REGISTRATION REPORT

Part B

Section 10

Assessment of the relevance of metabolites in groundwater

Detailed summary of the risk assessment

Product code: GLOB2111F

Product name(s): Starinta

Chemical active substance(s):

Bixafen, 125 g/L

Central Zone

Zonal Rapporteur Member State: Poland

CORE ASSESSMENT

(authorization)

Applicant: Globachem NV

Submission date: December 2023

zRMS Assessment : 09/08/2024

Version after commenting : 15/11/2024

Version history

When	What
August 2024	zRMS assesment
November 2024	After commenting period

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10 Relevance of metabolites in groundwater

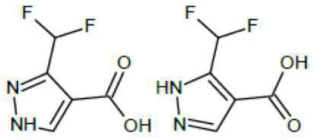
RMS comment: PEC_{GW} calculations after leaching from soil for the bixafen and its metabolite M44 performed using the model FOCUS PEARL 5.5.5 indicated the maximum M44 concentration at 1.134 µg/L (Part B, Section 8 Environmental Fate, Detailed summary of the risk assessment, dated December 2023), which requires an assessment of the toxicological relevance of the metabolite according to EC guidance document SANCO/221/2000 –rev.11.
For the metabolite M44 no conclusion can be drawn on its toxicological profile based on the data available in the bixafen dossier (EFSA Journal 2012;10(11):2917). However, it should be noted that M44 is common metabolite to other active substances such as fluxapyroxad, isopyrazam, sedaxane and benzovindyflupyr (EFSA Journal 2015;13(3):4043) for which the toxicological data are available. This metabolite has different code names, dependently on the parent substance: M44 for bixafen, M700F002 for fluxapyroxad, CSCD465008 for isopyrazam and sedaxane and NOA449410 for benzovindyflupyr.
The assessment of the metabolite relevance varies according to the parent substance and depends on the classification of the parent substance: for benzovindyflupyr and fluxapyroxad, M700F002 was considered non-relevant from the toxicological point of view with an ADI of 0.30 mg/kg bw/d and no ARfD (EFSA Journal 2015;13(3):4043 and EFSA Journal 2012;10(1):2522), for isopyrazam and sedaxane, CSCD465008 was regarded as relevant (EFSA Journal 2012;10(3):2600 and EFSA Journal 2013;11(1):3057).
Based on the available data, M44 does not demonstrate biological activity comparable to the parent bixafen. The metabolite screened for genotoxicity was found to be negative in the in an Ames test, an in vitro cytogenetic test, an in vitro mammalian cell gene mutation test and an in vivo bone marrow micronucleus assay.
As bixafen is not classified regarding toxicity, a detailed assessment of the acute or chronic toxicity of bixafen metabolite M44 is not required.
The PECgw for bixafen metabolite M44 was > 0.75 µg/L. Therefore the metabolite is considered to exceed the toxicological threshold of concern. The risk assessment demonstrates an acceptable risk for consumers. The estimated potential exposure values via drinking water for M44 are 0.057% of ADI (infants), 0.038% of ADI (children) and 0.013% of ADI (adults).
Currently, the evaluation of the significance of the M44 metabolite in groundwater has not been completed, but the available data and direct application of the requirements of the EC guideline SANCO/221/2000 -rev.11. indicate that the M44 metabolite may not meet the significance criteria.

10.1 General information

The metabolite M44, is predicted to occur in groundwater at concentrations above 0.1 µg/L (see dRR Part B, Section 8, chapter 8.8). 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.

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 8.8 of the dRR Part B, Section 8 (Environmental fate and behaviour).

Table 10.1-1: General information on the metabolite(s)

Name of active substance	Metabolite name and code	Structural/molecular formula	Trigger for relevance assessment	
Bixafen	M44 (3-(difluoromethyl)-1H-pyrazole-4- carboxylic acid)		Relevance assessment: Max PEC_{GW} Based on:	Yes 1.134 µg/L Calculations by using FOCUS PEARL 5.5.5 for winter cereals in Jokioinen

10.2 Relevance assessment of metabolite M44

Summary:

The groundwater metabolite M44 is 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 M44 is given in Table 10.2-1. Studies supporting PEC_{gw} data are evaluated in Section 8 (Environmental fate and behaviour).

Metabolite M44 of bixafen is a common metabolite of the active substance fluxapyroxad. Reference is therefore made to available genotoxicity and biological activity data for the metabolite M700F002 (M44) submitted during the EU Review of the active of the active substance fluxapyroxad (UK, 2011), which is out of protection.

Table 10.2-1: Summary of the relevance assessment for M44

	Assessment step		Result of assessment	
	STEP 1		Metabolite of no concern?	~~Yes~~ No
Quantification of groundwater contamination	STEP 2		Max PEC_{gw}	1.134 µg/L
			Based on	FOCUS PEARL 5.5.5, Jokioinen
Hazard assessment	STEP 3	Stage 1	Biological activity comparable to the parent?	No
		Stage 2	Genotoxic properties of metabo-lite	Non-genotoxic
		Stage 3	Toxic properties of metabolite;	Less toxic than parent
			Classification of parent	Not classified
			Classification of metabolite	Not classified
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)	0.057 % of ADI
		ADI based on	0.3 mg/kg bw/d (EFSA Journal 2012;10(1):2522)

10.2.1 STEP 1: Exclusion of degradation products of no concern

Bixafen metabolite M44 does not meet the criteria for products of no concern as defined in step 1 of the guidance and therefore needs further assessment.

10.2.2 STEP 2: Quantification of potential groundwater contamination

PEC_{gw} calculations after leaching from soil for metabolite M44 were performed (see Part B, Section 8, chapter 8.8). The threshold of 0.1 µg/L is exceeded for metabolite M44. 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 Guidance SANCO/221/2000 –rev.11 states that metabolites with a biological activity comparable or higher than the parent are considered as relevant.

The available data summarised during the EU review of bixafen and fluxapyrosad demonstrate that metabolite M44 does not have comparable or higher biological activity than to the parent bixafen.

In an *in planta* screen carried out during EU Review of the active of the active substance fluxapyroxad (UK, 2011), metabolite M44 showed negligible pesticide activity against nine major plant fungus pathogens (*Septoria tritici*, *Puccinia triticina*, *Pyrenophora teres*, *Rhynchosporium secalis*, *Phakopsora pachyrhizi*, *Alternaria solani*, *Sphaerotheca fuliginea*, *Botrytis cinerea*, *Venturia inaequalis*), all of which represent the fungicide profile of bixafen.

Additionally, when the ecotoxicity of bixafen and the metabolite M44 to sensitive non-target organisms (*Oncorhynchus mykiss, Daphnia magna,* and *Pseudokirchneriella subcapitata*) is compared, it is also clear that the toxicity of metabolite M44 is significantly reduced.

Group	Test item	Exposure system	Toxicity (mg/L)
Oncorhynchus mykiss	Bixafen	96 h, s	LC_{50} = 0.095
	M44	96 h, s	LC_{50} >100
Daphnia magna	Bixafen	48 h, s	EC_{50} = 1.2
	M44	48 h, s	EC_{50} >100
Pseudokirchneriella subcapitata	Bixafen	72 h, s	E_rC_{50} = 0.0965
	M44	72 h, s	E_rC_{50} = 26.52

Bixafen metabolite M44 is not considered relevant at this step of the assessment.

10.2.3.2 STEP 3, Stage 2: screening for genotoxicity

No genotoxic potential can be attributed to metabolite M44 based on the available genotoxicity studies conducted with this metabolite, summarized during the EU review of the active substance Fluxapyroxad (EFSA Journal 2012;10(1):2522). M44 was tested negative in a Ames test (Schulz and Landsiedel, 2007), an in vitro cytogenetic test (Schulz and Landsiedel, 2008a), an in vitro mammalian cell gene mutation test (Schulz and Landsiedel, 2008b) and an in vivo bone marrow micronucleus assay (Schulz and Landsiedel, 2009).
Bixafen metabolite M44 is not considered relevant regarding genotoxicity. The metabolite is therefore further screened in Stage 3.

10.2.3.3 STEP 3, Stage 3: screening for toxicity

According to the available toxicity data summarized during the EU review of the active substance Fluxapyroxad (EFSA Journal 2012;10(1):2522), metabolite M44 can be considered to be less toxic than the parent bixafen.

M44 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 (Kaspers et al., 2009), in a developmental toxicity study in rabbits (Schneider et al., 2009) no adverse effect was observed on the development of the foetuses up to 1000 mg/kg bw/day, while the maternal NOAEL was 300 mg/kg bw/day based on reduction of maternal body weight gain and decreased food intake. An ADI of 0.3 mg/kg bw/day was allocated, 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).

The parent bixafen is not classified as toxic or very toxic for acute or repeat dose toxicity, nor is it classified for reproductive toxicity or carcinogenicity. Based on the classification of the parent, bixafen, metabolite M44 is not expected to be relevant according to the SANCO/221/2000 –rev.11.

10.2.4 STEP 4: Exposure assessment – threshold of concern approach

Step 4 is 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 M44 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

Based on the hazard screening non-relevant metabolites require an exposure assessment to make sure that any contamination of groundwater will not lead to unacceptable exposure of consumers via their drinking water.

The highest PECgw value detected for M44 is 1.134 µg/L.

Calculation of risk (% ADI) for 5-kg bottle-fed infant (consuming 0.75 l/day):
Assuming a 5 kg infant drinking 0.75 litre of water per day, the drinking of water containing 1.134 µg/L will result in a daily intake of 0.170 µg M44/kg bw x d. This represents 0.057% of the ADI.

Calculation of risk (% ADI) for 10-kg child (consuming 1.0 l/day):
Assuming a 10 kg child drinking 1 litre of water per day, the drinking of water containing 1.134 µg/L will result in a daily intake of 0.113 µg M44/kg bw x d. This represents 0.038% of the ADI.

Calculation of risk (% ADI) for 60-kg adult (consuming 2.0 l/day):
Assuming a 60 kg person drinking 2 litres of water per day, the drinking of water containing 1.134 µg/L will result in a daily intake of 0.038 µg M44/kg bw x d. This represents 0.013 % of the ADI.

The risk assessment demonstrates an acceptable risk for consumers. The estimated potential exposure values via drinking water for M44 are 0.057% of ADI (infant), 0.038% of ADI (child) and 0.013% of ADI (adult).

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
KCP 6.4	Schulz M., Landsiedel R.	2007	Reg.No. 5435595 (metabolite of BAS 700 F) - *Salmonella typhimurium / Escherichia coli* reverse mutation assay (standard plate test and preincubation test). 2007/1051931 BASF AG GLP Unpublished	~~Y~~ N	BASF
KCP 6.4	Schulz M., Landsiedel R.	2008a	Reg.No. 5435595 (metabolite of BAS 700 F) - In vitro chromosome aberration assay in V79 cells. 2008/1002741 BASF SE GLP Unpublished	~~Y~~ N	BASF
KCP 6.4	Schulz M., Landsiedel R.	2008b	Reg.No. 5435595 (metabolite of BAS 700 F) - In vitro gene mutation test in CHO cells (HPRT locus assay). 2008/1014199 BASF SE GLP Unpublished	~~Y~~ N	BASF
KCP 6.4	[redacted]	2009	Reg.No. 5435595 (metabolite of BAS 700 F): Micronucleus test in bone marrow cells of the mouse. [redacted] GLP Unpublished	Y	BASF
KCP 6.4	[redacted]	2009	Reg.No. 5435595 (metabolite of BAS 700 F) - Prenatal developmental toxicity study in New Zealand white rabbits - Oral administration (gavage). [redacted]	Y	BASF

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
			GLP Unpublished		
KCP 6.4	[redacted]	2009	Reg.No. 5069089 (metabolite of BAS 700 F) - Repeated dose 90-day oral toxicity study in Wistar rats - Administration in the diet [redacted] GLP Unpublished	Y	BASF

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
KCP XX	Author	YYYY	Title Company Report N Source GLP/non GLP/GEP/non GEP Published/Unpublished	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
KCP XX	Author	YYYY	Title Company Report N Source GLP/non GLP/GEP/non GEP Published/Unpublished	Y/N	Owner