phenyl)-2-methoxy-acetamide CGA67868		Max PEC_{GW} Based on:	<0.001 µg/L All models / Sugar beet 0.65 g a.s./ha BBCH 00 All scenarios
Sedaxane	3-(difluoromethyl)-1-methyl1H-pyrazole-4-carboxylic acid CSAA798670		Max PEC_{GW} Based on:	0.004 µg/L Modelling result using FOCUS PEARL v4.4.4 / PELMO v5.5.3 / Sugar beet 0.65 g a.s./ha BBCH 00 Hamburg scenario
Sedaxane	3-Difluoromethyl-1-methyl1H-pyrazole-4-carboxylic acid[2-(3-cyclopropyl-1- hydroxy-3-oxo-propyl)- phenyl]-amide CSCD728931		Max PEC_{GW} Based on:	<0.001 µg/L All models / Sugar beet 0.65 g a.s./ha BBCH 00 All scenarios

Name of active substance	Metabolite name and code	Structural/molecular formula	Trigger for relevance assessment	
Sedaxane	N-desmethyl pyrazole acid CSCD465008		Max PEC_{GW} Based on:	**0.129 µg/L, Tier 1** 0.036 µg/L, Tier 2 Modelling result using FOCUS PEARL v4.4.4 / Sugar beet 0.65 g a.s./ha BBCH 00 Hamburg scenario

Assessment of carcinogenic potential of sedaxane

EFSA published its Conclusion on the peer review of the active substance sedaxane in July 2012[1]. On 30 January 2013, EFSA published a revised Conclusion[2] . The revised Conclusion is based on a re-valuation of the combined chronic/carcinogenicity studies, at the Pesticides Peer Review Meeting 98 (21-23 November 2012) and includes the following statements;

Carcinogenic effects were observed upon long-term administration of sedaxane to rats and mice. In rats, the highest dose level of 218 mg/kg bw per day resulted in increased incidences of hepatocellular adenomas and thyroid follicular cell adenomas in male rats, and uterine adenocarcinomas in female rats; general toxicity was also apparent by decreased body weight gain observed in both males (50%) and females (24%). In mice effects on the liver appeared at much higher dose levels than in rats; in male mice increased incidences of liver adenomas and carcinomas were observed at the highest dose level of 900 mg/kg bw per day, and were not associated with significant signs of general toxicity. The overall pattern of tumours in rats (multiple sited) and in mice suggests that classification regarding carcinogenicity would be required for sedaxane, as 'Carc cat 2, H351, suspected of causing cancer' but the final decision should be taken under Regulation (EC) No 1272/2008.

The metabolites CSAA798670 and CSCD465008 are relevant from the toxicological point of view according to the guidance document on the assessment of groundwater metabolites (European Commission, 2003) as there is no convincing evidence that these metabolites would not share the carcinogenic potential of the parent compound, sedaxane.

In March 2019, the ECHA RAC proposed to classify sedaxane as suspected of causing cancer (Carc. 2; H351). This classification triggers submission of confirmatory information for sedaxane regarding the relevance of the groundwater metabolite CSCD465008 within 6 months from application date of the Regulation classifying Sedaxane.[1]

The metabolite CSCD465008 is a difluoropyrazole metabolite, which together with the metabolite NOA449410, are common metabolites formed by degradation of the following SDHI active ingredients, benzovindiflupyr, sedaxane, isopyrazam, bixafen and fluxapyroxad.

Carcinogenicity testing to address the relevance of the metabolite CSCD465008

[1] EFSA Journal 2012;10(7):2823
[2] EFSA Journal 2013;11(1):3057

Following the RAC proposal in March 2019, and before undertaking any potential animal testing, Syngenta, and the SDHI Common Metabolite Task Force (SDHI CoMet TF), composed of BASF, Bayer and Syngenta generated a "Technical Position" to demonstrate that the difluoropyrazole metabolites (NOA449410 and CSCD465008) are chemically, biologically and toxicologically distinct from the SDHI parent active ingredients. On that basis, it is considered that there is convincing evidence to conclude that the SDHI common metabolites do not qualify with the same classification as the SDHI parent active ingredients, so they can be considered as non-relevant metabolites in accordance with the SANCO guidance.[2]

The "Technical Position" was submitted to the RMS for sedaxane in September 2019 with the response that the toxicological argumentation was not convincing evidence to address the relevance of the metabolite CSCD465008. Consequently, it was agreed upon with the RMS to conduct a 104-week oral (dietary) carcinogenicity study with a combined 52-week toxicity study to investigate whether CSCD465008 presents comparable carcinogenic potential to sedaxane, in accordance with the SANCO 221/2000 guidance on the relevance of metabolites in groundwater.

The timeframe by which the confirmatory information for sedaxane is required is challenging to complete long-term toxicological studies. The current expectation is to have data available from the 52 week terminations early Q1 2022 to fulfill the confirmatory data deadline. The final reporting for the combined chronic toxicity and carcinogenicity study in females is expected to be available by Q3 2023.

The purpose of the following assessment is to (a) show, based on a summary of the properties of sedaxane and its environmental metabolite why Syngenta believe this metabolite should be regarded as both qualitatively and quantitatively distinct from parent sedaxane and (b) to demonstrate that potential exposure to the worst case predicted groundwater concentrations for this metabolite would not present a health risk for consumers.

The identical metabolite designated CSCD465008 has also been tested in studies undertaken by BASF under the test substance code M700F002 (Regulatory Number 5435595), and hence the summaries for studies conducted by BASF refer to the test substance as M700F002 whereas the Syngenta study summaries refer to this metabolite using the test substance code CSCD465008.

10.2 Relevance assessment of sedaxane metabolite CSCD465008

Summary:

The relevance of the groundwater metabolite CSCD465008 has already been assessed at EU level (see Sedaxane – Final addendum to the Draft Assessment Report (DAR), June 2012), 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). Given that some of the toxicity studies were assessed at EU level not for sedaxane but for fluxapyroxad, a detailed assessment is presented hereafter to ensure that all the available information is taken into account.

The metabolite CSCD765008 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 10.1-1 and the corresponding studies are listed in the corresponding sections. 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 CSCD465008

	Assessment step		Result of assessment	
	STEP 1		Metabolite of no concern?	No
Quantification of groundwater contamination	STEP 2		Max PEC_{GW}	0.129 µg/L, Tier 1
			Based on	Modelling result using FOCUS PEARL v4.4.4 / Sugar beet 0.65 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	Non-genotoxic
		Stage 3	Toxic properties of metabolite :	• Oral LD50 >2000 mg/kg • 28-day dietary, rat: NOAEL ≥1000 mg/kg/day • 90-day dietary, rat: NOAEL ≥958.4/928.7mg/kg/day in M/F • Developmental toxicity, rabbit: Maternal NOAEL = 300 mg/kg/day LOAEL = 1000 mg/kg/day based on increased mortality and abortions. Fetal NOAEL >1000 mg/kg/day
			Classification of parent	See section 10.1
			Classification of metabolite	See section 10.1
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

10.2.1 STEP 1: Exclusion of degradation products of no concern

CSCD465008 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 CSCD465008 were performed (see UK Part B, Section 8, chapter 8.8). The scenario for which concentrations of CSCD465008 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 screening studies on the metabolite CSCD465008 have been previously considered within the EU peer review process for sedaxane. Biological activity of the metabolite CSCD465008 does not have comparable target activity as the parent active compound as shown in biological screening data.

10.2.3.2 STEP 3, Stage 2: screening for genotoxicity

CSCD465008 was screened for genotoxic activity by the following data package of *in vitro* genotoxicity studies: Ames test, gene mutation test with mammalian cells, and a chromosome aberration test. All studies have been previously EU peer reviewed under Regulation (EC) 91/414 and are referred in Part B Section 6, Chapter 6.4 and Appendix 1.

CSCD465008 was non-genotoxic as shown by a negative Ames test, negative gene mutation test with mammalian cells and negative chromosome aberration test. The genotoxicity studies[3] are summarised below.

Table 10.2-2: Summary of *in vitro* genotoxicity studies with CSCD465008

Test System	**CSCD465008**	
Bacterial reverse mutation	Negative	[redacted] (2008)
In vitro cytogenetics	Negative	[redacted] (2008)
Mammalian cell gene mutation (mouse lymphoma)	Negative	[redacted] (2008)

CSCD465008 is considered not genotoxic *in vitro* 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 classification status of parent is discussed in section 10.1 above. CSCD465008 has been subject to toxicological evaluation[4] which has been summarised below.

[3] See Sedaxane – Final addendum to the draft Assessment Report (DAR), June 2012.
[4] See Sedaxane – Final addendum to the Draft Assessment Report (DAR), June 2012 and Fluxapyroxad – Draft Assessment Report (DAR), February 2011.

Extensive toxicity testing of the active substance sedaxane has been carried out and the results are described in detail in the Final addendum to the Draft Assessment Report for sedaxane (June 2012).

Sedaxane is not acutely toxic by oral, dermal or inhalation routes of administration, nor is it a skin or eye irritant or a skin sensitizer. Sedaxane is not genotoxic in vitro or in vivo.

For comparison with the metabolite CSCD465008, toxicity results with sedaxane show the following;

- A low potential for acute oral toxicity in rats (oral LD50 = 5000 mg/kg).
- Negative for genotoxicity.
- In 28-day rat studies, a NOAEL = 37.8 mg/kg/day and LOAEL = 153.5 mg/kg/day.
- In a 90-day rat study, a NOAEL = 28.3 mg/kg/day and LOAEL = 186 mg/kg/day.
- In a rabbit developmental toxicity study, no treatment-related malformations and a maternal and fetal NOAEL = 100 mg/kg/day.

Comparative Toxicity of Metabolite CSCD465008

CSCD465008 was not a quantifiably detectable metabolite in the samples analysed as part of the rat biotransformation study and as such is unlikely to have contributed to any toxicity seen in sedaxane studies. For comparison to parent sedaxane, the toxicological properties of CSCD465008 are shown in Table 10.2-3. The large database of toxicology studies with CSCD465008[5] shows the following:

- CSCD465008 has an acute oral LD_{50} >2000 mg/kg indicating that it is non-hazardous via the oral route of exposure.
- CSCD465008 was negative for genotoxicity in a bacterial reverse mutation assay, an in vitro cytogenetics assay and a mouse lymphoma assay.
- In both 28-day and 90-day dietary toxicity studies in the rat, CSCD465008 failed to produce any adverse effects up to the limit dose of around 1000 mg/kg/day, which was the NOAEL in these studies. This indicates that CSCD465008 is much less toxic than parent sedaxane in rats, the most sensitive species. Based on the ratio of NOAEL values, CSCD465008 has at least a 26-fold lower potential for toxicity compared to sedaxane. The 90-day study was not included in the dossier submitted for sedaxane. It was evaluated as part of the fluxapyroxad peer review and is co-owned by Syngenta (in relation to fluxapyroxad; this metabolite is designated as M700F002 or Reg 5069089).
- In a developmental toxicity study in rabbits, CSCD465008 had a maternal NOAEL of 300 mg/kg/day. At the LOAEL of 1000 mg/kg/day, increased mortality and abortions were observed in the dams. However, the fetal NOAEL was >1000 mg/kg/day, based on a lack of effects in fetuses at a limit dose. Based on comparison of the NOAEL values, CSCD465008 was shown to have lower maternal and developmental toxicity compared to sedaxane. This study was not included in the dossier submitted for sedaxane. It was evaluated as part of the fluxapyroxad peer review and is co-owned by Syngenta (in relation to fluxapyroxad; this metabolite is designated as M700F002 or Reg 5069089).

[5] See Sedaxane – Final addendum to the Draft Assessment Report (DAR), June 2012 and Fluxapyroxad - Draft Assessment Report (DAR), February 2011

Table 10.2-3: Summary of Toxicity Studies with CSCD465008

Study	Result
Acute Oral	LD_{50} >2000 mg/kg
Bacterial reverse mutation	Negative
In vitro cytogenetics	Negative
Mammalian cell gene mutation (mouse lymphoma)	Negative
28-day dietary toxicity in the rat	NOAEL ≥1000 mg/kg/day
90-day dietary toxicity in the rat	NOAEL ≥958.4/928.7 mg/kg/day in M/F
Developmental toxicity in rabbits	Maternal NOAEL = 300 mg/kg/day LOAEL = 1000 mg/kg/day based on increased mortality and abortions Foetal NOAEL >1000 mg/kg/day

Based on the above evaluation, it can be concluded that the metabolite CSCD465008 is not relevant according to the "Guidance document on the assessment of the relevance of metabolites in groundwater of substances regulated under Council Directive 91/414/EEC. (SANCO/221/2000 –rev.10- final. 25 February 2003)".

The toxicity studies on the metabolite CSCD465008 have been previously considered within the EU peer review process for sedaxane and for fluxapyroxad and are, therefore, not summarized. All studies are referred in Part B Section 6, Chapter 6.4 and Appendix 1.

The metabolite CSCD465008 was not further evaluated in Step 4 as PECgw < 0.75 µg/L.

Appendix 1 Lists of data considered in support of the evaluation

Tables considered not relevant can be deleted as appropriate.

MS to blacken authors of vertebrate studies in the version made available to third parties/public.

List of data submitted by the applicant and relied on

Data point	Author(s)	Year	Title Company Report No. Source (where different from company) GLP or GEP status Published or not	Vertebrate study Y/N	Owner

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

Data point	Author(s)	Year	Title Company Report No. Source (where different from company) GLP or GEP status Published or not	Vertebrate study Y/N	Owner

The following tables are to be completed by MS

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