FINAL REGISTRATION REPORT

Part B

Section 10

Assessment of the relevance of metabolites in groundwater

Detailed summary of the risk assessment

Product code: DNT-162OD-R-CPd

Product name: EVRITELL 162 OD

Chemical active substance(s):
Dicamba, 110 g/L

Nicosulfuron, 40 g/L

Thifensulfuron-methyl, 12 g/L

Central Zone

Zonal Rapporteur Member State: Poland

CORE ASSESSMENT

(authorization)

Applicant: QEMETICA Agricultural Solutions Poland S.A. (formerly: CIECH Sarzyna S.A.).

Submission date: 01/2024

Correction date 10/2024

MS Finalisation date: 11/2024, 03/2025

Version history

When	What
January 2024	First submission to zRMS
October 2024	Additional calculations for groundwater modeling performed by the applicant
November 2024	ZRMs evaluated initial dRR submitted by Applicant.
March 2025	Final Registration Report

Table of Contents

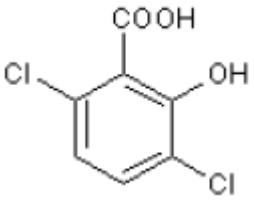
10 Relevance of metabolites in groundwater

10.1 General information

The ground water concentration of metabolites of three active substances dicamba, nicosulfuron and thifensulfuron methyl were simulated using the latest version of FOCUS groundwater models – PEARL 5.5.5 and PELMO 6.6.4. The application scenarios of the formulated product EVRITELL 162 OD are provided in Table 10.2-; Table 10.1-2 & Table 10.1-3. Simulations were conducted with EU-reviewed endpoints for dicamba (EFSA, 2011), nicosulfuron (EFSA, 2007) and thifensulfuron methyl (EFSA, 2015).

The metabolites listed below are predicted to occur in groundwater at concentrations above 0.1 µg/L (see dRR B section 8). Assessment of the relevance of these metabolites according to the stepwise procedure of the EC guidance document SANCO/221/2000 –rev.11 is therefore required. General information on the metabolites is provided in Table 10.2-; Table 10.1-2 & Table 10.1-3.

Table 10.1-1: General information on the metabolites of dicamba

Name of active sub-stance	Metabolite name and code	Structural/molecular formula	Trigger for relevance assessment	
Dicamba	DCSA		Max. PEC_{gw} Based on:	<0.001 µg/L FOCUS models (see chapter 8.8 of the dRR Part B, Section 8)

10.2 Relevance assessment of DCSA

Not applicable.

Table 10.2-2: General information on the metabolites of nicosulfuron

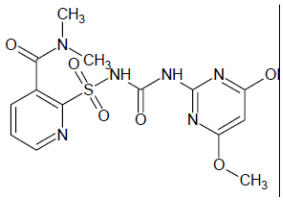
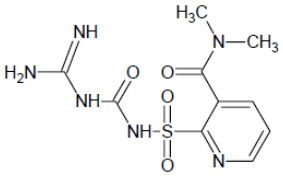
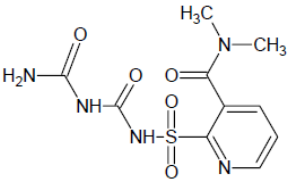
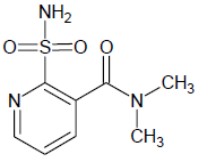
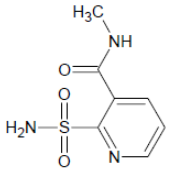
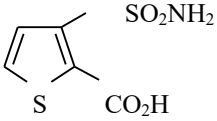
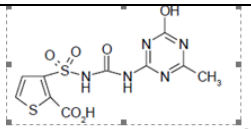
Name of active sub-stance	Metabolite	Chemical structure	Trigger for relevance assessmnent	
nicosulfuron	HMUD (2-[(4,6-dimethoxypyrimidin-2-ylcarbamoyl)sulfamoyl]-N,N-dimethylnicotinamide)		Max PEC_{gw} Based on:	~~1.01~~ 0.57 µg/L FOCUS PEARL 5.5.4 / Hamburg
nicosulfuron	AUSN 2-[(carbamimidoylcarbamoyl)sulfamoyl]-N,N-dimethylpyridine-3-carboxamide		Max PEC_{gw} Based on:	~~3.19~~ 2.20 µg/L FOCUS PEARL 5.5.4 / Thiva
nicosulfuron	UCSN 2-[(carbamoylcarbamoyl)sulfamoyl]-N,N-dimethylpyridine-3-carboxamide		Max PEC_{gw} Based on:	~~1.84~~ 1.54 µg/L FOCUS PEARL 5.5.4 / Thiva
nicosulfuron	ASDM N,N-dimethyl-2-sulfamoylpyridine-3-carboxamide		Max PEC_{gw} Based on:	~~1.79~~ 1.43 µg/L FOCUS PEARL 5.5.4 / Thiva
nicosulfuron	MU-466 *N*-methyl-2-sulfamoylpyridine-3-carboxamide		Max PEC_{gw} Based on:	~~0.15~~ 0.12 µg/L FOCUS PEARL 5.5.4 / Thiva

Table 10.2-3: General information on the metabolites of thifensulfuron methyl

Name of active sub-stance	Metabolite	Chemical structure	Trigger for relevance assessmnent	
thifensulfuron methyl	IN-L9223		Max PEC_{gw} Based on:	0.782 µg/L FOCUS PEARL 5.5.5/ Thiva
thifensulfuron methyl	IN-JZ789		Max PEC_{gw} Based on:	0.309 µg/L FOCUS PEARL 5.5.5 / Hamburg

10.3 Relevance assessment of HMUD

Comments of ZRMs:

- The metabolite HMUD was not considered relevant according to EFSA Scientific Report (2007). The metabolite has a very similar structure to the parent substance. The results of *in vitro* studies showed that HMUD is not genotoxic (negative in a bacterial assay and chromosomal aberrations test on mammalian cells.
- The parent substance (nicosulfuron) is not classified regarding mammalian toxicology.
- The maximum PECgw of HMUD (acc. to the application rate presented in the GAP table) amounts to 0.57 µg/L.
- The predicted max. PECgw value is above the upper limit for metabolites (≥0.75 µg/L); the consumer risk calculation for this metabolite is required.

	Exposure (µg/kg b.w./d)	% ADI (parent substance)
Adults (60 kg b.w.)	0.019	0.001
Toddlers (10 kg b.w.)	0.57	0.003
Infants (5 kg b.w.)	0.09	0.0043

Conclusions:

Taking into account the toxicological data, the metabolite HMUD is considered toxicologically non-relevant. The results of consumer risk calculations indicate that the use of DNT-162OD-R-CPd/ EVRITELL 162 OD according to the list of intended uses presented in GAP Table, causes no risk for health for the adults, toddlers and infants.

The relevance of the groundwater metabolite HMUD has already been assessed at EU level (see EFSA Scientific Report (2007) 120, 1-91). The relevance assessment is applicable for the GAP and groundwater scenarios considered in this dRR, as well. HMUD was not considered relevant according to the criteria laid down in the EC guidance document SA CO/221/2000 –rev.11; even though more data might be needed in future. A summary of the relevance assessment is given in the following table.

Table 10.3.1: Summary of the relevance assessment for HMUD

	Assessment step		Result of assessment	
	STEP 1		Metabolite of no concern?	no
Quantification of groundwater contamination	STEP 2		Max PEC_{gw}	~~1.01~~ 0.57 µg/L
			Based on	FOCUS PEARL 5.5.4 / Hamburg
Hazard assessment	STEP 3	Stage 1	Biological activity comparable to the parent?	No (EFSA, 2007)

		Stage 2	Genotoxic properties of metabolite	Non genotoxic (EFSA, 2007)
		Stage 3	Toxic properties of metabolite;	no studies available
			Classification of parent	no toxicological classification
			Classification of metabolite	no toxicological classification
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)	<0.01% of ADI (infant) <0.01% of ADI (child) <0.01% of ADI (adult)
			ADI based on	2 mg/kg/bw/day parent compound nicosulfuron according to EFSA Scientific Report (2007) 120, 1-91

10.3.1 STEP 1: Exclusion of degradation products of no concern

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

10.3.2 STEP 2: Quantification of potential groundwater contamination

PEC_{gw} calculations after leaching from soil for HMUD were performed (see Part B, Section 8, chapter 8.8). The uses for which concentrations of HMUD were considered to exceed 0.1 µg/L are listed in Table 10.3-1.

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 HMUD does not have comparable target activity as the parent active compound as shown in biological screening data on terrestrial plants stated in the EFSA Scientific Report (2007) 120, 1-91. HMUD is considered not relevant and is further evaluated in Stage 2.
Full summaries of biological screening studies on the metabolite that have not been previously considered within an EU peer review process are described in detail in.

10.3.3.2 STEP 3, Stage 2: screening for genotoxicity

HMUD 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 (summarized in the next table). HMUD was non-genotoxic as shown by a negative Ames test, negative gene mutation test with mouse lymphoma cells and negative chromosome aberration test with human lymphocytes. Based on these negative results, further *in vivo* testing is not necessary. It must be noted that according to the EFSA Supporting publication 2020:EN-1837, the chromosomal aberration does not adequately

address the endpoint aneugenic potential. This endpoint will need to be assessed with a micronucleus a say, e.g as per OECD TG 487 in the next EU approval procedure at the latest.

Table 10.3-2: Summary of genotoxicity studies conducted with HMUD

Type of test, species (Guideline)	Result	Details	Reference[a]
Bacterial Reverse Mutation Assay *S. typhimurium* and *E. coli*	Non-genotoxic	Dosed to 5000 µg/plate	Matsumoto, 2004a
In vitro mammalian cell gene mutation test	Non-genotoxic	Mouse lymphoma L5178Y cells Dosed to 3964 µg/plate (10 mM)	Matsumoto, 2004b
In vitro chromosome aberration test	Non-genotoxic	Human lymphocytes Dosed to 3964 µg/mL (10 mM)	Matsumoto, 2004c

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

HMUD is not considered relevant and is further evaluated in Stage 3. The genotoxicity studies are evaluated and referenced in RAR from 2005 and EFSA Conclusion from 2007.

10.3.3.3 STEP 3, Stage 3: screening for toxicity

The parent substance nicosulfuron is not classified (in accordance to Regulation (EC) No 1272/2008) as acutely or chronically toxic or very toxic, for reproductive toxicity or as a mutagen or carcinogen. Extensive toxicity testing of the active substance nicosulfuron has been carried out and the results are described in detail in the EFSA Scientific Report (2007) 120, 1-91.

Toxicological studies with HMUD are not available. According to the conclusion of the assessment at EU level (EFSA Scientific Report (2007) 120, 1-91) HMUD has a structure very similar to the parent compound. Hence, it can be expected that HMUD is not more toxic than the parent substance nicosulfuron. HMUD is therefore not considered relevant in step 3, stage 3 here.

10.3.4 STEP 4: Exposure assessment – threshold of concern approach

The potential exposure to HMUD is > 0.75 µg/L but < 10 µg/L. A further assessment in step 5 is required

10.3.5 STEP 5: Refined risk assessment

A refined assessment of the potential toxicological relevance of HMUD is presented here, based on the ADI of 2 mg/kg bw for nicosulfuron. Potential exposure to HMUD is compared to the ADI below table.

Table 10.3-3: Calculation of exposure to HMUD via drinking water

Consumer group	Groundwater contamination (µg/L)	Consuming of drinking water (L/day)	Body weight (kg)	Exposure (mg/kg bw/day)	Exposure (% of ADI)
Bottle-fed infant	~~1.01~~ 0.57	0.75	5	~~0.00015~~ 0.00009	~~0.008~~ 0.004
Child		1	12	~~0.00008~~ 0.00005	~~0.004~~ 0.002
Adult		2	70	~~0.00003~~ 0.00002	0.001

Metabolite HMUD contributes to <0.1% of the ADI. The consumer risk assessment of indicated levels of the HMUD metabolite in drinking water following the proposed use of nicosulfuron indicates that a concern for human health is not expected.

10.4 Relevance assessment of AUSN

Comments of ZRMs:

- The metabolite AUSN was not considered relevant according to EFSA Scientific Report (2007). The results of the studies showed low acute toxicity of the metabolite (LD50 in rats >2000 mg/kg bw) and no genotoxic prosperities (negative results in a bacterial mutagenicity assay and in an *in vitro* clastogenicity and an *in vitro* cell mutation test with mammalian cells.
- The parent substance (nicosulfuron) is not classified regarding mammalian toxicology.
- The maximum PECgw of AUSN (acc. to the application rate presented in the GAP table) amounts to 2.20 µg/L.
- The predicted max. PECgw value is above the upper limit for metabolites (≥0.75 µg/L); the consumer risk calculation for this metabolite is required (the ADI of nicosulfuron is applied).

	Exposure (µg/kg b.w./d)	% ADI (parent substance)
Adults (60 kg b.w.)	0.073	0.004
Toddlers (10 kg b.w.)	0.22	0.011
Infants (5 kg b.w.)	0.48	0.017

Conclusions:

Taking into account the toxicological data, the metabolite AUSN is considered toxicologically non-relevant. The results of consumer risk calculations indicate that the use of DNT-162OD-R-CPd/ EVRITELL 162 OD according to the list of intended uses presented in GAP Table, causes no risk for health for the adults, toddlers and infants.

Summary:

The relevance of the groundwater metabolite AUSN has already been assessed at EU level (see EFSA Scientific Report (2007) 120, 1-91). The relevance assessment is applicable for the GAP and groundwater scenarios considered in this dRR, as well. AUSN was not considered relevant according to the criteria laid down in the EC guidance document SANCO/221/2000 –rev.11; even though more data might be needed in future. A summary of the relevance assessment is given in the following table.

Table 10.44-1: Summary of the relevance assessment for AUSN

	Assessment step	**Result of assessment**	
	STEP 1		
groundw	STEP 2	Max PEC_{gw}	~~3.19~~ 2.20 µg/L

			Based on	FOCUS PEARL 5.5.4 / Thiva
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;	low acute toxicity, no short-term studies available
			Classification of parent	no toxicological classification
			Classification of metabolite	no toxicological classification
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)	0.02% of ADI (infant) 0.01% of ADI (child) <0.01% of ADI (adult)
			ADI based on	2 mg/kg/bw/day parent compound nicosulfuron according to EFSA Scientific Report (2007) 120, 1-91

10.4.1 STEP 1: Exclusion of degradation products of no concern

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

10.4.2 STEP 2: Quantification of potential groundwater contamination

PEC_{gw} calculations after leaching from soil for AUSN were performed (see Part B, Section 8, chapter 8.8). The uses for which concentrations of AUSN were considered to exceed 0.1 µg/L are listed in Table 10.4-1. Possible reductions of the expected groundwater concentrations by applying risk mitigation measures are not presented here. Details on the groundwater risk assessment 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 AUSN does not have comparable target activity as the parent active compound as shown in biological screening data on terrestrial plants stated in the EFSA Scientific Report (2007) 120, 1-91. AUSN is considered not relevant and is further evaluated in Stage 2.

10.4.3.2 STEP 3, Stage 2: screening for genotoxicity

AUSN 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. AUSN was nongenotoxic as shown by a negative Ames test, negative gene mutation test with mouse lymphoma cells and negative chromosome aberration test with Chinese hamster cells (summarized in the f table). Based on these negative results, further *in vivo* testing is not necessary.

It must be noted that according to the EFSA Supporting publication 2020:EN-1837, the chromosomal aberration does not adequately address the endpoint aneugenic potential. This endpoint will need to be assessed with a micronucleus assay, e.g as per OECD TG 487 in the EU approval procedure at the latest.

Table 10.4-2: Summary of genotoxicity studies conducted with AUSN

Test	Result	Details	Reference [a]
Bacterial Reverse Mutation Assay *S. typhimurium and E. coli*	Non-genotoxic	Not fully compliant with current guideline	Wollny, 1995a
In vitro mammalian cell gene mutation test	Non-genotoxic	Mouse lymphoma L5178Y cells	Wollny, 2003b
In vitro chromosome aberration test	Non-genotoxic	Chinese Hamster V79 cells	Schulz, 2003a

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

AUSN is not considered relevant and is further evaluated in Stage 3. The genotoxicity studies are evaluated and referenced in RAR from 2005 and EFSA Conclusion from 2007.

10.4.3.3 STEP 3, Stage 3: screening for toxicity

The parent substance nicosulfuron is not classified (in accordance to Regulation (EC) No 1272/2008) as acutely or chronically toxic or very toxic, for reproductive toxicity or as a mutagen or carcinogen. Extensive toxicity testing of the active substance nicosulfuron has been carried out and the results are described in detail in the EFSA Scientific Report (2007) 120, 1-91.

AUSN was tested in an acute oral toxicity study in rats. No mortality or clinical signs were observed in this study and the LD50 was >2000 mg/kg bw (Allard, 1996). This study was included in the 2005 DAR (RMS U.K) and was therefore previously reviewed during the EU active substance peer review (see EFSA 2007).

The metabolite was not considered relevant during the EU active substance peer review for nicosulfuron (EFSA 2007) and is therefore not considered relevant in step 3, stage 3 here.

10.4.4 STEP 4: Exposure assessment – threshold of concern approach

The potential exposure to AUSN is > 0.75 µg/L but <10 µg/L. A further assessment in Step 5 is required.

10.4.5 STEP 5: Refined risk assessment

A refined assessment of the potential toxicological relevance of AUSN is presented here, based on the ADI of 2 mg/kg bw for nicosulfuron. This ADI was derived from the repeat dose rat study, applying a safety factor of 100 as per the EFSA Conclusion for nicosulfuron. Repeat dose (28-day, 90-day and 1-year) studies supported this. No repeat dose toxicity studies with AUSN have been performed. Potential exposure to AUSN is compared to the ADI in the next table.

Table 10.4-3: Calculation of exposure for AUSN via drinking water

Consumer group	Groundwater contamination (µg/L)	Consuming of drinking water (L/day)	Body weight (kg)	Exposure (mg/kg bw/day)	Exposure (% of ADI)
Bottle-fed infant	~~3.19~~ 2.20	0.75	5	~~0.00048~~ 0.00033	~~0.024~~ 0.017
Child		1	12	~~0.00027~~ 0.00018	~~0.013~~ 0.009
Adult		2	70	~~0.00009~~ 0.00006	~~0.005~~ 0.003

The calculated exposure of consumers to the metabolite via groundwater at the given concentration poses no unacceptable risk. As such, the given concentration of this metabolite in groundwater is permissible. There is no consumer exposure via other routes.

According to the current scientific standards, the conclusion of the previous assessment at EU level (EFSA Scientific Report (2007) 120, 1-91): "The experts concluded that AUSN was a non-relevant groundwater metabolite for which the ADI of nicosulfuron can be applied") is not sufficiently justified. Due to the major structural differences between the parent substance nicosulfuron and the metabolite AUSN, it will become necessary to provide a detailed justification (read-across analysis or other data) for further use of the ADI of nicosulfuron for AUSN at the latest in the context of the next application for the approval of nicosulfuron according to Reg. (EC) No 1107/2009.

10.5 Relevance assessment of UCSN

<table>
<tr>
<td>Comments of ZRMs:</td>
<td>
- The metabolite UCSN was not considered relevant according to EFSA Scientific Report (2007). The results of the studies showed low acute toxicity of the metabolite (LD50 in rats >2000 mg/kg bw) and no genotoxic prosperities (negative results in a bacterial mutagenicity assay and in an in vitro clastogenicity and an in vitro cell mutation test with mammalian cells.
- The parent substance (nicosulfuron) is not classified regarding mammalian toxicology.
- The maximum PECgw of UCSN (acc. to the application rate presented in the GAP table) amounts to 1.54 µg/L.
- The predicted max. PECgw value is above the upper limit for metabolites (≥0.75 µg/L); the consumer risk calculation for this metabolite is required (the ADI of nicosulfuron is applied).
<table>
<tr><td></td><td>Exposure (µg/kg b.w./d)</td><td>% ADI (parent substance)</td></tr>
<tr><td>Adults</td><td>0.05</td><td>0.0026</td></tr>
</table>
</td>
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</table>

(60 kg b.w.)			
Toddlers (10 kg b.w.)	0.154	0.008	
Infants (5 kg b.w.)	0.231	0.012	

Conclusions:

Taking into account the toxicological data, the metabolite UCSN is considered toxicologically non-relevant. The results of consumer risk calculations indicate that the use of DNT-162OD-R-CPd/ EVRITELL 162 OD according to the list of intended uses presented in GAP Table, causes no risk for health for the adults, toddlers and infants.

The relevance of the groundwater metabolite UCSN has already been assessed at EU level (see EFSA Scientific Report (2007) 120, 1-91). The relevance assessment is applicable for the GAP and groundwater scenarios considered in this dRR as well. UCSN was not considered relevant according to the criteria laid down in the EC guidance document SANCO/221/2000 –rev.11; even though more data might be needed in future. A summary of the relevance assessment is given in the next table.

Table 10.55-1: Summary of the relevance assessment for UCNS

	Assessment step		**Result of assessment**	
	STEP 1		Metabolite of no concern?	no
Quantification of groundwater contamination	STEP 2		Max PEC_{gw}	~~1.84~~ 1.54 µg/L
			Based on	FOCUS PEARL 5.5.5 / Thiva
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;	low acute toxicity, no short-term studies available
			Classification of parent	no toxicological classification
			Classification of metabolite	no toxicological classification
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)	0.01% of ADI (infant) 0.01% of ADI (child) <0.01% of ADI (adult)
		ADI based on	2 mg/kg/bw/day parent compound nicosulfuron according to EFSA Scientific Report (2007) 120, 1-91

10.5.1 STEP 1: Exclusion of degradation products of no concern

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

10.5.2 STEP 2: Quantification of potential groundwater contamination

PEC_{gw} calculations after leaching from soil for UCSN were performed (see Part B, Section 8, chapter 8.8). The uses for which concentrations of UCSN were considered to exceed 0.1 µg/L are listed in Table 10.5-1. Possible reductions of the expected groundwater concentrations by applying risk mitigation measures are not presented. Possible reductions of the expected groundwater concentrations by applying risk mitigation measures are not presented here. Details on the groundwater risk assessment on the groundwater risk assessment are given in Part B, Section 8, chapter 8.8.

10.5.3 STEP 3: Hazard assessment – identification of relevant metabolites

10.5.3.1 STEP 3, Stage 1: screening for biological activity

The biological activity of UCSN does not have comparable target activity as the parent active compound as shown in biological screening data on terrestrial plants stated in the EFSA Scientific Re-port (2007) 120, 1-91. UCSN is considered not relevant and is further evaluated in Stage 2.

10.5.3.2 STEP 3, Stage 2: screening for genotoxicity

UCSN 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. UCSN was non-genotoxic as shown by a negative Ames test, a negative gene mutation test with mouse lymphoma cells and a negative chromosome aberration test with Chinese hamster cells (tests are summarized in Table 10.5-2). Based on these negative results, further *in vivo* testing is not necessary.

It must be noted that according to the EFSA Supporting publication 2020:EN-1837, the chromosomal aberration does not adequately address the endpoint aneugenic potential. This endpoint will need to be assessed with a micronucleus assay, e.g as per OECD TG 487 in the EU approval procedure at the latest.

Table 10.5-2: Summary of genotoxicity studies conducted with UCSN

Type of test, species (Guideline)	Result	Details	Reference[a]
Bacterial Reverse Mutation Assay *S. typhimurium* and *E. coli*	Non-genotoxic	Not fully compliant with current guidelines Dosed up to 5000ug/plate	Wollny (1995b)
In vitro mammalian cell gene mutation test	Non-genotoxic	Mouse lymphoma L5178Y cells Dosed up to 10 mM	Wollny (2003c)
In vitro chromosome aberration test	Non-genotoxic	Chinese Hamster V79 cells Dosed up to 10 mM	Schulz (2003c)

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

UCSN is not considered relevant and is further evaluated in Stage 3. The genotoxicity studies are evaluated and referenced in RAR from 2005 and EFSA Conclusion from 2007.

10.5.3.3 STEP 3, Stage 3: screening for toxicity

The parent substance nicosulfuron is not classified (in accordance to Regulation (EC) No 1272/2008) as acutely or chronically toxic or very toxic, for reproductive toxicity or as a mutagen or carcinogen. Extensive toxicity testing of the active substance nicosulfuron has been carried out and the results are described in detail in the EFSA Scientific Report (2007) 120, 1-91.

UCSN was tested in an acute oral toxicity study in rats. No mortality or clinical signs were observed in this study and the LD50 was >2000 mg/kg bw (Allard, 1996). This study was included in the 2005 DAR (RMS U.K) and was therefore previously reviewed during the EU active substance peer review (see EFSA 2007).

The metabolite was not considered relevant during the EU active substance peer review for nicosulfuron (EFSA 2007) and is therefore not considered relevant in step 3, stage 3 here.

10.5.4 STEP 4: Exposure assessment – threshold of concern approach

The potential exposure to UCSN is > 0.75 µg/L but < 10 µg/L. A further assessment in step 5 is required

10.5.5 STEP 5: Refined risk assessment

A refined assessment of the potential toxicological relevance of UCSN is presented here, based on the ADI of 2 mg/kg bw for nicosulfuron. This ADI was derived from the repeat dose rat study, applying a safety factor of 100 as per the EFSA Conclusion for nicrosulfuron. Repeat dose (28-day, 90-day and 1-year) with dogs supported this. No repeat dose toxicity studies with UCSN have been performed. Potential exposure to UCSN is compared to the ADI in the next table.

Table 10.5-3: Calculation of exposure to UCSN via drinking water

Consumer group	Groundwater contamination (µg/L)	Consuming of drinking water (L/day)	Body weight (kg)	Exposure (mg/kg bw/day)	Exposure (% of ADI)

Bottle-fed infant	~~1.84~~ 1.54	0.75	5	~~0.00028~~ 0.00023	~~0.014~~ 0.012
Child		1	12	~~0.00015~~ 0.00013	~~0.008~~ 0.006
Adult		2	70	~~0.00005~~ 0.00004	~~0.003~~ 0.002

The calculated exposure of consumers to the metabolite via groundwater at the given concentration poses no unacceptable risk. As such, the given concentration of this metabolite in groundwater is permissible. There is no consumer exposure via other routes.

According to the current scientific standards, the conclusion of the previous assessment at EU level (EFSA Scientific Report (2007) 120, 1-91) that UCSN was a non-relevant metabolite is not sufficiently justified. Due to the major structural differences between the parent substance nicosulfuron and the metabolite UCSN, it will become necessary to provide a detailed justification (read-across analysis or other data) for further use of the ADI of nicosulfuron for UCSN at the latest in the context of the next application for the approval of nicosulfuron according to Reg. (EC) No 1107/2009.

10.6 Relevance assessment of ASDM

Comments of ZRMs:

- The metabolite ASDM was not considered relevant according to EFSA Scientific Report (2007). The results of the studies showed low acute toxicity of the metabolite (LD50 in rats >2000 mg/kg bw, LD50 in mice >5000 mg/kg bw). The metabolite is not irritant to the skin and eye and has no genotoxic prosperities (negative results in in vitro bacterial- and mammalian cell mutation, mammalian clastogenicity tests, and in an in vivo mouse micronucleus test). ASDM does not influence reproduction.
- ASDM was found to be a skin sensitiser (Guinea pig maximisation test).
- The parent substance (nicosulfuron) is not classified regarding mammalian toxicology.
- The maximum PECgw of ASDM (acc. to the application rate presented in the GAP table) amounts to 1.43 µg/L.
- The predicted max. PECgw value is above the upper limit for metabolites (≥0.75 µg/L); the consumer risk calculation for this metabolite is required (the ADI of nicosulfuron is applied).

	Exposure (µg/kg b.w./d)	% ADI (parent substance)
Adults (60 kg b.w.)	0.048	0.002
Toddlers (10 kg b.w.)	0.143	0.007
Infants (5 kg b.w.)	0.2	0.011

Conclusions:

Taking into account the toxicological data, the metabolite ASDM is considered toxicologically non-relevant. The results of consumer risk calculations indicate that the use of DNT-162OD-R-CPd/ EVRITELL 162 OD according to the list of intended uses presented in GAP Table, causes no risk for health for the adults, toddlers and infants.

The relevance of the groundwater metabolite ASDM has already been assessed at EU level (see EFSA Scientific Report (2007) 120, 1-91), based on an extensive data package. The relevance assessment is applicable for the GAP and groundwater scenarios considered in this dRR as well. ASDM 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 the next table.

Table 10.66-1: Summary of the relevance assessment for ASDM

	Assessment step	**Result of assessment**	
	STEP 1	Metabolite of no concern?	no
on of groundwater con-	STEP 2	Max PEC_{gw}	~~1.79~~ 1.43 µg/L

			Based on	FOCUS PEARL 5.5.5 / Thiva
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;	no higher toxicity as compared to parent compound
			Classification of parent	no toxicological classification
			Classification of metabolite	no toxicological classification
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)	0.01% of ADI (infant) 0.01% of ADI (child) <0.01% of ADI (adult)
			ADI based on	2 mg/kg/bw/day parent compound nicosulfuron according to EFSA Scientific Report (2007) 120, 1-91

10.6.1 STEP 1: Exclusion of degradation products of no concern

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

10.6.2 STEP 2: Quantification of potential groundwater contamination

PEC_{gw} calculations after leaching from soil for ASDM were performed (see Part B, Section 8, chapter 8.8). The uses for which concentrations of ASDM were considered to exceed 0.1 µg/L are listed in Table 10.6-1. Possible reductions of the expected groundwater concentrations by applying risk mitigation measures are not presented here. Details on the groundwater risk assessment are given in Part B, Section 8, chapter 8.8.

10.6.3 STEP 3: Hazard assessment – identification of relevant metabolites

10.6.3.1 STEP 3, Stage 1: screening for biological activity

The biological activity of ASDM does not have comparable target activity as the parent active compound as shown in biological screening data on terrestrial plants stated in the EFSA Scientific Report (2007) 120, 1-91. ASDM is considered not relevant and is further evaluated in Stage 2.

10.6.3.2 STEP 3, Stage 2: screening for genotoxicity

ASDM was screened for genotoxic activity by the following data package of in vitro genotoxicity studies: Ames tests, a gene mutation test with mouse lymphoma cells and a chromosome aberration test with human lymphocytes (tests are summarized in the next table). Ames tests as well as the gene mutation test were negative. However, ASDM showed clastogenic effects at high concentrations in human lymphocytes. Therefore, micronuclei formation was investigated *in vivo* in mice. Because ASDM proved also negative *in vivo*, it is not considered to be relevant.

Table 10.6-2: Summary of genotoxicity studies conducted with ASDM

Type of test, species (Guideline)	Result	Details	Reference [a]
In vitro bacterial reverse mutation assay *S. typhimurium* and *E. coli*	Non-genotoxic	*S. typhimurium* TA100, TA1535, TA98, TA1537..*E. coli* WP2 uvrA. Dosed at 5000 µg/plate	Seki, 1988
In vitro bacterial reverse mutation assay *S. typhimurium*	Non-genotoxic	*S. typhimurium* TA100, TA1535, TA98, TA1537. Dosed at 5000 µg/plate	May, 1993
In vitro chromosome aberration test Human lymphocytes	Genotoxic	Clastogenic at high concentrations (>10 mm) without metabolic activation	Dance, 1993
In vitro mammalian cell gene mutation test	Non-genotoxic	Mouse lymphoma L5178Y cells Dosed up to 10 mM	Wollny, 2003a
In vivo micronucleus test Mouse	Non-genotoxic	Dosed up to 5000 mg/kg intraperitoneally	Edwards, 1995

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

ASDM is not considered relevant and is further evaluated in Stage 3. The genotoxicity studies are evaluated and referenced in RAR from 2005 and EFSA Conclusion from 2007.

According to EFSA conclusions on nicosulfuron (2007; page 44), the metabolite ASDM was shown to be non-genotoxic *in vitro or in vivo*. As a result, ASDM is not considered relevant in step 3, stage 2 and is further evaluated in step 3, stage 3.

10.6.3.3 STEP 3, Stage 3: screening for toxicity

The parent substance nicosulfuron is not classified (in accordance to Regulation (EC) No 1272/2008) as acutely or chronically toxic or very toxic, for reproductive toxicity or as a mutagen or carcinogen. Extensive toxicity testing of the active substance nicosulfuron has been carried out and the results are described in detail in the EFSA Scientific Report (2007) 120, 1-91.

In addition, ASDM has been evaluated in a number of acute and repeat dose toxicity studies. These studies were included in the 2005 DAR (RMS U.K) and were therefore previously reviewed during the EU active substance peer review (see EFSA 2007).

Table 10.6-3: Summary of the acute and repeat dose toxicity studies with ASDM

Test	Result	Reference [a]
Acute oral toxicity rat	LD_{50}: > 2000 mg/kg bw	Johnson, 1993
Acute oral toxicity mouse	LD_{50}: > 5000 mg/kg bw	Shutoh, 1992
Acute dermal toxicity rat	LD_{50}: > 2000 mg/kg bw	Johnson, 1993
28 day oral toxicity study in the rat (gavage)	NOAEL: > 1000 mg/kg bw/d	Imatanaka, 1993
90 day oral toxicity study in the rat	NOAEL: > 1000 mg/kg bw/d	Martin, 1998
One generation reproduction study	NOAEL: > 1000 mg/kg bw/d	Barton, 1999
Developmental toxicity study in the rat	NOAEL maternal: > 1000 mg/kg bw/d NOAEL developmental: = 200 mg/kg bw/d	Barton, 1998

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

ASDM was found to be of low acute oral toxicity in the rat and mouse and of low dermal toxicity. No treatment-related adverse effects were seen in a 28- day and a 90-day study in the rat. No effects on reproduction were seen in a one-generation study in the rat. No evidence of maternal toxicity was seen in a rat developmental study at dose levels of up to 1000 mg/kg bw/day while at the top dose in pups an increased incidence of dilated ureters were observed.

ASDM is not more toxic than the parent substance nicosulfuron. ASDM is therefore not considered relevant in step 3, stage 3.

10.6.4 STEP 4: Exposure assessment – threshold of concern approach

The potential exposure to ASDM is > 0.75 µg/L but < 10 µg/L. A further assessment in Step 5 is required.

10.6.5 STEP 5: Refined risk assessment

A refined assessment of the potential toxicological relevance of ASDM is presented here, based on the ADI of 2 mg/kg bw for nicosulfuron as per the EFSA Conclusion for nicrosulfuron. This ADI was derived from the repeat dose rat study, applying a safety factor of 100. Repeat dose (28-day, 90-day and 1-year) studies in dogs supported this. Potential exposure to ASDM is compared to the ADI in the next table.

Table 10.6-4: Calculation of exposure to ASDM via drinking water

Consumer group	Groundwater contamination (µg/L)	Consuming of drinking water (L/day)	Body weight (kg)	Exposure (mg/kg bw/day)	Exposure (% of ADI)
Bottle-fed infant	~~1.79~~ 1.43	0.75	5	~~0.00027~~ 0.00021	~~0.013~~ 0.011
Child		1	12	~~0.00015~~ 0.00012	~~0.007~~ 0.006
Adult		2	70	~~0.00005~~ 0.00004	~~0.003~~ 0.002

The calculated exposure of consumers to the metabolite via groundwater at the given concentration poses no unacceptable risk. As such, the given concentration of this metabolite in groundwater is permissible. There is no consumer exposure via other routes.

10.7 Relevance assessment of MU-466

Comments of ZRMs:	- The metabolite MU-466 was not considered relevant according to EFSA Scientific Report (2007). The results of the studies showed low acute toxicity of the metabolite (LD50 in rats >2000 mg/kg bw) and no genotoxic prosperities (negative results in a bacterial mutagenicity assay and in an in vitro clastogenicity and an in vitro cell mutation test with mammalian cells. - The parent substance (nicosulfuron) is not classified regarding mammalian toxicology. - The maximum PECgw of ASDM (acc. to the application rate presented in the GAP table) amounts to 0.12 µg/L. - The predicted max. PECgw value is below the upper limit for metabolites (≥0.75 µg/L); the consumer risk calculation for this metabolite is not required.

The relevance of the groundwater metabolite MU-466 has already been assessed at EU level (see EFSA Scientific Report (2007) 120, 1-91). The relevance assessment is applicable for the GAP and groundwater scenarios considered in this dRR, as well. MU-466 was not considered relevant according to the criteria laid down in the EC guidance document SA CO/221/2000 –rev.11; even though more data might be needed in future. A summary of the relevance assessment is given in the following table.

Table 10.7.1: Summary of the relevance assessment for MU-466

	Assessment step		Result of assessment	
	STEP 1		Metabolite of no concern?	no
Quantification of groundwater contamination	STEP 2		Max PEC_{gw}	~~0.15~~ 0.12 µg/L
			Based on	FOCUS PEARL 5.5.4 / Thiva
Hazard assessment	STEP 3	Stage 1	Biological activity comparable to the parent?	No (EFSA, 2007)
		Stage 2	Genotoxic properties of metabolite	Non genotoxic (EFSA, 2007)
		Stage 3	Toxic properties of metabolite;	no studies available
			Classification of parent	no toxicological classification
			Classification of metabolite	no toxicological classification
Consumer health risk assessment	STEP 4		Estimated consumer exposure via drinking water and other sources; threshold of concern approach	Below acceptable limit of 0.75 µg/L
	STEP 5		Refined risk assessment	Not acceptable
			Predicted exposure (% of ADI)	Not acceptable
			ADI based on	Not acceptable

10.7.1 STEP 1: Exclusion of degradation products of no concern

The metabolite MU-466 does not meet the criteria for products of no concern as defined in step 1 of the guidance and therefore needs further assessment.

10.7.2 STEP 2: Quantification of potential groundwater contamination

PEC_{gw} calculations after leaching from soil for MU-466 were performed (see Part B, Section 8, chapter 8.8). The uses for which concentrations of MU-466 were considered to exceed 0.1 µg/L are listed in Table 10.7-1.

10.7.3 STEP 3: Hazard assessment – identification of relevant metabolites

10.7.3.1 STEP 3, Stage 1: screening for biological activity

The biological activity of MU-466 does not have comparable target activity as the parent active compound as shown in biological screening data on terrestrial plants stated in the EFSA Scientific Report (2007) 120, 1-91. MU-466 is considered not relevant and is further evaluated in Stage 2.

10.7.3.2 STEP 3, Stage 2: screening for genotoxicity

MU-466 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. MU-466 was non-genotoxic as shown by a negative Ames test, a negative gene mutation test with mouse lymphoma cells and a negative chromosome aberration test with Chinese hamster cells (tests are summarized in Table 10.7-2). Based on these negative results, further *in vivo* testing is not necessary.

It must be noted that according to the EFSA Supporting publication 2020:EN-1837, the chromosomal aberration does not adequately address the endpoint aneugenic potential. This endpoint will need to be assessed with a micronucleus assay, e.g as per OECD TG 487 in the EU approval procedure at the latest.

Table 10.7-2: Summary of genotoxicity studies conducted with MU-466

Type of test, species (Guideline)	Result	Details	Reference[a]
Bacterial Reverse Mutation Assay *S. typhimurium* and *E. coli*	Non-genotoxic	Not fully compliant with current guidelines Dosed up to 5000 ug/plate	Wollny 1996
In vitro mammalian cell gene mutation test	Non-genotoxic	Mouse lymphoma L5178Y cells Dosed up to 15 mM	Wollny 2003d
In vitro chromosome aberration test	Non-genotoxic	Chinese Hamster V79 cells Dosed up to 10 mM	Schulz 2003c

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

MU-466 is not considered relevant and is further evaluated in Stage 3. The genotoxicity studies are evaluated and referenced in RAR from 2005 and EFSA Conclusion from 2007.

10.7.3.3 STEP 3, Stage 3: screening for toxicity

The parent substance nicosulfuron is not classified (in accordance to Regulation (EC) No 1272/2008) as acutely or chronically toxic or very toxic, for reproductive toxicity or as a mutagen or carcinogen. Extensive toxicity testing of the active substance nicosulfuron has been carried out and the results are described in detail in the EFSA Scientific Report (2007) 120, 1-91.

MU-466 was tested in an acute oral toxicity study in rats. No mortality or clinical signs were observed in this study and the LD_{50} was >2000 mg/kg bw (Arcelin, 1996). This study was included in the 2005 DAR (RMS U.K) and was therefore previously reviewed during the EU active substance peer review (see EFSA 2007).

The metabolite was not considered relevant during the EU active substance peer review for nicosulfuron (EFSA 2007) and is therefore not considered relevant in step 3, stage 3 here.

10.7.4 STEP 4: Exposure assessment – threshold of concern approach

The potential exposure to MU-466 is < 0.75 µg/L. A further assessment in step 5 is not required.

10.7.5 STEP 5: Refined risk assessment

Not applicable.

10.8 Relevance assessment of IN-L9223

Comments of ZRMs:

- According to available toxicological data, the metabolite IN-L9223 is considered not genotoxic and has no pesticidal activity. However, the toxicological profile of this metabolite is incomplete and does not allow for establishing a reference dose. The results from the OECD QSAR toolbox indicate that IN-L9223 might be more toxic than the parent substance (predicted oral LD50 value) (RAR, Thifensulfuron-methyl - Volume 3, Annex B.6: Toxicology and Metabolism).
- The parent substance is not classified regarding mammalian toxicology. The ECHA RAC did not classify thifensulfuron-methyl regarding reprotoxicity and carcinogenicity, which means that it is not necessary to consider the relevance of the metabolites IN-L9223.
- The maximum PECgw of IN-L9223 (acc. to the application rate presented in the GAP table) amounts to 0.782 µg/L.
- The predicted max. PECgw value is above the upper limit for metabolites (≥0.75 µg/L); the consumer risk calculation for this metabolite is required. Although no reference dose has been established, the consumer exposure with drinking water was assessed also using maximum allowable concentration (MAC) based on 10% of thifensulfuron - methyl ADI value.

	MAC (µg/L) (based on 10% ADI, as conservative approach)	% of MAC	Exposure (µg/kg b.w./d)	% ADI (parent substance)
Adults (60 kg b.w.)	30	**2.6**	0.026	0.26
Toddlers (10 kg b.w.)	10	**7.82**	0.078	0.78
Infants (5 kg b.w.)	3.75	**20.9**	0.117	1.17

Conclusions:

Taking into account the toxicological data, the metabolite IN-L9223 is considered toxicologically non-relevant. The results of consumer risk calculations indicate that the use of DNT-162OD-R-CPd/ EVRITELL 162 OD according to the list of intended uses presented in GAP Table, causes no risk for health for the adults, toddlers and infants.

Table 10.8-1: Summary of the relevance assessment for IN-L9223

	Assessment step		**Result of assessment**	
	STEP 1		Metabolite of no concern?	no
Quantification of groundwater contamination	STEP 2		Max PEC_{gw}	0.782 µg/L
			Based on	FOCUS PEARL 5.5.5 / Thiva
ard assess	STEP 3	Stage 1	Biological activity comparable to	No

			the parent?	
		Stage 2	Genotoxic properties of metabolite	Non genotoxic
		Stage 3	Toxic properties of metabolite;	Non toxic
			Classification of parent	no toxicological classification
			Classification of metabolite	no toxicological classification
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)	1.2% of ADI (infant) 0.7% of ADI (child) 0.2% of ADI (adult)
			ADI based on	0.01 mg/kg/bw/day parent compound thifensulfuron methyl according to EFSA Scientific Report (2015)

10.8.1 STEP 1: Exclusion of degradation products of no concern

The metabolite IN-L9223 does not meet the criteria for products of no concern as defined in step 1 of the guidance and therefore needs further assessment.

10.8.2 STEP 2: Quantification of potential groundwater contamination

PEC_{gw} calculations after leaching from soil for IN-L9223 were performed (see Part B, Section 8). The uses for which concentrations of IN-L9223 were considered to exceed 0.1 µg/L are listed in Table 10.8-1.

10.8.3 STEP 3: Hazard assessment – identification of relevant metabolites

10.8.3.1 STEP 3, Stage 1: screening for biological activity

The biological activity of IN-L9223 does not have comparable target activity as the parent active compound as shown in biological screening data on terrestrial plants stated in the EFSA Scientific Report (2015); 13(7):4201. IN-L9223 is considered not relevant and is further evaluated in Stage 2.

10.8.3.2 STEP 3, Stage 2: screening for genotoxicity

IN-L9223 was screened for genotoxic activity and was found to be negative in the following *in vitro* genotoxicity studies: Ames assay (DuPont-31622), gene mutation assay with mammalian cells (DuPont-31624), and a chromosome aberration test (DuPont-31623). All studies are summarized in the Thifensulfuron methyl RAR, Volume 3, Annex B.6, 2014.
As a result, IN-L9223 is not considered relevant in step 3, stage 2 and is further evaluated in step 3, stage 3.

10.8.3.3 STEP 3, Stage 3: screening for toxicity

Thifensulfuron methyl, the parent to IN-L9223, is not classified for any toxicity. Extensive toxicity testing of the parent compound thifensulfuron methyl has been carried out and the results are described in detail in the thifensulfuron methyl RAR, Volume 3, Annex B.6, 2014. thifensulfuron methyl had a low acute oral, dermal, and inhalation toxicity, and currently it is not classified for chronic toxicity, or carcinogenicity. The environmental metabolite IN-L9223 was also a rat metabolite and presumed to be present during the development of the toxicology database for thifensulfuron methyl. Therefore, it is reasonable to also expect that they were tested in parallel in the studies performed. In addition, the OECD Toolbox predicted the oral LD_{50} value for IN-L9223 to be 800 mg/kg (thifensulfuron methyl RAR, Volume 3, Annex B.6, 2014).
Because IN-L9223 has passed stage 3 of step 3 and is considered as 'not relevant', an exposure assessment (STEP 4) is required.

10.8.4 STEP 4: Exposure assessment – threshold of concern approach

IN-L9223 was not considered relevant in the hazard assessment of Step 3.

The potential exposure to IN-L9223 is > 0.75 µg/L but <10 µg/L. A further assessment in Step 5 is required. A refined risk assessment is provided the following section.

10.8.5 STEP 5: Refined risk assessment

IN-L9223 has a PEC_{gw} between 0.75 µg/L and 10 µg/L and is identified as requiring a refined risk assessment. The highest concentration estimated in the FOCUS groundwater modelling was 0.782 µg/L. A refined assessment of the potential toxicological significance including the selected ADI is presented here. In accordance with the assessment agreed at EU level (EFSA 2015) the refined risk assessment for IN-L9223 has been performed using the ADI of thifensulfuron methyl (0.01mg/kg bw/day).
The consumer risk assessment demonstrates an acceptable risk. The estimated safety margin including potential exposure via other routes besides drinking water for IN-L9223 are 1.2% of ADI (infant), 0.7% of ADI (child) and 0.2% of ADI (adult). Potential exposure to IN-L9223 is compared to the ADI in the below table.

Table 10.8-2: Calculation of exposure to IN-L9223 via drinking water

Consumer group	Groundwater contamination (µg/L)	Consuming of drinking water (L/day)	Body weight (kg)	Exposure (mg/kg bw/day)	Exposure (% of ADI)
Bottle-fed infant	0.782	0.75	5	0.00012	1.173
Child		1	12	0.00007	0.652
Adult		2	70	0.00002	0.223

10.9 Relevance assessment of IN-JZ789

Comments of ZRMs:	- According to available toxicological data the metabolite IN-JZ789 is considered not genotoxic. - The parent substance is not classified in regard to mammalian toxicology. The ECHA RAC did not classify thifensulfuron-methyl regarding reprotoxicity and carcinogenicity, which means that it is not necessary to consider the relevance of the metabolites IN-JZ789.

	- The maximum PECgw of IN-JZ789 (acc. to the application rate presented in the GAP table) amounts to 0.309 µg/L. - The predicted max. PECgw value is below the upper limit for metabolites (≥0.75 µg/L), the consumer risk calculation for this metabolite is not required. Conclusions: Taking into account the toxicological data, the metabolite IN-JZ789 is considered toxicologically non-relevant. The use of DNT-162OD-R-CPd/ EVRITELL 162 OD according to the list of intended uses presented in GAP Table, causes no risk for health for the adults, toddlers and infants.

Table 10.9-1: Summary of the relevance assessment for IN-JZ789

	Assessment step		**Result of assessment**	
	STEP 1		Metabolite of no concern?	no
Quantification of groundwater contamination	STEP 2		Max PEC_{gw}	0.309 µg/L
			Based on	FOCUS PEARL 5.5.5 / Thiva
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;	Non toxic
			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	acceptable (<0.75 µg/L)
	STEP 5		Refined risk assessment	n.a
			Predicted exposure (% of ADI)	n.a
			ADI based on	n.a

10.9.1 STEP 1: Exclusion of degradation products of no concern

The metabolite IN-JZ789 does not meet the criteria for products of no concern as defined in step 1 of the guidance and therefore needs further assessment.

10.9.2 STEP 2: Quantification of potential groundwater contamination

PEC_{gw} calculations after leaching from soil for IN-JZ789 were performed (see Part B, Section 8). The uses for which concentrations of IN-JZ789 were considered to exceed 0.1 µg/L are listed in Table 10.9-1.

10.9.3 STEP 3: Hazard assessment – identification of relevant metabolites

10.9.3.1 STEP 3, Stage 1: screening for biological activity

According to the RAR of thifensulfuron-methyl (2014), no information on the biological activity of IN-JZ789 has been provided by either DuPont or the EU TSM Task Force. Therefore, no conclusion can be reached about the relevance or non-relevance of this metabolite in relation to its pesticidal activity. However, while we await this information, IN-JZ789 could be further screened in stage 2.

10.9.3.2 STEP 3, Stage 2: screening for genotoxicity

IN-JZ789 was screened for genotoxic activity, and was found to be negative in the following *in vitro* genotoxicity studies: Ames test (DGV0081), micronucleus test (DGV0082)) are summarised in the thifensulfuron methyl RAR, Volume 3, Annex B.6, 2014.
As a result, IN-JZ789 is not considered relevant in step 3, stage 2 and is further evaluated in step 3, stage 3.

10.9.3.3 STEP 3, Stage 3: screening for toxicity

IN-JZ789 is structurally related to rat metabolite IN-L9225. However thifensulfuron methyl, the parent to IN-L9225, is not classified for any toxicity.
Therefore, the acute toxicity data available for IN-L9225 may be used as a surrogate for IN-JZ789. As stated in RAR (Volume 3, Annex B.6, 2014), oral LD_{50} value for IN-L9225 was >2000 mg/kg in female rats. Based on the acute oral LD_{50} of IN-L9225, it is concluded that IN-JZ789 does not meet the hazard criteria for relevant metabolites and is further evaluated in Step 4.

10.9.4 STEP 4: Exposure assessment – threshold of concern approach

IN-JZ789 was not considered relevant in the hazard assessment of Step 3.

The PEC_{GW} for this metabolite IN-JZ789 is below < 0.75 µg/L and does not exceed the toxicological threshold of concern as defined in EC guidance document SANCO/221/2000 –rev.11.

10.9.5 STEP 5: Refined risk assessment

The potential exposure to IN-JZ789 is < 0.75 µg/L and further assessment in Step 5 is not required.

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
KIIA 5.8	Wollny, H.	1995a	Salmonella typhimurium reverse mutation assay with AUSN Report no. CCR 521300; 1995-11-29 GLP: Yes Published: No	N	ISK
KIIA 5.8	Wollny, H.	2003b	Cell mutation assay at the thymidine kinase locus (TK+/-) in mouse lymphoma L5178Y cells, with AUSN Report no. 786402, 2023-08-19 GLP: Yes Published: No	N	ISK

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**
KIIA 5.8	Schulz, M.	2003a	In vitro chromosomes abberation test in chinese hamster V79 cells with AUSN Report no. 786401, 2003-08-27 GLP: Yes Published	N	ISK
KIIA 5.8	[redacted]	1996	Acute oral toxicity study with AUSN in rats Report no. RCC 601863 GLP: Yes Published	Y	ISK
KIIA 5.8	[redacted]	1996	Acute oral toxicity study with UCSN in rats RCC 601874 GLP: Yes Published	Y	ISK
KIIA 5.8	Wollny, H.-E.	1995	Salmonella typhimurium reverse mutation assay with UCSN Report no. RCC 601918 CCR 521400 GLP: Yes Published: No	N	ISK
KIIA 5.8	Wollny, H.	2003	Cell Mutation Assay at the Thymidine Kinase Locus (TK+/-) in Mouse Lymphoma L5178Y Cells with UCSN Report no. 786502 GLP: Yes Published	N	ISK
KIIA 5.8	Schulz, M.	2003	In vitro chromosomes abberation test in chinese hamster V79 cells with UCSN Report no. 786501 GLP: Yes Published	N	ISK
KIIA 5.8	Seki, H.	1991	A reverse mutation assay of N,N-dimethyl-2-aminosulfonyl-3-pyridinecarboxyamide using bacteria Report no. 1970 GLP: No Published	N	ISK
KIIA 5.8	May, K.	1993	ASDM: Assessment of mutagenic potential in histidine auxotrophs of salmonella typhimurium (the Ames test) Report no. 93/0572 ! ISK/200 ! 93/ISK200/0572 GLP: Yes Published	N	ISK
KIIA 5.8	Dance, C. A.	1993	In vitro assessment of the clastogenic activity of ASDM in cultured human lymphocytes Report no. 93/0728 ! ISK/201 ! 93/ISK201/0728 GLP: Yes Published	N	ISK

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
KIIA 5.8	Wollny, H.	2003	Cell mutation assay at the thymidine kinase locus (TK+/-) in mouse lymphoma L5178Y cells with ASDM Report no. 786700 GLP: Yes Published	N	ISK
KIIA 5.8	[redacted]	1995	ASDM: Mouse micronucleus test to comply with O.E.C.D. Guideline 474 (1983) Report no. 95/ISK214/0633 ! 95/0633 GLP: Yes Published	Y	ISK
KIIA 5.8	[redacted]	1993	ASDM: Acute oral toxicity study in the rat Report no. 93/0591 ! ISK/195 ! 93/ISK195/0591 GLP: Yes Published	Y	ISK
KIIA 5.8	[redacted]	1992	ASDM: Acute oral toxicity study in mice Report no. IET 92-0103 GLP: Yes Published	Y	ISK
KIIA 5.8	[redacted]	1993	ASDM: Acute percutaneous toxicity study in the rat Report no. 93/0605 ! ISK/196 ! 93/ISK196/0605 GLP: Yes Published	Y	ISK
KIIA 5.8	[redacted]	1993	Twenty-eight-day repeated-dose oral toxicity study of ASDM in rats Report no. D-3335 ! D92-1087 ! B11-0183 GLP: Yes Published	Y	ISK
KIIA 5.8	[redacted]	1998	DAM 520: 13 week toxicity study in rats with administration by gavage Report no. 15167 ! 453683 GLP: Yes Published	Y	ISK
KIIA 5.8	[redacted]	1998	DAM 520: One generation reproduction study in rats Report no. 16041 ! 491776 GLP: Yes Published	Y	ISK
KIIA 5.8	[redacted]	1998	DAM 520: Developmental toxicity study in rats Report no. 15251 ! 491760 GLP: Yes Published	Y	ISK

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
KIIA 5.8	Matsumoto, K.	2004a	HMUD: Reverse mutation test Institute of Environmental Toxicology, Japan IET 04-0052 GLP: Yes Published: No	N	ISK Task Force Nicosulfuron
KIIA 5.8	Matsumoto, K.	2004b	HMUD: Gene mutation test in mouse lymphoma cells Institute of Environmental Toxicology, Japan IET 04-0054 GLP: Yes Published: No	N	ISK Task Force Nicosulfuron
KIIA 5.8	Matsumoto, K.	2004c	HMUD: In vitro chromosome aberration test Institute of Environmental Toxicology, Japan IET 04-0053 GLP: Yes Published: No	N	ISK Task Force Nicosulfuron

Appendix 2 Additional information

Comments of zRMS:	