REGISTRATION REPORT

Part B

Section 10

Assessment of the relevance of metabolites in groundwater

Detailed summary of the risk assessment

Product code: ADM.4651.H.1.A (former A18032E)

Product name(s): NIKITA

Chemical active substances:

Dicamba, 312.5 g/kg
Mesotrione, 150 g/kg
Nicosulfuron, 100 g/kg

Central Zone

Zonal Rapporteur Member State: Poland

CORE ASSESSMENT

Sponsor: ADAMA

Applicant: ADAMA

Submission date: June 2020

MS Finalisation date: December 2021 (initial Core Assessment)

June 2022 (final Core Assessment)

Version history

When	What
June 2020	Applicant initial dRR
December 2021	Initial assessment by the zRMS 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~~.
June 2022	Final report (Core Assessment updated following the commenting period). Additional information/assessments included by the zRMS in the report in response to comments received from the cMS and the Applicant are highlighted in yellow. Information no longer relevant ~~is struck through and shaded~~.

ADAMA use the code ADM.4651.H.1.A for the formulation but for consistency the former Syngenta code A18032E is used throughout the dRR. Table of Contents

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Several risk assessments of this dRR are based on the worst case GAP for C-EU with a higher application rate and are therefore more conservative compared to the applied GAP in Poland.

Reviewer comments:

This part of dossier has been submitted to support registration of the herbicide NIKITA (ADM-4651.H.1.A = A18032E) according art. 33 of 1107/2009.
Document summarizes data related to the relevance of metabolites in groundwater. Information contained in dRR Part B10 has been reviewed for the purposes of ongoing registration and considered as sufficient and appropriate for risk assessment.
Refinement has been added to STEP 5 for the following nicosulfuron methabolites (HUMD, AUSN, UCSN, ASDN) reflecting EFSA recommendation (*EFSA Scientific Committee; Guidance on selected default values to be used by the EFSA Scientific Committee, Scientific Panels and Units in the absence of actual measured data. EFSA Journal 2012;10(3):2579. [32 pp.] doi:10.2903/j.efsa.2012.2579*) regarding child bodyweight for dietary exposure assessment.

10 Relevance of metabolites in groundwater

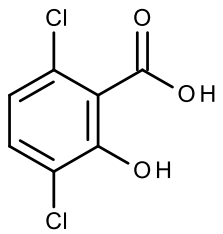
10.1 General information

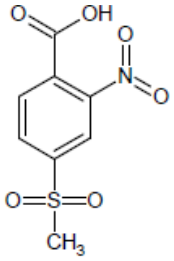
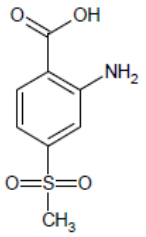
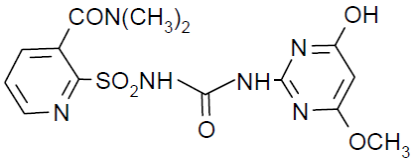
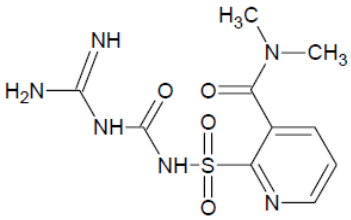
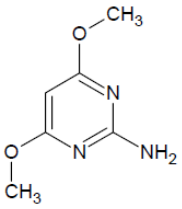
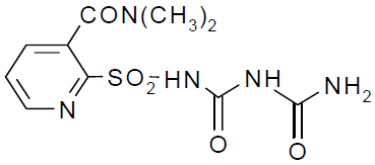
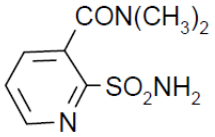
PEC_{GW} of the metabolites of dicamba (DCSA, 3,6-dichloro-2-hydroxybenzoic acid) and mesotrione (MNBA, 4-(methylsulfonyl)-2-nitrobenzoic acid and AMBA, 2-amino-4-(methylsulfonyl) benzoic acid) as well as the metabolite ADMP (4,6-dimethoxypyrimidin-2-amine) of nicosulfuron were all < 0.1 µg/L in the relevant application patterns (please see dRR Part B, Section 8, chapter 8.8.2 and Table 10.1-1 below). No assessment is thus required for any metabolite of mesotrione or dicamba, and for metabolite ADMP of nicosulfuron.

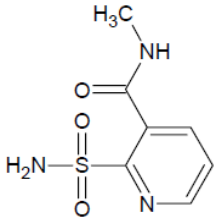
The nicosulfuron metabolites HMUD (2-{[(4-hydroxy-6-methoxypyrimidin-2-yl)carbamoyl] sulfamoyl}-N,N-dimethylpyridine-3-carboxamide), AUSN(2-[carbaminidoylcarbamoyl)sulfamoyl]-N,N-dimethyl-pyridine-3-carboxamide), UCSN (2-[(carbamoylcarbamoyl)sulfamoyl]-N,N-dimethylpyridine-3-carboxamide), ASDM (N,N-dimethyl-2-sulfamoylpyridine-3-carboxamide) and MU-466 (N-methyl-2-sulfamoylpyridine-3-carboxamide) are predicted to occur in groundwater at concentrations above 0.1 µg/L (see chapter 8.8.2). Assessment of the relevance of these metabolites according to the stepwise procedure of the EC guidance document SANCO/221/2000 –rev.10 is therefore required.

General information on the metabolites is provided in Table 10.1-1. The impact of the relevance assessment on whether a particular GAP use leads to acceptable risk or not is presented in the summary of the cGAP evaluation in chapter 8.1 of the dRR Part B, Section 8 (Environmental fate and behaviour).

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

Name of active substance	Metabolite name and code	Structural/molecular formula	Trigger for relevance assessment	
Dicamba	NOA414746 (DCSA)		Max PEC_{GW} Based on:	Maize (1 x 264 g a.s./ha, early post-emergence): < 0.001 µg/L All models and scenarios

Name of active sub-stance	Metabolite name and code	Structural/molecular formula	Trigger for relevance assessment	
Mesotrione	MNBA (NOA437130)		Max PEC$_{GW}$ Based on:	Maize (1 x 75 ~~100~~ g a.s./ha, early post-emergence): 0.083 µg/L ~~0.075 µg/L~~ FOCUS-PELMO 5.5.3, scenario Hamburg, acidic soils
	AMBA (NOA422848)		Max PEC$_{GW}$ Based on:	Maize (1 x 75 ~~100~~ g a.s./ha, early post-emergence): 0.015 µg/L ~~0.020 µg/L~~ FOCUS-PEARL 4.4.4 ~~PELMO 5.5.3~~, scenario Hamburg (Okehampton not relevant for Poland) ~~Okehampton~~
Nicosulfuron	HMUD		Max PEC$_{GW}$ Based on:	Maize (1 x 40 ~~60~~ g a.s./ha, early post-emergence): 0.256 µg/L ~~1.87 µg/L~~ FOCUS-PEARL 4.4.4, scenario Hamburg, triennial application
	AUSN		Max PEC$_{GW}$ Based on:	Maize (1 x 40 ~~60~~ g a.s./ha, early post-emergence): 0.667 µg/L ~~4.53 µg/L~~ FOCUS-PEARL 4.4.4, scenario Hamburg, triennial application (Thiva not relevant for Poland) ~~Thiva~~
	ADMP		Max PEC$_{GW}$ Based on:	Maize (1 x 40 ~~60~~ g a.s./ha, early post-emergence): <0.001 µg/L ~~0.002 µg/L~~ FOCUS-PEARL 4.4.4, all scenarios, triennial application ~~scenario Hamburg / Okehampton~~
	UCSN		Max PEC$_{GW}$ Based on:	Maize (1 x 40 ~~60~~ g a.s./ha, early post-emergence): 0.397 µg/L ~~3.41 µg/L~~ FOCUS-PEARL 4.4.4, scenario Hamburg, triennial application (Thiva not relevant for Poland) ~~Thiva~~
	ASDM		Max PEC$_{GW}$ Based on:	Maize (1 x 40 ~~60~~ g a.s./ha, early post-emergence): 0.426 µg/L ~~3.21 µg/L~~ FOCUS-PEARL 4.4.4, scenario Hamburg, triennial application (Thiva not relevant for Poland) ~~Thiva~~

Name of active sub-stance	Metabolite name and code	Structural/molecular formula	Trigger for relevance assessment	
	MU-466		Max PEC_{GW} Based on:	Maize (1 x 40 ~~60~~ g a.s./ha, early post-emergence): 0.026 µg/L ~~0.226 µg/L~~ FOCUS-PELMO 5.5.3 ~~PEARL 4.4.4~~, scenario Châteaudun, triennial application (Thiva not relevant for Poland) ~~Thiva~~

zRMS comments:

Table above was corrected accordingly with consideration of the outcome of groundwater exposure assessment performed in area of Section 8. Since Poland is the only cMS indicated in the GAP table, only results for scenarios representative for Poland were taken into account.

Due to potential leaching of nicosulfuron, uses of A18032E had to be restricted to single use every third year, which significantly reduced PEC_{GW} values for nicosulfuron metabolites, which at triennial use of the product at 0.4 kg/ha are all <0.75 µg/L and no further consumer risk assessment is deemed necessary since all nicosulfuron groundwater metabolites are toxicologically not relevant.

Nevertheless, the evaluation below has been checked and corrected, if relevant, as being protective for the accepted use pattern of A18032E. Assessment was based on PEC_{GW} initially proposed by the Applicant as representing extremely worst case for triennial application.

After the commenting period additional corrections were made in Table 10.1-1 since the reported application rates did not corresponded with rates considered in zRMS modelling performed in area of Section 8. Furthermore, for mesotrione metabolite AMBA and nicosulfuron metabolite MU-466 not correct models were mentioned as giving the highest PEC_{GW} values. Introduced changes had no impact on the outcome of the evaluation since PEC_{GW} remained the same as reported in the initial Core Assessment.

10.2 Relevance assessment of the nicosulfuron metabolite HMUD

Summary:

The relevance of the groundwater metabolite HMUD has already been assessed and the assessment agreed at EU level (see EFSA Scientific Report, 2007). HMUD is considered not 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 10.2-1 and the corresponding studies are listed in the corresponding sections.

Table 10.2-1: 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} Based on	Maize (1 x 40 g a.s./ha, early post-emergence): 1.23 µg/L FOCUS-PEARL 4.4.4, scenario Hamburg
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: Classification of parent Classification of metabolite	 No classification No 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)	< 0.1 % of ADI (ADI = 2 mg nicosulfuron / kg bw / day)
			ADI based on	28, 90 and 1-year toxicity studies in the dog and the chronic rat study, safety factor of 100

10.2.1 STEP 1: Exclusion of degradation products of no concern

10.2.2 STEP 2: Quantification of potential groundwater contamination

PEC_{GW} calculations after leaching from soil for HMUD were performed (see Part B, Section 8, chapter 8.8.2). The uses for which concentrations of HMUD were considered to exceed 0.1 µg/L are listed in Table 10.2-1. Details are given in Part B, Section 8, chapter 8.8.2.

10.2.3 STEP 3: Hazard assessment – identification of relevant metabolites

10.2.3.1 STEP 3, Stage 1: screening for biological activity

The biological activity of HMUD has been assessed within the last EU peer review process (EFSA Conclusion 2007) considering herbicidal activity on algae and Lemna. Full details are provided in the dRR Part B9. Information on herbicidal screening for biological activity is included within the Draft Assessment Report for nicosulfuron. From these studies, it can be concluded that the herbicidal activity of HMUD is far less than 50% of the activity of the parent molecule. HUMD is therefore considered not relevant and is further evaluated in Stage 2.

10.2.3.2 STEP 3, Stage 2: screening for genotoxicity

HMUD was screened for genotoxic activity in the studies listed below:

Table 10.2-2: Summary of genotoxicity studies conducted with HMUD

Type of test, species (Guideline)	Result	Details	Reference
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)*

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

HMUD was shown to be non-genotoxic. HMUD is considered not relevant for this step and is further evaluated in Step 3, Stage 3.

10.2.3.3 STEP 3, Stage 3: screening for toxicity

The parent molecule, nicosulfuron, is not classified as acutely or chronically toxic or very toxic, for reproductive toxicity or as a carcinogen (or corresponding classification in accordance to CLP 1272/2008). 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. There are no reasons to expect that HMUD may be toxic or highly toxic. HMUD has not been subject to targeted testing but is structurally very similar to the parent nicosulfuron on which an assessment of toxicity of HMUD can be based (see Step 5). HMUD is considered not relevant in this step and is further evaluated in Step 4/5.

10.2.4 STEP 4: Exposure assessment – threshold of concern approach

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

10.2.5 STEP 5: Refined risk assessment

HMUD has a PEC_{GW} between 0.75 µg/L and 10 µg/L. A refined assessment of the potential toxicological significance including the selected ADI is presented here.

The consumer risk assessment demonstrates an acceptable risk. The estimated safety margin for HMUD is > 99.9 % of ADI for infant, child and adult. Potential exposure via other routes besides drinking water was not considered in these calculations. However, this can be considered acceptable due to the very large safety margin.

Justification for the selected ADI:
The structure of HMUD is very similar to that of nicosulfuron. In soil, HMUD is formed by O-demethylation of a methoxy group on the pyrimidine ring of nicosulfuron. From a toxicological perspective, the removal of a single methyl group is minor and is likely to result in a toxicology profile comparable to that of the active substance. For this reason the nicosulfuron ADI is considered appropriate for the refined risk assessment for HMUD. The ADI for nicosulfuron was derived from the 28, 90 and 1-year toxicity studies in the dog and the chronic rat study using a safety factor of 100 (see table below).

Table 10.2-3: Acceptable Daily Intake endpoint for parent (nicosulfuron)

Study type	NO(A)EL (mg/kg bw/day)	Safety factor	ADI (mg/kg bw/day)
28, 90 and 1-year toxicity studies in the dog and the chronic rat study	200	100	2.0

The calculation of the risk (% ADI) for a 5-kg bottle-fed infant (consuming 0.75 L/day), ~~10 kg~~ **12 kg** child (consuming 1.0 L/day) and a 70-kg adult (consuming 2.0 L/day) is shown in the following table.

Table 10.2-4: Refined risk assessment – TMDI of HMUD and the parent ADI

Person	Maximum residues in ground water (µg/L) **PECgw**	Exposure (L/day)	Individual body weight (kg)	TMDI (mg/kg bw /day)	% of ADI
1 x 40 g a.s./ha, early post-emergence					
Bottle-fed infant	1.23	0.75	5	1.85E-04	0.0092%
Child		1	~~10~~ **12**	~~1.23E-04~~ **$1.025x10^{-4}$**	~~0.0062%~~ **$5.125x10^{-3}$%**
Adult		2	70	3.51E-05	0.0018%

The maximum consumption of the ADI is that for a bottle fed infant 60 g a.s/ha early post-emergent scenario where 0.014% of the ADI is used. Based on this minimal consumption of the ADI in the most conservative scenario, HMUD can be considered as non-relevant.

10.3 Relevance assessment of the nicosulfuron metabolite AUSN

Summary:

The relevance of the groundwater metabolite AUSN has already been assessed and the assessment agreed at EU level (see EFSA Scientific Report, 2007). AUSN is considered not relevant according to the criteria laid down in the EC guidance document SANCO/221/2000 –rev.10. A summary of the relevance assessment is given in Table 10.3-1 and the corresponding studies are listed in the corresponding sections.

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

	Assessment step		Result of assessment	
	STEP 1		Metabolite of no concern?	No
Quantification of groundwater contamination	STEP 2		Max PEC_{GW} Based on	Maize (1 x 40 g a.s./ha, early post-emergence): 2.99 µg/L FOCUS-PEARL 4.4.4, scenario 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: Classification of parent Classification of metabolite	 No classification No 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)	< 0.1 % of ADI (ADI = 2 mg nicosulfuron / kg bw / day)
			ADI based on	28, 90 and 1-year toxicity studies in the dog and the chronic rat study, safety factor of 100

10.3.1 STEP 1: Exclusion of degradation products of no concern

10.3.2 STEP 2: Quantification of potential groundwater contamination

PEC_{GW} calculations after leaching from soil for AUSN were performed (see Part B, Section 8, chapter 8.8.2). The uses for which concentrations of AUSN were considered to exceed 0.1 µg/L are listed in Table 10.3-1. Details are given in Part B, Section 8, chapter 8.8.2.

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 AUSN has been assessed within the last EU peer review process (EFSA Conclusion 2007) considering herbicidal activity on algae and Lemna. Full details are provided in the dRR Part B9. Information on herbicidal screening for biological activity is included within the Draft Assessment Report for nicosulfuron. From these studies, it can be concluded that the herbicidal activity of AUSN is far less than 50% of the activity of the parent molecule. AUSN is therefore considered not relevant and is further evaluated in Stage 2.

10.3.3.2 STEP 3, Stage 2: screening for genotoxicity

AUSN was screened for genotoxic activity in the studies listed below.

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

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

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

AUSN was shown to be non-genotoxic. AUSN is considered not relevant in this step and is further evaluated in Step 3, Stage 3.

10.3.3.3 STEP 3, Stage 3: screening for toxicity

The parent molecule, nicosulfuron, is not classified as acutely or chronically toxic or very toxic, for reproductive toxicity or as a carcinogen (or corresponding classification in accordance to CLP 1272/2008). AUSN has been tested in an acute toxicity study:

Table 10.3-3: Summary of acute toxicity of AUSN

Test	Result	Reference
Acute oral toxicity rat	LD_{50} >2000 mg/kg	xxxxxxxxxxxxxAllard (1996)[a]

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

AUSN is of low toxicity by the acute oral route and is, therefore, not more toxic than parent. AUSN is considered not relevant in this step and is further evaluated in Step 4/5.

10.3.4 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.

10.3.5 STEP 5: Refined risk assessment

AUSN has a PEC_{GW} between 0.75 µg/L and 10 µg/L. A refined assessment of the potential toxicological significance including the selected ADI is presented here.

The consumer risk assessment demonstrates an acceptable risk. The estimated safety margin for AUSN is > 99.9 % of ADI for infant, child and adult. Potential exposure via other routes besides drinking water was not considered in these calculations. However, this can be considered acceptable due to the very large safety margin.

Justification for the selected ADI:
As no repeat dose toxicity studies are available for AUSN the risk assessment has been performed using the ADI of nicosulfuron of 2 mg/kg, derived from the 28, 90 and 1-year toxicity studies in the dog and the chronic rat study, and using a safety factor of 100.

Table 10.3-4: Acceptable Daily Intake endpoint for AUSN

Molecule used as basis for the ADI	Study type	NO(A)EL (mg/kg bw/day)	Safety factor	ADI (mg/kg bw/day)
Nicosulfuron	28, 90 and 1-year toxicity studies in the dog and the chronic rat study	200	100	2.0

The calculation of the risk (% ADI) for a 5-kg bottle-fed infant (consuming 0.75 L/day), ~~10 kg~~ **12kg** child (consuming 1.0 L/day) and a 70-kg adult (consuming 2.0 L/day) is shown in the following table.

Table 10.3-5: Refined risk assessment – TMDI of AUSN based on the parent ADI

Compound on which ADI is based	Person	Maximum residues in ground water (µg/L)	Exposure (L/day)	Individual body weight (kg)	TMDI (mg/kg bw /day)	% of ADI
Nicosulfuron	***1 x 40 g a.s./ha, early post-emergence***					
	Bottle-fed infant	2.99	0.75	5	4.49E-04	0.022%
	Child		1	~~10~~ **12**	~~2.99E-04~~ **$2.49x10^{-4}$**	~~0.015%~~ **0.0124%**
	Adult		2	70	8.54E-05	0.0043%

The maximum consumption of the ADI is that for a bottle fed infant 60 g a.s/ha early post-emergent scenario where 0.034% of the ADI of nicosulfuron. Based on this minimal consumption of the AUSN can be considered as non-relevant.

10.4 Relevance assessment of the nicosulfuron metabolite UCSN

Summary:

The relevance of the groundwater metabolite UCSN has already been assessed and the assessment agreed at EU level (see EFSA Scientific Report, 2007). UCSN is considered not relevant according to the criteria laid down in the EC guidance document SANCO/221/2000 –rev.10. A summary of the relevance assessment is given in Table 10.4-1 and the corresponding studies are listed in the corresponding sections.

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

	Assessment step		Result of assessment	
	STEP 1		Metabolite of no concern?	No
Quantification of groundwater contamination	STEP 2		Max PEC_{GW} Based on	Maize (1 x 40 g a.s./ha, early post-emergence): 2.27 µg/L FOCUS-PEARL 4.4.4, scenario 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: Classification of parent Classification of metabolite	 No classification No 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)	< 0.1 % of ADI (ADI = 2 mg nicosulfuron / kg bw / day)
			ADI based on	28, 90 and 1-year toxicity studies in the dog and the chronic rat study, safety factor of 100

10.4.1 STEP 1: Exclusion of degradation products of no concern

10.4.2 STEP 2: Quantification of potential groundwater contamination

PEC_{GW} calculations after leaching from soil for UCSN were performed (see Part B, Section 8, chapter 8.8.2). The uses for which concentrations of UCSN were considered to exceed 0.1 µg/L are listed in Table 10.4-1. Details are given in Part B, Section 8, chapter 8.8.2.

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 UCSN does not have comparable target activity as the parent active compound as shown in biological screening data. Information on screening for biological activity is included within the Draft Assessment Report for nicosulfuron. UCSN is considered not relevant and is further evaluated in Stage 2.

10.4.3.2 STEP 3, Stage 2: screening for genotoxicity

UCSN was screened for genotoxic activity in the studies listed below.

Table 10.4-2: 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)[a]
In vitro mammalian cell gene mutation test	Non-genotoxic	Mouse lymphoma L5178Y cells Dosed up to 10 mM	Wollny (2003c)[a]
In vitro chromosome aberration test	Non-genotoxic	Chinese Hamster V79 cells Dosed up to 10 mM	Schulz (2003c)[a]

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

UCSN was shown not to be genotoxic. UCSN is considered not relevant at this step and is further evaluated in Step 3, Stage 3.

10.4.3.3 STEP 3, Stage 3: screening for toxicity

The parent molecule, nicosulfuron, is not classified as acutely or chronically toxic or very toxic, for reproductive toxicity or as a carcinogen (or corresponding classification in accordance to CLP 1272/2008). UCSN has been tested for acute toxicity:

Table 10.4-3: Summary of acute toxicity testing of UCSN

Test	Result	Reference
Acute oral toxicity rat	LD_{50} > 2000 mg/kg	Allard (1996)[a]

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

UCSN is of low toxicity by the acute oral route and is, therefore, not more toxic than parent. UCSN is considered not relevant in this step and is further evaluated in Step 4/5.

10.4.4 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.

10.4.5 STEP 5: Refined risk assessment

UCSN has a PEC_{GW} between 0.75 µg/L and 10 µg/L. A refined assessment of the potential toxicological significance including the selected ADI is presented here.

The consumer risk assessment demonstrates an acceptable risk. The estimated safety margin for UCSN is > 99.9 % of ADI for infant, child and adult. Potential exposure via other routes besides drinking water was not considered in these calculations. However, this can be considered acceptable due to the very large safety margin.

Justification for the selected ADI:
In the absence of toxicological information on UCSN, and in the knowledge that the structurally very similar compound AUSN was of very low toxicity in a repeat dose study, the parent (nicosulfuron) acceptable daily intake (ADI) value may be used. The ADI for nicosulfuron was derived from the 28, 90 and 1-year toxicity studies in the dog and the chronic rat study, using a safety factor of 100 (see table below).

Intake endpoint for parent (nicosulfuron)

Study type	NO(A)EL (mg/kg bw/day)	Safety factor	ADI (mg/kg bw/day)
28, 90 and 1-year toxicity studies in the dog and the chronic rat study	200	100	2.0

The calculation of the risk (% ADI) for a 5-kg bottle-fed infant (consuming 0.75 L/day), ~~10 kg~~ **12kg** child (consuming 1.0 L/day) and a 70-kg adult (consuming 2.0 L/day) is shown in the following table.

Table 10.4-4: Refined risk assessment – TMDI of UCSN based on the parent ADI

Person	Maximum residues in ground water (µg/L)	Exposure (L/day)	Individual body weight (kg)	TMDI (mg/kg bw /day)	% of ADI
1 x 40 g a.s./ha, early post-emergence					
Bottle-fed infant	2.27	0.75	5	3.41E-04	0.017%
Child		1	~~10~~ **12**	~~2.27E-04~~ **$1.892x10^{-4}$**	~~0.011%~~ **$9.45x10^{-3}$%**
Adult		2	70	6.49E-05	0.0032%

The maximum consumption of the ADI is that for a bottle fed infant 60 g a.s/ha early post-emergent scenario where 0.026% of the ADI is used. Based on this minimal consumption of the ADI in the most conservative scenario, UCSN can be considered as non-relevant.

10.5 Relevance assessment of the nicosulfuron metabolite ASDM

Summary:

The relevance of the groundwater metabolite ASDM has already been assessed and the assessment agreed at EU level (see EFSA Scientific Report, 2007). ASDM is considered not 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 10.5-1 and the corresponding studies are listed in the corresponding sections.

Table 10.5-1: Summary of the relevance assessment for ASDM

	Assessment step		Result of assessment	
	STEP 1		Metabolite of no concern?	No
Quantification of groundwater contamination	STEP 2		Max PEC_{GW} Based on	Maize (1 x 40 g a.s./ha, early post-emergence): 2.13 µg/L FOCUS-PEARL 4.4.4, scenario 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: Classification of parent Classification of metabolite	 No classification No 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)	< 0.1 % of ADI (ADI = 2 mg nicosulfuron / kg bw / day)
			ADI based on	28, 90 and 1-year toxicity studies in the dog and the chronic rat study, safety factor of 100

10.5.1 STEP 1: Exclusion of degradation products of no concern

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

- It is not CO_2 or an inorganic compound, not containing a heavy metal;
- It is not an organic compound of aliphatic structure, with a chain length of 4 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;
- It is not 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.

10.5.2 STEP 2: Quantification of potential groundwater contamination

PEC_{GW} calculations after leaching from soil for ASDM were performed (see Part B, Section 8, chapter 8.8.2). The uses for which concentrations of ASDM were considered to exceed 0.1 µg/L are listed in Table 10.5-1. Details are given in Part B, Section 8, chapter 8.8.2.

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 ASDM does not have comparable target activity as the parent active compound as shown in biological screening data. Information on screening for biological activity is included within the Draft Assessment Report for nicosulfuron. ASDM is considered not relevant and is further evaluated in Stage 2.

10.5.3.2 STEP 3, Stage 2: screening for genotoxicity

ASDM was screened for genotoxic activity in the following studies:

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

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

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

ASDM has been evaluated in a variety of genotoxicity studies and has been shown not to be genotoxic. ASDM is, therefore, considered not relevant at this step and is further evaluated in Step 3, Stage 3.

10.5.3.3 STEP 3, Stage 3: screening for toxicity

The parent molecule, nicosulfuron, is not classified as acutely or chronically toxic or very toxic, for reproductive toxicity or as a carcinogen (or corresponding classification in accordance to CLP 1272/2008). ASDM has been evaluated in a number of acute and repeat dose toxicity studies.

Table 10.5-3: Summary of acute and repeat dose toxicity studies conducted with ASDM

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

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

ASDM is a rat metabolite, up to 5.7% of a 10 mg/kg dose of nicosulfuron administered to rats being excreted in this form in the urine. It is not acutely toxic and the NOAEL exceeded 1,000 mg/kg (the limit dose for this study type) in the 28 and 90 day studies. Hence, it can be concluded that ASDM is of low toxicity and is not more toxic than the parent nicosulfuron. ASDM is therefore not relevant in this step and is considered further in Steps 4/5.

10.5.4 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.

10.5.5 STEP 5: Refined risk assessment

ASDM has a PEC_{GW} between 0.75 µg/L and 10 µg/L. A refined assessment of the potential toxicological significance including the selected ADI is presented here.

The consumer risk assessment demonstrates an acceptable risk. The estimated safety margin for ASDM is > 99.9 % of ADI for infant, child and adult. Potential exposure via other routes besides drinking water was not considered in these calculations. However, this can be considered acceptable due to the very large safety margin.

Justification for the selected ADI:
The ADI for ASDM could be based on the 90 day study outcome, allowing a 200 fold safety factor to account for the conversion from a subchronic to a chronic study giving an ADI of 5mg/kg bw/day. However and adopting a conservative approach, the ADI for ASDM could be derived from the parent nicosulfuron. In this case, the ADI was derived from the 28, 90 and 1-year toxicity studies in the dog and the chronic rat study, using a safety factor of 100.

Table 10.5-4: Acceptable Daily Intake endpoint for parent (nicosulfuron)

	Study type	NO(A)EL (mg/kg bw/day)	Safety factor	ADI (mg/kg bw/day)
Nicosulfuron	28, 90 and 1-year toxicity studies in the dog and the chronic rat study	200	100	2.0
ASDM	90 day rat	1000	200	5.0

The calculation of the risk (% ADI) for a 5-kg bottle-fed infant (consuming 0.75 L/day), ~~10 kg~~ **12kg** child (consuming 1.0 L/day) and a 70-kg adult (consuming 2.0 L/day) is shown in the following table.

Table 10.5-5: Refined risk assessment – Comparison between TMDI of ASDM and the parent ADI

Compound on which ADI is based	Person	Maximum residues in ground water (µg/L)	Exposure (L/day)	Individual body weight (kg)	TMDI (mg/kg bw /day)	% of ADI
Nicosulfuron **ADI=2 mg/kg bw/day**	***1 x 40 g a.s./ha, early post-emergence***					
	Bottle-fed infant	2.13	0.75	5	3.20E-04	0.016%
	Child		1	~~10~~ **12**	~~2.13E-04~~ **1.775x10^{-4}**	~~0.011%~~ **8.875x10^{-3}**
	Adult		2	70	6.09E-05	0.0030%
ASDM **ADI= 5 mg/kg bw/day**	***1 x 40 g a.s./ha, early post-emergence***					
	Bottle-fed infant	2.13	0.75	5	3.20E-04	0.0064%
	Child		1	~~10~~ **12**	~~2.13E-04~~ **1.775x10^{-4}**	~~0.0043%~~ **3.55x10^{-3}**
	Adult		2	70	6.09E-05	0.0012%

The maximum consumption of the ADI is that for a bottle fed infant 60 g a.s/ha early post-emergent scenario where 0.024% of the ADI of nicosulfuron and 0.01% of the ADI based on ASDM is used. Based on this minimal consumption of the ADI in the most conservative scenario, ASDM can be considered as non-relevant.

10.6 Relevance assessment of the nicosulfuron metabolite MU-466

Summary:

The relevance of the groundwater metabolite MU-466 has already been assessed and the assessment agreed at EU level (see EFSA Scientific Report, 2007). MU-466 is considered not 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 10.6-1 and the corresponding studies are listed in the corresponding sections.

Table 10.6-1: 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} Based on	Maize (1 x 40 g a.s./ha, early post-emergence): 0.149 µg/L FOCUS-PEARL 4.4.4, scenario 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: Classification of parent Classification of metabolite	 No classification No classification
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	Not required
			Predicted exposure (% of ADI)	-
			ADI based on	-

10.6.1 STEP 1: Exclusion of degradation products of no concern

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 because:

- It is not CO_2 or an inorganic compound, not containing a heavy metal;
- It is not an organic compound of aliphatic structure, with a chain length of 4 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;
- It is not 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.

10.6.2 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 8.8.2). The uses for which concentrations of MU-466 were considered to exceed 0.1 µg/L are listed in Table 10.6-1. Details are given in Part B, Section 8, chapter 8.8.2.

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 MU-466 does not have comparable target activity as the parent active compound as shown in biological screening data. Information on screening for biological activity is included within the Draft Assessment Report for nicosulfuron. MU-466 is considered not relevant and is further evaluated in Stage 2.

10.6.3.2 STEP 3, Stage 2: screening for genotoxicity

MU-466 was screened for genotoxic activity in the following studies:

Table 10.6-2: 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* (OECD 471, 1983)	Non-genotoxic	*S typhimurium* TA1535, TA1537, TA98 ,TA100. Dose up to 5000 µg/plate	Wollny (1996)[a]
In vitro mammalian cell gene mutation test (OECD 476, 1997)	Non-genotoxic	Mouse lymphoma L5178Y cells Dosed up to 10 mM	Wollny (2003d)[a]
In vitro chromosome aberration test (OECD 473, 1997)	Non-genotoxic	Chinese hamster V79 cells Dosed up to 10 mM	Schulz (2003c)[a]

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

MU-466 was considered not to pose a mutagenic risk. The weak responses in two of the studies were considered to show the characteristics of a cytotoxic effect, rather than a genotoxic effect. MU-466 is considered not relevant at this step and is further evaluated in Step 3, Stage 3.

10.6.3.3 STEP 3, Stage 3: screening for toxicity

MU-466 was tested in an acute toxicity study

Table 10.67-3: Summary of acute toxicity study conducted with MU-466

Test	Result	Reference
Acute oral toxicity rat	LD_{50} >2000 mg/kg	xxxxxxxxxxxx (1996)[a]

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

The parent molecule, nicosulfuron, is not classified as acutely or chronically toxic or very toxic, for reproductive toxicity or as a carcinogen (or corresponding classification in accordance to CLP 1272/2008). MU-466 is of low toxicity by the acute oral route. MU-466 is considered not relevant in this step and is further evaluated in Step 4.

10.6.4 STEP 4: Exposure assessment – threshold of concern approach

The PEC_{GW} for MU-466 was < 0.75 µg/L. Exposure of consumers via other routes is not expected. MU-466 is not considered to exceed the toxicological threshold of concern as defined in EC guidance document SANCO/221/2000 –rev.10. Therefore, a further assessment at Step 5 is not required.

10.6.5 STEP 5: Refined risk assessment

Not required for MU-466.

Appendix 1 Lists of data considered in support of the evaluation

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
-	-	-	-	-	-

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

Not required.