REGISTRATION REPORT

Part B

Section 10

Assessment of the relevance of metabolites in groundwater

Detailed summary of the risk assessment

Product code: ADM.03503.F.1.A

Product name(s): see Part A

Chemical active substances:

Fluxapyroxad, 75 g/L
Prothioconazole, 150 g/L

Central Zone

Zonal Rapporteur Member State: Poland

CORE ASSESSMENT

(authorization)

Applicant: Country organisation / representative

as specified in Part A

Submission date: April 2022

MS Finalisation date: May 2023 (initial Core Assessment)

November 2023 (final Core Assessment)

Version history

When	What
2022/04	Version 1 Applicant
May 2023	Initial zRMS assessment 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) No additional information or assessments after the commenting period.

DATA PROTECTION CLAIM

In order to present a dossier fully compliant with today's requirements (Reg. 284/2013), studies have been performed on ADM.03503.F.1.A. Under Article 59, Regulation 1107/2009/EC, on behalf of the Sponsor Company the applicant claims data protection for the studies conducted with ADM.03503.F.1.A. The data protection status and corresponding justification as valid for the respective country will be confirmed in the respective PART A.

STATEMENT FOR OWNERSHIP

The summaries and evaluations contained in this document may be based on unpublished proprietary data submitted for the purpose of the assessment undertaken by the regulatory authority that prepared it. Other registration authorities should not grant, amend, or renew a registration on the basis of the summaries and evaluation of unpublished proprietary data contained in this document unless they have received the data on which the summaries and evaluation are based, either –

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- following expiry of any period of exclusive use, by offering – in certain jurisdictions – mandatory compensation, unless the period of protection of the proprietary data concerned has expired.

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10 Relevance of metabolites in groundwater

Reviewer comments:

This part of dossier has been submitted to support registration of the plant protection product ADM.03503.F.1.A 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.
In case of Fluxapyroxad metabolite M700F002 zRMS provided discussion regarding consumer health risk assessment and additional Step 5 has been done by the zRMS.

10.1 General information

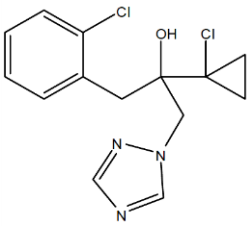
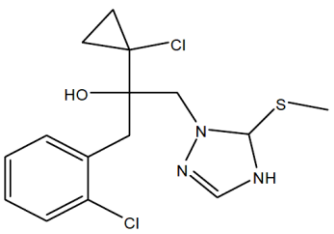
The prothioconazole metabolites prothioconazole-desthio (JAU-Desthio, 15.1 - 46.5 % AR) and prothioconazole-S-methyl (JAU-S-Methyl, 1.5 - 14.6 % AR)[1] are predicted to occur in groundwater at concentrations below 0.1 µg/L (see dRR part B 8, chapter 8.8.2 of the core assessment). Assessment of the relevance of these metabolites according to the stepwise procedure of the EC guidance document SANCO/221/2000 –rev.10 is therefore not required.

The fluxapyroxad metabolite M700F001 is predicted to occur in groundwater at concentrations above 0.1 µg/L in the Jokioinen scenario only (see dRR part B 8, chapter 8.8.2 of the core assessment). However an assessment of relevance of this metabolites according to the stepwise procedure of the EC guidance document SANCO/221/2000 –rev.10 is presented below for information.

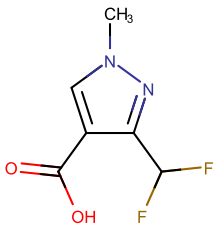
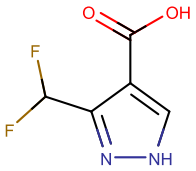
The fluxapyroxad metabolite M700F002 is predicted to occur in groundwater at concentrations above 0.1 µg/L(see dRR part B 8, chapter 8.8.2 of the core assessment). An assessment of relevance of this metabolites according to the stepwise procedure of the EC guidance document SANCO/221/2000 –rev.10 is presented below.

General information on the metabolites together with their maximum PEC_{gw} values is provided in Table 10.1-1 below. For details on the critical GAP uses of the formulated product ADM.03503.F.1.A , please refer to Table 8.1-1 of the dRR, part B 8 (Environmental Fate) of the core assessment.

Table 10.1-1: General information on the metabolites

Name of active substance	Metabolite name and code	Structural/molecular formula	Trigger for relevance assessment
Prothioconazole	prothioconazole-desthio (JAU-Desthio)		Max PEC_{gw}: < 0.001 µg/L Based on: FOCUS PELMO 5.5.3, all intended uses/scenarios
	prothioconazole-S-methyl (JAU-S-Methyl)		Max PEC_{gw}: < 0.001 µg/L Based on: FOCUS PELMO 5.5.3, all intended uses/scenarios

[1] Results of soil degradation studies according to EFSA Scientific Report (2007) 106, 1-98, Conclusion on the peer review of prothioconazole

Name of active substance	Metabolite name and code	Structural/molecular formula	Trigger for relevance assessment	
Fluxapyroxad	M700F001		Max PEC_{gw} Based on:	0.118 µg/L FOCUS PELMO, sping cereals, Jokioinen
	M700F002		Max PEC_{gw} Based on:	1.054 µg/L FOCUS PEARL, winter cereals, Jokioinen (1.045 µg/L, spring cereals, Hamburg)

10.2 Relevance assessment of prothioconazole-desthio and prothioconazole-S-methyl

Summary

As evaluated in model calculations provided in Part B Section 8, 8.8.2, the prothioconazole metabolites prothioconazole-desthio and prothioconazole-S-methyl did not exceed the groundwater threshold value of 0.1 µg/L (see Table 10.3-1 to Table 10.2-2).

Table 10.2-1: Summary of the relevance assessment for metabolite prothioconazole-desthio

	Assessment step	Result of assessment	
	STEP 1	Metabolite of no concern?	no (cannot be excluded)
Quantification of groundwater contamination	STEP 2	Max PEC_{gw}	< 0.001 µg/L
		Based on	FOCUS PELMO 5.5.3 (80th Percentile PEC_{gw} at 1 m soil depth); all intended uses/scenarios

Table 10.2-2: Summary of the relevance assessment for metabolite prothioconazole-S-methyl

	Assessment step	Result of assessment	
	STEP 1	Metabolite of no concern?	no (cannot be excluded)
Quantification of groundwater contamination	STEP 2	Max PEC_{gw}	< 0.001 µg/L
		Based on	FOCUS PELMO 5.5.3 (80th Percentile PEC_{gw} at 1 m soil depth); all intended uses/scenarios

10.3 Relevance assessment of M700F001

Summary:

The relevance of the groundwater metabolite M700F001 has already been assessed and the assessment agreed at EU level (see EFSA Conclusion EFSA Journal 2012;10(1):2522) is applicable as well for the GAP and groundwater scenarios considered in this dRR (i.e., the conclusions reached at Step 4 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 between 0.1 and 0.75 µg/L). M700F001 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.

Table 10.3-1: Summary of the relevance assessment for M700F001

	Assessment step		**Result of assessment**	
	STEP 1		Metabolite of no concern?	no
Quantification of groundwater contamination	STEP 2		Max PEC_{gw}	0.118 µg/L
			Based on	FOCUS PELMO, sping cereals, Jokioinen
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;	See table 6.4-1 Part B6
			Classification of parent	Lact, H362
			Classification of metabolite	None
Consumer health risk assessment	STEP 4		Estimated consumer exposure via drinking water and other sources; threshold of concern approach	acceptable (<0.75 µg/L)
	STEP 5		Refined risk assessment	N/A*
			Predicted exposure (% of ADI)	N/A*
			ADI based on	N/A*

* N/A: not applicable

10.4 Relevance assessment of M700F002

Summary:

The relevance of the groundwater metabolite M700F002 has already been assessed and the assessment agreed at EU level (see EFSA Conclusion, EFSA Journal 2012;10(1):2522), is applicable 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 with regard to the PEC_{gw} calculated for the GAP and groundwater scenarios considered in this dRR). M700F002 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.

Table 10.4-1: Summary of the relevance assessment for M700F002

	Assessment step		**Result of assessment**	
	STEP 1		Metabolite of no concern?	no
Quantification of groundwater contamination	STEP 2		Max PEC_{gw}	1.054 µg/L
			Based on	FOCUS PEARL, winter cereals, Jokioinen
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;	See table 6.4-2 Part B6
			Classification of parent	Lact, H362
			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	~~Max. 5.03 µg/L was considered non-relevant in EFSA Conclusion~~ Acceptable
			Predicted exposure (% of ADI)	~~N/A*~~ 0.05 % of ADI (infant), 0.04 % of ADI (child), 0.01 % of ADI (adult)
			ADI based on	~~EFSA Conclusion~~ ADI is 0.3 mg/kg bw/day, based on the NOAEL of 300 mg/kg bw/day from the developmental toxicity study in rabbits with an AF of 1000

~~* N/A: not applicable~~

Reviewer comment:

zRMS do not accept discussion regarding consumer health risk assessment concluded by the notifier, therefore Step 5 has been provided by the zRMS. Metabolite M700F002 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 below.

Note: The groundwater and plant metabolite **M700F002,** found in groundwater above 0.75 µg/L according to environmental fate and behavior models is non-relevant from the toxicological point of view according to the guidance document on the assessment of groundwater metabolites (European Commission, 2003), as the studies provided sufficient evidence that this metabolite does not share the mode of action leading to carcinogenicity as observed with the parent fluxapyroxad (BAS 700 F). Metabolite M700F002 presented low oral acute and short-term toxicity, no adverse effects were observed up to 1000 mg/kg bw/day (limit dose) in a 90-day dietary study in rats; in a developmental toxicity study in rabbits no adverse effect was observed on the development of the foetuses up to 1000 mg/kg bw/day (limit dose), while the maternal NOAEL was 300 mg/kg bw/day based on reduction of maternal body weight gain and decreased food intake. No genotoxic potential is attributed to metabolite M700F002.

M700F002 can be considered to be less toxic than the parent compound. If reference values are needed for this metabolite, no ARfD is allocated and the ADI is 0.3 mg/kg bw/day, based on the NOAEL of 300 mg/kg bw/day from the developmental toxicity study in rabbits with an AF of 1000 applied to account for the limited database available (no long-term, multigeneration or rat developmental toxicity study available) (refer *Conclusion on the peer review of the pesticide risk assessment of the active substance fluxapyroxad (BAS 700 F). EFSA Journal 2012;10(1):2522*).

The consumer risk assessment demonstrates an acceptable risk. The estimated safety margin including potential exposure via other routes besides drinking water for M700F002 are 0.05 % of ADI (infant), 0.04 % of ADI (child), 0.01 % of ADI (adult).

Justification for the selected ADI:

The ADI as defined in the LoEP EFSA Journal 2012;10(1):2522 has been set as specific ADI for M700F002, based on the NOAEL of 300 mg/kg bw/day from the developmental toxicity study in rabbits with an AF of 1000.

ADI = 0.3 mg/kg bw/d

= 300 µg/kg bw/d

According to EU/WHO the worst case dietary exposure via water is calculated to be

$$(daily\ water\ consumption\ [L/day] \times PECgw\ [\mu g/L])/(body\ weight\ [kg]) = \text{worst case daily dietary exposure [µg/kg bw/day]}$$

The calculation of the risk (% ADI) is performed according to the following equation:

$$(worst\ case\ daily\ dietary\ exposure\ [\mu g/kg\ \text{bw/day}]\ /\text{ADI [µg/kg bw/day]}) \times 100 = \text{ADI consumption}[\%]$$

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

Worst case daily dietary exposure of 5-kg bottle fed infant = 0.16 µg/kg bw/d
Risk for 5-kg bottle fed infant (% ADI) = 0.05 %

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

Worst case daily dietary exposure of 10 kg child = 0.1 µg/kg bw/d
Risk for 10 kg child (% ADI) = 0.04%

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

Worst case daily dietary exposure of 60-kg adult = 0.04 µg/kg bw/d
Risk for 60-kg adult (% ADI) = 0.01 %

Appendix 1 Lists of data considered in support of the evaluation

List of data submitted by the applicant and relied on

No new product studies are submitted to support relevance of metabolites in groundwater.

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
-	-	-	-	-	-