

# REGISTRATION REPORT

## Part B

### Section 10

#### **Assessment of the relevance of metabolites in groundwater**

Detailed summary of the risk assessment

Product code: GF-3969

Chemical active substances:

Rimsulfuron, 148.15 g/kg  
Thifensulfuron methyl, 92.6 g/kg  
Isoxadifen-ethyl, 111.1 g/kg

Central Zone

Zonal Rapporteur Member State: Poland

#### CORE ASSESSMENT

(authorization)

Applicant: Corteva/DuPont/DowAgroScience/Pioneer\*

Submission date: 18/12/2020

MS Finalisation date: December 2021 (initial Core Assessment)

May 2022 (final Core Assessment)

\*Corteva Agriscience is new Legal Entity in most of EU countries and should be treated as an Applicant for GF-3969 registration. Information about Applicant for each country is provided in dRR Part A.

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### Version history

When	What
18 December 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 <del>struck through and shaded for transparency</del> .
May 2022	Final report (Core Assessment updated following the commenting period) No additional information or assessments after the commenting period.

## Table of Contents

<b>10</b>	<b>Relevance of metabolites in groundwater .....</b>	<b>7</b>
10.1	General information .....	7
10.2	Relevance assessment of IN-70941 .....	12
10.2.1	STEP 1: Exclusion of degradation products of no concern.....	13
10.2.2	STEP 2: Quantification of potential groundwater contamination.....	13
10.2.3	STEP 3: Hazard assessment – identification of relevant metabolites .....	14
10.2.3.1	STEP 3, Stage 1: screening for biological activity.....	14
10.2.3.2	STEP 3, Stage 2: screening for genotoxicity.....	14
10.2.3.3	STEP 3, Stage 3: screening for toxicity .....	14
10.2.4	STEP 4: Exposure assessment – threshold of concern approach .....	14
10.2.5	STEP 5: Refined risk assessment.....	14
10.3	Relevance assessment of IN-70942 .....	15
10.3.1	STEP 1: Exclusion of degradation products of no concern.....	16
10.3.2	STEP 2: Quantification of potential groundwater contamination.....	16
10.3.3	STEP 3: Hazard assessment – identification of relevant metabolites .....	16
10.3.3.1	STEP 3, Stage 1: screening for biological activity.....	16
10.3.3.2	STEP 3, Stage 2: screening for genotoxicity.....	17
10.3.3.3	STEP 3, Stage 3: screening for toxicity .....	17
10.3.4	STEP 4: Exposure assessment – threshold of concern approach .....	17
10.3.5	STEP 5: Refined risk assessment.....	17
10.4	Relevance assessment of IN-E9260 .....	17
10.4.1	STEP 1: Exclusion of degradation products of no concern.....	18
10.4.2	STEP 2: Quantification of potential groundwater contamination.....	18
10.4.3	STEP 3: Hazard assessment – identification of relevant metabolites .....	19
10.4.3.1	STEP 3, Stage 1: screening for biological activity.....	19
10.4.3.2	STEP 3, Stage 2: screening for genotoxicity.....	19
10.4.3.3	STEP 3, Stage 3: screening for toxicity .....	19
10.4.4	STEP 4: Exposure assessment – threshold of concern approach .....	20
10.4.5	STEP 5: Refined risk assessment.....	20
10.5	Relevance assessment of IN-L9225 .....	21
10.5.1	STEP 1: Exclusion of degradation products of no concern.....	21
10.5.2	STEP 2: Quantification of potential groundwater contamination.....	21
10.5.3	STEP 3: Hazard assessment – identification of relevant metabolites .....	22
10.5.3.1	STEP 3, Stage 1: screening for biological activity.....	22
10.5.3.2	STEP 3, Stage 2: screening for genotoxicity.....	22
10.5.3.3	STEP 3, Stage 3: screening for toxicity .....	22
10.5.4	STEP 4: Exposure assessment – threshold of concern approach .....	22
10.5.5	STEP 5: Refined risk assessment.....	22
10.6	Relevance assessment of IN-L9223 .....	23
10.6.1	STEP 1: Exclusion of degradation products of no concern.....	23
10.6.2	STEP 2: Quantification of potential groundwater contamination.....	23
10.6.3	STEP 3: Hazard assessment – identification of relevant metabolites .....	24
10.6.3.1	STEP 3, Stage 1: screening for biological activity.....	24
10.6.3.2	STEP 3, Stage 2: screening for genotoxicity.....	24
10.6.3.3	STEP 3, Stage 3: screening for toxicity .....	24
10.6.4	STEP 4: Exposure assessment – threshold of concern approach .....	24
10.6.5	STEP 5: Refined risk assessment.....	24
10.7	Relevance assessment of IN-JZ789 .....	25
10.7.1	STEP 1: Exclusion of degradation products of no concern.....	27
10.7.2	STEP 2: Quantification of potential groundwater contamination.....	27
10.7.3	STEP 3: Hazard assessment – identification of relevant metabolites .....	28

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10.7.3.1	STEP 3, Stage 1: screening for biological activity.....	28
10.7.3.2	STEP 3, Stage 2: screening for genotoxicity.....	28
10.7.3.3	STEP 3, Stage 3: screening for toxicity .....	28
10.7.4	STEP 4: Exposure assessment – threshold of concern approach .....	29
10.7.5	STEP 5: Refined risk assessment.....	29
<b>Appendix 1</b>	<b>Lists of data considered in support of the evaluation .....</b>	<b>30</b>

### Reviewer comments:

This part of dossier has been submitted to support registration of the plant protection product GF-3969 according art. 33 of 1107/2009 and has been reviewed by the ZRMS for the purposes of ongoing registration and also checked its compliance with the current guidelines. Information has been considered as sufficient and appropriate for concluding. Document refers data related to the forming of metabolites in the environment (see dRR B8).

A key element of the assessment is to exclude or confirm the toxicological relevance of metabolites. With regard to the rimsulfuron metabolites, EFSA indicated that this was not relevant.

Regarding rimsulfuron metabolite IN-E9260 notifier submitted addition genotoxicity study (Clare, K. 2018); which address aneugenicity assessment. This is in line with EFSA Technical report on the outcome of the pesticides peer review meeting on general recurring issues in mammalian toxicology. EFSA supporting publication 2016:EN-1074. 24 pp. refer point 2.3.2 (..) *EFSA commented that the genotoxic potential of a metabolite should be clearly excluded, in particular when carcinogenicity and reproductive toxicity studies on the metabolite are not available*(..) Thus study has been reviewed and accepted by the ZRMS and considered as reliable for assessing genotoxicity potential of rimsulfuron ground water metabolite IN-E9260. (see also dRR B6). Based on available data mentioned above metabolite IN-E9260 is not toxicologically relevant.

Regarding thifensulfuron-methyl, it was concluded that thifensulfuron-methyl is not classified or proposed to be classified as carcinogenic category 2 but is proposed to be classified as toxic for reproduction category 2 by the EFSA peer review (EFSA Journal 2015;13(7):4201).

(..) Toxicological studies were provided on **metabolites** IN-A4098 (plant and groundwater), IN-L9223 (plant and groundwater), thifensulfuron (IN-L9225; plant and groundwater), IN-W8268 (groundwater, plant and live-stock), IN-JZ789 (groundwater), IN-V7160 (plant), and IN-A5546 (plant). (..)

(..) Since thifensulfuron-methyl has been proposed to be classified as reproductive toxicant, all groundwater metabolites should be considered toxicologically relevant, since their potential for reproductive toxicity cannot be excluded leading to a critical area of concern.(..) (refer EFSA Journal 2015;13(7):4201)

During parallel per review process provided by the EChA/RAC, due to discrepancies between the existing harmonised classification and the recommendations in the EFSA conclusion, the DS's CLH proposal is targeted at the hazard classes developmental toxicity and carcinogenicity. Additionally, the endpoints mutagenicity and repeated dose toxicity were assessed by RAC. (refer: *Committee for Risk Assessment RAC Opinion proposing harmonised classification and labelling at EU level of thifensulfuron-methyl (ISO); methyl 3-(4-methoxy-6-methyl- 1,3,5-triazin-2-ylcarbamoylsulfamoyl)thiophene-2-carboxylate; EC Number: -; CAS Number: 79277-27-3; CLH-O-0000001412-86-136/F; Adopted 9 December 2016*)

Based on CLH dossier evaluated by the RAC, experts concluded that:

1) (..) RAC pointed out that this rat strain (Sprague-Dawley) is known to have a high spontaneous incidence of mammary gland tumours and that the weak dose-response relationship is insufficient to support the assumption of a treatment-related effect. Overall, RAC agrees with the dossiers submitters proposal that classification for carcinogenicity is not warranted.

2) (..) no adverse effects on fertility and reproductive performance were observed after continuous treatment of rats during two generations with thifensulfuron-methyl. On this basis, RAC is of the opinion that there is no indication that thifensulfuron-methyl interferes with sexual function and fertility. (..)

3) (..) there is no evidence for developmental toxicity in rabbits. The malformation seen in the kidneys and eyes of rat foetuses in one development toxicity study could not be confirmed, either in the more recently conducted developmental reproductive toxicity study in rats with a longer exposure time, or in the 2 generation toxicity study. Both studies were conducted with the same (relevant) rat strain. Additionally, the incidences of microphthalmia observed were not statistically significant, and were within the historical control range. Therefore, RAC concluded that the evidence for developmental toxicity was not sufficient for classification.

**Overall, RAC agrees with the dossiers submitters proposal that classification for reproductive toxicity is not warranted. (..).**

Taking into account mentioned above information ZRMS PL concluded that all thifensulfuron-methyl ground-water metabolites should NOT be considered toxicologically relevant, since their potential for reproductive

toxicity has been excluded (SANCO/221/2000 –rev.10) due to the confirmed lack of developmental and reproductive potential for parent compound (refer ECHA/RAC Opinion and final harmonised classification <https://echa.europa.eu/information-on-chemicals/cl-inventory-database/-/discli/details/128758> ATP 13) thus all STEP 5: Refined risk assessments are reliable.

Some adjustments has been added by the ZRMS to STEP 5 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 and adults default bodyweight for dietary exposure assessment: (..) A body weight of 70 kg should be used as default for the European adult population (above 18 years old). The Scientific Committee considers that using 70 rather than 60 kg is now a more realistic estimate of the average bodyweight of the European adult population. When a particular subpopulation is identified as a focus for the risk assessment, actual data for this specific group should be used instead of the default value.

For dietary exposure assessment, a body weight of 12 kg should be used as default for European toddlers (aged 1-3 years).

For dietary exposure assessment, a body weight of 5 kg should be used as default for European infants (aged 0-12 months). (..)

This document is to be used by the applicant of a plant protection product for authorization at Member State level. It has been designed to provide guidance on the preparation of Part B Section 10 (Relevance of groundwater metabolites) of the draft registration report (dRR) and on information required specifically for this section. The guidance is applicable to the core assessment and the national addenda.

## 10 Relevance of metabolites in groundwater

### 10.1 General information

The ground water concentration of metabolites of two active substances rimsulfuron and thifensulfuron methyl and the safener isoxadifen-ethyl were simulated using the latest version of FOCUS groundwater models – PEARL 4.4.4 and PELMO 5.5.3.

The application scenarios of the formulated product GF-3969 are provided in Table 10.1-1. Simulations were conducted with EU-reviewed endpoints for rimsulfuron (EFSA, 2005; EFSA, 2018) and thifensulfuron methyl (EFSA, 2015).

The EFSA conclusion for active substance renewal of rimsulfuron in Europe was published in 2018, although its approval is still pending. As supplemental information, the  $PEC_{gw}$  of rimsulfuron metabolites simulated with both 2005 and 2018 EFSA endpoints are provided.

In the simulation with the 2018 EFSA endpoints, the Tier 2  $PEC_{gw}$  of rimsulfuron IN-E9260 was refined with the field-derived degradation endpoints, and demonstrated to be  $<0.1 \mu\text{g/L}$ .

The maximum concentrations of metabolites in ground water for rimsulfuron (EFSA, 2005), rimsulfuron (EFSA, 2018), thifensulfuron methyl (EFSA, 2015), and the safener isoxadifen-ethyl are summarized in Table 10.1-2, Table 10.1-3, Table 10.1-4, and Table 10.1-5, respectively.

Based on the trigger concentration of  $>0.1 \mu\text{g/L}$ , the following metabolites require toxicological relevance assessment:

Rimsulfuron (EFSA, 2005): IN-70941, IN-70942 and IN-E9260;

Rimsulfuron (EFSA, 2018): IN-70941, IN-70942 and IN-E9260;

Thifensulfuron (EFSA, 2015): IN-L9225, IN-L9223, and IN-JZ789;

Isoxadifen-ethyl (safener): None.

The details of groundwater simulation can be found in Core Part B, Section 8 (Environmental fate and behaviour).

**Table 10.1-1: Critical use pattern of GF-3969 simulated for uses on maize in FOCUS groundwater modelling**

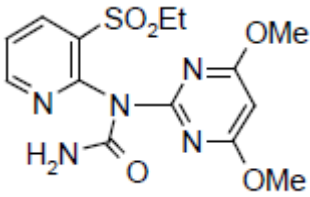
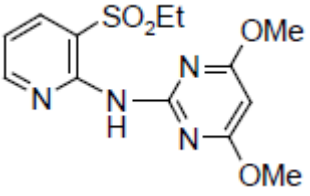
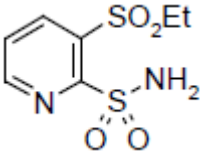
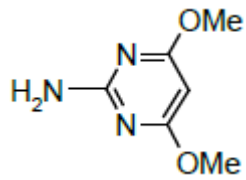
Use	Application Timing (BBCH)	Number of applications	Application interval (days)	Application rate (g a.s./ha)
Maize	11-18	1	-	Rimsulfuron: 20 Thifensulfuron methyl: 12.5 Isoxadifen-ethyl (Safener): 15
		2	7	Rimsulfuron: $2 \times 10$ Thifensulfuron methyl: $2 \times 6.25$ Isoxadifen-ethyl (Safener): $2 \times 7.5$
		2	7	Rimsulfuron: $12.59 + 7.41$ Thifensulfuron methyl: $7.87 + 4.63$ Isoxadifen-ethyl (Safener): $9.44 + 5.56$

GF-3969 contains 2 active substances (rimsulfuron and thifensulfuron methyl) and safener (isoxadifen-ethyl). Several rimsulfuron metabolites (IN-70941, IN-70942, and IN-E9260) and thifensulfuron metabolites (IN-L9225, IN-L9223, and IN-JZ789) are predicted to occur in groundwater at concentrations above 0.1 µg/L (Table 10.1-2 to Table 10.1-4) (see Part B, Section 8). Assessment of the relevance of these metabolites proceeded according to the stepwise procedure of the EC guidance document SANCO/221/2000 –rev.10 is therefore required.

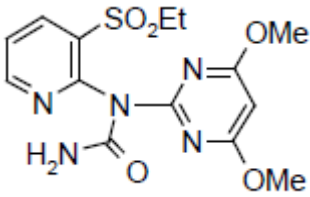
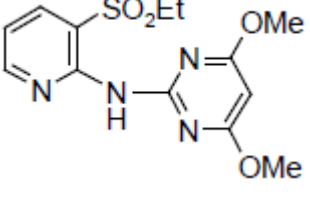
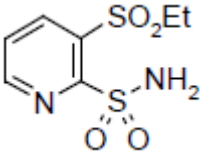
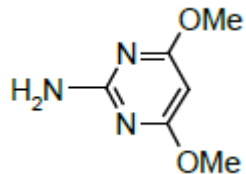
General information on the metabolites are provided in Table 10.1-2 to Table 10.1-5. Evaluation of rimsulfuron metabolites has been provided using both 2005 and 2018 EFSA conclusions. The impact of the relevance assessment on whether a particular GAP use leads to acceptable risk or not is presented in the summary of the cGAP evaluation in the dRR Part B, Section 8 (Environmental fate and behaviour).



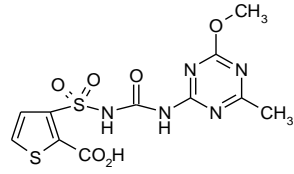
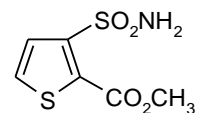
**Table 10.1-2: General information on the metabolites of rimsulfuron (EFSA 2005)**

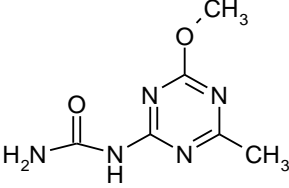
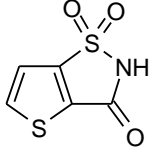
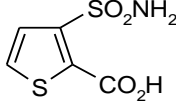
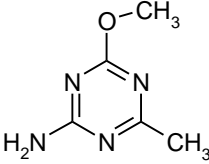
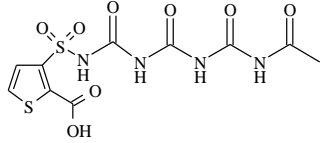
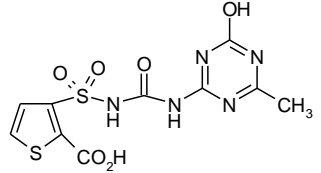
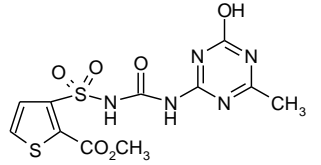
Name of active substance	Metabolite name and code	Structural/molecular formula	Trigger for relevance assessment	
Rimsulfuron Application rates: 1×20 g a.s./ha, 2×10 g a.s./ha, and 12.59+7.41 g a.s./ha	IN-70941		Max PEC <sub>gw</sub> >0.75 µg/L  Based on: Modeling with 2005 EFSA endpoints	1.114 µg/L (Tier 1)  PEARL/Thiva scenario/ 2×10 g a.s./ha  0.965 µg/L (Tier 2)  PEARL/ Hamburg scenario
	IN-70942		Max PEC <sub>gw</sub> >0.1 µg/L  Based on: Modeling with 2005 EFSA endpoints	0.117 µg/L (Tier 1)  PEARL/Thiva scenario  0.096 µg/L (Tier 2)  PEARL/Thiva scenario
	IN-E9260		Max PEC <sub>gw</sub> Tier 1 <0.75 µg/L  Based on: Modeling with 2005 EFSA endpoints	0.668 µg/L (Tier 1)  PEARL/Thiva scenario  0.648 µg/L (Tier 2)  PEARL/Thiva scenario
	IN-J0290		Max PEC <sub>gw</sub> <0.1 µg/L  Based on: Modeling with 2005 EFSA endpoints	<0.001 µg/L  PEARL and PELMO / All scenarios

**Table 10.1-3: General information on the metabolites of rimsulfuron (EFSA 2018)**

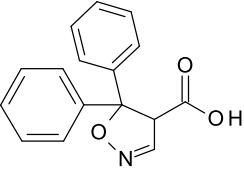
Name of active substance	Metabolite name and code	Structural/molecular formula	Trigger for relevance assessment	
Rimsulfuron Application rates: 1×20 g a.s./ha, 2×10 g a.s./ha, and 12.59 + 7.41 g a.s./ha	IN-70941		Max PEC <sub>gw</sub> >0.75 µg/L  Based on: Modeling with 2018 EFSA endpoints	4.300 µg/L (pH <6) - Thiva scenario (Tier 1)  0.263 µg/L (pH >7) - Hamburg scenario (Tier 1)/PEARL  0.706 µg/L (Tier 2) PEARL/ Hamburg scenario
	IN-70942		Max PEC <sub>gw</sub> <0.75 µg/L  Based on: Modeling with 2018 EFSA endpoints	0.314 µg/L (pH <6) - Thiva scenario (Tier 1)  0.129 µg/L (pH >7) - Hamburg scenario (Tier 1)  PEARL/ 2×10 g a.s./ha  0.036 µg/L (Tier 2)  PEARL/ Hamburg scenario
	IN-E9260		Max PEC <sub>gw</sub> Tier 1: >0.75 µg/L Tier 2 <0.75 µg/L  Based on: Modeling with 2018 EFSA endpoints	1.913 µg/L (Tier 1)  PEARL/Thiva scenario/ 2×10 g a.s./ha  0.114 µg/L (Tier 2)  PEARL/ Hamburg scenario
	IN-J0290		Max PEC <sub>gw</sub> <0.10 µg/L  Based on: Modeling with 2018 EFSA endpoints	<0.001 µg/L  PEARL and PELMO / All scenarios

**Table 10.1-4: General information on the metabolites of thifensulfuron methyl**

Name of active substance	Metabolite name and code	Structural/molecular formula	Trigger for relevance assessment	
Thifensulfuron methyl Application rates: 1×12.5 g a.s./ha, 2×6.25 g a.s./ha, and 7.87+4.63 g a.s./ha	IN-L9225		Max PEC <sub>gw</sub> <0.75 µg/L  Based on: Modeling with 2015 EFSA endpoints	0.110 µg/L  PEARL/ Hamburg scenario
	IN-A5546		Max PEC <sub>gw</sub> <0.1 µg/L  Based on:	<0.001 µg/L  PEARL and PELMO/ All scenarios

Name of active substance	Metabolite name and code	Structural/molecular formula	Trigger for relevance assessment	
			Modeling with 2015 EFSA endpoints	
	IN-V7160		Max PEC <sub>gw</sub> <0.1 µg/L  Based on: Modeling with 2015 EFSA endpoints	<0.001 µg/L  PEARL and PELMO/ All scenarios
	IN-W8268		Max PEC <sub>gw</sub> <0.1 µg/L  Based on: Modeling with 2015 EFSA endpoints	0.078 µg/L  PEARL/ Hamburg scenario
	IN-L9223		Max PEC <sub>gw</sub> >0.75 µg/L  Based on: Modeling with 2015 EFSA endpoints	0.831 µg/L  PEARL/ Thiva scenario
	IN-A4098		Max PEC <sub>gw</sub> <0.1 µg/L  Based on: Modeling with 2015 EFSA endpoints	0.085 µg/L  PEARL/ Thiva scenario
	IN-U5F72 (2-acid-3-triuret)		Max PEC <sub>gw</sub> <0.1 µg/L  Based on: Modeling with 2015 EFSA endpoints	0.075 µg/L  PEARL/ Hamburg scenario
	IN-JZ789		Max PEC <sub>gw</sub> >0.1 µg/L  Based on: Modeling with 2015 EFSA endpoints	0.328 µg/L  PEARL/ Hamburg scenario
	IN-L9226		Max PEC <sub>gw</sub> <0.1 µg/L  Based on: Modeling with 2015 EFSA endpoints	<0.001 µg/L  PEARL and PELMO/ All scenarios

**Table 10.1-5: General information on the metabolite of isoxadifen-ethyl**

Name of active substance	Metabolite name and code	Structural/molecular formula	Trigger for relevance assessment	
Isoxadifen-ethyl (Safener) Application rates: 1×15 g a.s./ha, 2×7.5 g a.s./ha, and 9.44+5.56 g a.s./ha	AE F129431		Max PEC <sub>gw</sub> <0.1 µg/L  Based on: Modeling with the 2002 endpoints evaluated by UBA in Germany	<0.001 µg/L  PEARL and PELMO / All scenarios

## 10.2 Relevance assessment of IN-70941

### Summary:

The relevance of the groundwater metabolite IN-70941 has already been assessed and the assessment agreed at EU level (see EFSA Scientific Report (2005) 45, 1-61), but the relevance assessment is not applicable for the GAP and groundwater scenarios considered in this dRR due to changes in the 2018 EFSA conclusion on rimsulfuron. Therefore, the assessment and conclusions are presented here (see Table 10.1-2 and Table 10.1-3). Further, assessment of IN-70941 utilized the more conservative 2018 EFSA endpoints as evaluation at the endpoints indicated in the 2005 EFSA conclusion on rimsulfuron would be superfluous. Based on the results of this evaluation, IN-70941 is not considered relevant according to the criteria laid down in the EC guidance document SANCO/221/2000 –rev.10. A summary of the relevance assessment is given in Table 10.2-1 and the corresponding studies are listed in the corresponding sections.

**Table 10.2-1: Summary of the relevance assessment for IN-70941**

Table 10.2-1: Summary of the Relevance Assessment for IN-70941				
	Assessment step		Result of assessment	
	STEP 1		Metabolite of no concern?	No
Quantification of groundwater contamination	STEP 2		Max PEC <sub>gw</sub>	4.300 µg/L
			Based on	Thiva Scenario (Tier 1)
Hazard assessment	STEP 3	Stage 1	Biological activity comparable to the parent?	No
		Stage 2	Genotoxic properties of metabolite	Non-Genotoxic (Genotox studies were conducted and it was negative)
		Stage 3	Toxic properties of metabolite	IN-70941 is formed in rats which then forms IN-70942 by contraction of the sulfonylurea bridge at 4-6% of the administered dose. Therefore the toxicity profile of the parent is representative of the metabolite. Additional acute tox and repeat dose studies with IN-70941 showed minimal toxicity.
			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	PEC <sub>gw</sub> was 4.300 µg/L (see the Core Part B, Section 8). Assuming 2 L of water consumption, the exposure would be of 8.4 µg/L, which is above the TTC of 1.5 µg/L.
	STEP 5		Refined risk assessment	Acceptable
			Predicted exposure (% of ADI)	0.65% of ADI (Infant); 0.43 0.35% of ADI (Child); 0.14 0.12% of ADI (Adult)
			ADI based on	Based on parent: Rimsulfuron ADI = 0.1 mg/kg bw/day

### 10.2.1 STEP 1: Exclusion of degradation products of no concern

IN-70941 does not meet the criteria for products of no concern as defined in Step 1 of the guidance and therefore needs further assessment.

### 10.2.2 STEP 2: Quantification of potential groundwater contamination

PEC<sub>gw</sub> calculations after leaching from soil for IN-70941 were performed (see Core Part B, Section 8). The uses for which concentrations of IN-70941 were considered to exceed 0.1 µg/L are listed in Table 10.2-1. Details are given in the Core Part B, Section 8.

## **10.2.3 STEP 3: Hazard assessment – identification of relevant metabolites**

### **10.2.3.1 STEP 3, Stage 1: screening for biological activity**

The biological activity of IN-70941 does not have comparable target activity as the parent active compound as shown in biological screening data (DuPont-6787, summarised in the Rimsulfuron Dossier, Annex IIA, Document M-II, Section 6, DuPont-5004 EU). IN-70941 is considered not relevant and is further evaluated in Stage 2.

### **10.2.3.2 STEP 3, Stage 2: screening for genotoxicity**

IN-70941 was screened for genotoxic activity by the following data package of *in vitro* genotoxicity studies: Ames test (Reynolds, 1989), gene mutation test with mammalian cells (San & Clark, 2003), and a chromosome aberration test (Gudi & Rao, 2004). IN-70941 was non-genotoxic as shown by a negative Ames test, negative gene mutation test with mammalian cells, and negative chromosome aberration test. IN-70941 is considered not relevant and is further evaluated in Stage 3. The studies are evaluated in Part B, Section 6; studies are summarised in Rimsulfuron DAR, Germany, Volume 3, Annex B.6, 2003-2005.

### **10.2.3.3 STEP 3, Stage 3: screening for toxicity**

In a single dose study with IN-70941, there were no deaths in rats dosed via oral intubation at up to 11000 mg/kg body weight (Sarver, 1989, HLR 199-89, Rimsulfuron DAR, Volume 3, Annex B.6, 2003-2005). A 10-dose study is available in which rats were administered IN-70941 via oral intubation at 0 (corn oil vehicle) and 2200 mg/kg body weight/day (Sarver, 1989, HLR 526-89, Rimsulfuron DAR, Volume 3, Annex B.6, 2003-2005). Although this is a non-standard study, it demonstrates only minimal effects expressed as reduced body weight, increased absolute and relative liver weights, and hepatocellular hypertrophy at a dose that exceeded the 1000 mg/kg body weight/day limit-test (e.g., OECD test guidelines 407 and 408). In addition, the liver effects were reversed after 14-days recovery which suggests that this was an adaptive or physiological effect often observed in rats following administration of test chemicals. The increased absolute and relative liver weights observed in the 10-dose study with IN-70941 were similar to the increased absolute and relative liver weights observed in the rimsulfuron 90-day rat study (Bogdanffy, 1989, HLR 43-89, Rimsulfuron DAR, Volume 3, Annex B.6, 2003-2005). There was no evidence of the liver changes observed with rimsulfuron progressing to a more pronounced or severe lesion or of effects in different target organs.

Further, rimsulfuron, the parent to IN-70941, is not classified in any category. Given that IN-70941 is the major mammalian metabolite, formed at 4-6% of the administered dose, there are no reasons to expect that IN-70941 may be toxic or highly toxic. Therefore, IN-70941 is not considered relevant and is further evaluated in Step 4.

## **10.2.4 STEP 4: Exposure assessment – threshold of concern approach**

IN-70941 was not considered relevant in the hazard assessment of Step 3. The potential exposure to IN-70941 is >0.75 µg/L but <10 µg/L. A further assessment in Step 5 is required.

## **10.2.5 STEP 5: Refined risk assessment**

IN-70941 has a PEC<sub>gw</sub> 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 estimated safety margin including potential exposure via other routes besides drinking water for

IN-70941 are all below the ADI. Potential drinking water exposure assuming a maximum water concentration of 4.3 µg/L are 0.65% of ADI (infant), ~~0.43~~ 0.35% of ADI (child), and ~~0.14~~ 0.12% of ADI (adult). Potential consumer exposure via other routes besides drinking water are based on a highly conservative approach assuming IN-70941 residues present on all crops in the EFSA dietary model at the same LOQ levels as the parent and has the same ADI as rimsulfuron. Based on the EFSA PRIMO (rev 3.1), the highest Theoretical Maximum Daily Intake (TMDI) is 2% of the ADI for the Netherlands toddler. A detailed consumer risk assessment is provided in the Core Part B, Section 7.

#### Justification for the selected ADI:

IN-70941 ADI: 0.1 mg/kg bw/day – same as parent: Rimsulfuron (EFSA, 2005):

#### Infant:

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

$$\begin{aligned} &= 4.3 \text{ µg/L PEC}_{\text{gw}} \times 0.75 \text{ L water/day} \div 5 \text{ kg body weight} \\ &= 0.65 \text{ µg/kg bw/day} \equiv 0.00065 \text{ mg/kg bw/day} \\ &= (0.00065 \text{ mg/kg bw/day} \div 0.1 \text{ mg/kg bw/day}) \times 100\% = 0.65\% \text{ of the ADI} \end{aligned}$$

#### Child:

Calculation of risk (% ADI) for ~~10~~ 12-kg child (consuming 1.0 L/day):

$$\begin{aligned} &= 4.3 \text{ µg/L PEC}_{\text{gw}} \times 1.0 \text{ L water/day} \div 12 \text{ kg body weight} \\ &= ~~0.43~~ 0.35 \text{ µg/kg bw/day} \equiv ~~0.00043~~ 0.00035 \text{ mg/kg bw/day} \\ &= (~~0.00043~~ 0.00035 \text{ mg/kg bw/day} \div 0.1 \text{ mg/kg bw/day}) \times 100\% = ~~0.43~~ 0.35\% \text{ of the ADI} \end{aligned}$$

#### Adult:

Calculation of risk (% ADI) for ~~60~~ 70-kg adult (consuming 2.0 L/day):

$$\begin{aligned} &= 4.3 \text{ µg/L PEC}_{\text{gw}} \times 2.0 \text{ L water/day} \div 70 \text{ kg body weight} \\ &= ~~0.14~~ 0.12 \text{ µg/kg bw/day} \equiv ~~0.00014~~ 0.00012 \text{ mg/kg bw/day} \\ &= (~~0.00014~~ 0.00012 \text{ mg/kg bw/day} \div 0.1 \text{ mg/kg bw/day}) \times 100\% = ~~0.14~~ 0.12\% \text{ of the ADI} \end{aligned}$$

In conclusion, a conservative refined risk assessment for the IN-70941 metabolite of rimsulfuron shows that there would be no risk to consumers from predicted groundwater concentrations, even potentially up to 4.3 µg/L.

### 10.3 Relevance assessment of IN-70942

#### Summary:

The groundwater metabolite IN-70942 is not considered as relevant according to the criteria laid down in the EC guidance document SANCO/221/2000 –rev.10. A summary of the relevance assessment for IN-70942 is given in Table 10.3-1. Studies supporting  $\text{PEC}_{\text{gw}}$  data are evaluated in the Core Part B, Section 8 (Environmental fate and behaviour), the genotoxicity studies are evaluated in Core Part B, Section 6 (Mammalian Toxicology). Further, assessment of IN-70942 utilized the more conservative 2018 EFSA endpoints as evaluation at the endpoints indicated in the 2005 EFSA conclusion on rimsulfuron would be superfluous.

**Table 10.3-1: Summary of the relevance assessment for IN-70942**

	Assessment step	Result of assessment	
	STEP 1	Metabolite of no concern?	No
Quantification of	STEP 2	Max $\text{PEC}_{\text{gw}}$	0.314 µg/L

groundwater contamination			Based on	Thiva Scenario (Tier 1)
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	IN-70942 is formed from IN-70941 in rats by contraction of the sulfonylurea bridge. It is found at concentrations <1% of the administered dose. However, IN-70942 is a metabolite of IN-70941 and so it is covered by testing on IN-70941, which showed minimal toxicity.
			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	PEC <sub>gw</sub> was 0.314 µg/L (see the Core Part B, Section 8). Assuming 2 L of water consumption, the exposure would be of 0.628 µg/L, which is below the TTC of 1.5 µg/L.
	STEP 5		Refined risk assessment	N/A*
			Predicted exposure (% of ADI)	N/A*
			ADI based on	N/A*

\* N/A: not applicable

### 10.3.1 STEP 1: Exclusion of degradation products of no concern

IN-70942 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<sub>gw</sub> calculations after leaching from soil for IN-70942 were performed (see Core Part B, Section 8). The uses for which concentrations of IN-70942 were considered to exceed 0.1 µg/L are listed in Table 10.3-1. Details are given in the Core Part B, Section 8.

### 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 IN-70942 does not have comparable target activity as the parent active compound as shown in biological screening data (DuPont-6787, summarised in the Rimsulfuron Dossier, Annex IIA, Document M-II, Section 6, DuPont-5004 EU). IN-70942 is considered not relevant and is further evaluated in Stage 2.



### **10.3.3.2 STEP 3, Stage 2: screening for genotoxicity**

IN-70942 was screened for genotoxic activity by the following data package of *in vitro* genotoxicity studies: Ames test (Wagner & Vandyke, 2013), gene mutation test with mammalian cells (Clarke, 2013), and a chromosome aberration test (Roy & Jois, 2013). IN-70942 was non-genotoxic as shown by a negative Ames test, negative gene mutation test with mammalian cells, and negative chromosome aberration test. IN-70942 is considered not relevant and is further evaluated in Stage 3. The studies are evaluated in Core Part B, Section 6; studies are summarised in Rimsulfuron RAR, Slovenia, Volume 3, Annex B.6, 2017.

### **10.3.3.3 STEP 3, Stage 3: screening for toxicity**

Rimsulfuron, the parent to IN-70942, is not classified as toxic in any category. There are no reasons to expect that IN-70942 may be toxic or highly toxic. While IN-70942 has not been subject to targeted testing, IN-70942 was also observed as a mammalian metabolite, but at concentrations below 1%. However, as it is a metabolite of IN-70941, it is considered to be covered by testing on IN-70941. Therefore, IN-70942 is not considered relevant and is further evaluated in Step 4.

### **10.3.4 STEP 4: Exposure assessment – threshold of concern approach**

IN-70942 was not considered relevant in the hazard assessment of Step 3. The  $PEC_{gw}$  for IN-70942 was  $<0.75 \mu\text{g/L}$ . There is no consumer exposure via other routes. IN-70942 is not considered to exceed the toxicological threshold of concern as defined in EC guidance document SANCO/221/2000 –rev.10.

### **10.3.5 STEP 5: Refined risk assessment**

The European Commission has established that metabolites, such as IN-70942, that pass Step 3 and are below a threshold concentration of  $0.75 \mu\text{g/L}$  in drinking water (or  $0.02 \mu\text{g/kg bw/day}$ ), need no further assessments.

## **10.4 Relevance assessment of IN-E9260**

### **Summary:**

The relevance of the groundwater metabolite IN-E9260 has already been assessed and the assessment agreed at EU level (see EFSA Scientific Report (2005) 45, 1-61), but the relevance assessment is not applicable for the GAP and groundwater scenarios considered in this dRR due to changes in the 2018 EFSA conclusion on rimsulfuron. Therefore, the assessment and conclusions are presented here (see Table 10.1-2 and Table 10.1-3). Further, assessment of IN-E9260 utilized the more conservative 2018 EFSA endpoints as evaluation at the endpoints indicated in the 2005 EFSA conclusion on rimsulfuron would be superfluous. Based on the results of this evaluation, IN-E9260 is not considered relevant according to the criteria laid down in the EC guidance document SANCO/221/2000 –rev.10. A summary of the relevance assessment is given in Table 10.4-1 and the corresponding studies are listed in the corresponding sections.

**Table 10.4-1: Summary of the relevance assessment for IN-E9260**

	Assessment step		Result of assessment	
	STEP 1		Metabolite of no concern?	No
<b>Quantification of groundwater contamination</b>	STEP 2		Max PEC <sub>gw</sub>	1.913 µg/L
			Based on	PEARL/Thiva scenario/ 2×10 g a.s./ha
<b>Hazard assessment</b>	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	IN-E9260 is formed in rats by cleavage of the sulfonylurea bridge at concentrations 7-10% of the administered dose and thus expected to be covered by the toxicity studies on parent and to have a similar toxicological profile. However, additional acute oral toxicity, dermal toxicity, dermal irritation, eye irritation, skin sensitization, and repeat oral studies were performed with minimal toxicity.
			Classification of parent	Not classified
			Classification of metabolite	Not classified
<b>Consumer health risk assessment</b>	STEP 4		Estimated consumer exposure via drinking water and other sources; threshold of concern approach	PEC <sub>gw</sub> was 1.913 µg/L (see the Core Part B, Section 8). Assuming 2 L of water consumption, the exposure would be of 3.826 µg/L, which is above the TTC of 1.5 µg/L.
	STEP 5		Refined risk assessment	Acceptable
			Predicted exposure (% of ADI)	0.3% of ADI (Infant); <del>0.2</del> 0.166% of ADI (Child); <del>0.07</del> 0.06% of ADI (Adult)
			ADI based on	Based on parent: Rimsulfuron ADI = 0.1 mg/kg bw/day

#### 10.4.1 STEP 1: Exclusion of degradation products of no concern

IN-E9260 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<sub>gw</sub> calculations after leaching from soil for IN-E9260 were performed (see Core Part B, Section 8). The uses for which concentrations of IN-E9260 were considered to exceed 0.1 µg/L are listed in Table 10.4-1. Details are given in the Core Part B, Section 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 IN-E9260 does not have comparable target activity as the parent active compound as shown in biological screening data (DuPont-6787, summarised in the Rimsulfuron Dossier, Annex IIA, Document M-II, Section 6, DuPont-5004 EU). IN-E9260 is considered not relevant and is further evaluated in Stage 2.

### **10.4.3.2 STEP 3, Stage 2: screening for genotoxicity**

IN-E9260 has been extensively tested to evaluate its genotoxicity potential using *in vitro* and *in vivo* genotoxicity studies. Ames and HPRT studies indicated no mutagenic activity either with or without metabolic activation at dose levels up to the limit concentration (5000 µg/plate or 10 mM, respectively) in bacterial reverse mutation test and mammalian cell forward mutation test systems *in vitro* (Reynolds, 1989; Clarke, 2013).

IN-E9260 was then tested in an *in vitro* chromosomal aberration and micronucleus assays. In the *in vitro* chromosomal aberration assay, IN-E9260 was negative for clastogenicity in human peripheral blood lymphocytes tested up to the limit concentration of 5 mg/mL (Forichon, 1992). Similarly, in the *in vitro* micronucleus test, IN-E9260 was negative for clastogenicity and aneugenicity in TK6 human lymphoblastoid cells tested up to the limit concentration of 2000 µg/mL (Clare, 2018, summarised in Core Part B, Section 6). An *in vivo* comet study was also conducted (Beevers, C., 2016). The results demonstrated a lack of DNA-damage in male rats dosed orally with IN-E9260 at 500, 1000, and 2000 mg/kg/day. 2000 mg/kg/day is the maximum recommended dose for *in vivo* comet studies (OECD TG 489) and generated clear negative results.

EFSA identified a micronucleus test with IN-E9260 as a data gap. The required (*in vitro*) micronucleus test was performed as soon as the EFSA conclusion was known and submitted it to the RMS, other MSs, the Commission and the EFSA. The results demonstrated an unequivocal negative response for clastogenicity and aneugenicity. Therefore, IN-E9260 is considered not relevant and is further evaluated in Stage 3.

The studies are evaluated in Core Part B, Section 6; unless otherwise noted above, studies are summarised in Rimsulfuron DAR, Germany, Volume 3, Annex B.6, 2003-2005 or Rimsulfuron RAR, Slovenia, Volume 3, Annex B.6, 2017.

### **10.4.3.3 STEP 3, Stage 3: screening for toxicity**

In an acute oral LD<sub>50</sub> study with IN-E9260, there were no deaths among male and female rats at the limit dose of 2000 mg/kg body weight (*i.e.*, LD<sub>50</sub> >2000 mg/kg) (Lheritier, 1991, 110304, Rimsulfuron DAR, Volume 3, Annex B.6, 2003-2005).

A 28-day study is available in which this metabolite was administered via oral intubation to male and female rats (Woehrle, 1992, 35291, Rimsulfuron DAR, Volume 3, Annex B.6, 2003-2005). Although this is difficult to compare to the 90-day rimsulfuron feeding study because of likely differences in pharmacokinetics between gavage and feeding studies, the NOAEL for IN-E9260 is higher than that for rimsulfuron in the 90-day feeding study (NOAEL 50 mg IN-E9260/kg body wt versus a NOEL of 3.4 and 4.1 mg rimsulfuron/kg body wt/day for male and female rats, respectively (50 ppm in the feed)). The target organs or key effects expressed in the 28 day IN-E9260 study were qualitatively similar to those for rimsulfuron, *e.g.*, increased liver weight and decreased body weight. IN-E9260 is not a skin sensitiser or irritant. It is a mild eye irritant but does not trigger classification.

Rimsulfuron, the parent to IN-70942, is not classified for any toxicity endpoint. Further, IN-E9260 is a primary mammalian metabolite and so toxicity for IN-E9260 is covered by the toxicology evaluations for rimsulfuron. Therefore, there are no reasons to expect that IN-E9260 may be toxic or highly toxic. IN-E9260 is not considered relevant and is further evaluated in Step 4.

#### 10.4.4 STEP 4: Exposure assessment – threshold of concern approach

IN-E9260 was not considered relevant in the hazard assessment of Step 3. The potential exposure to IN-E9260 is  $>0.75 \mu\text{g/L}$  but  $<10 \mu\text{g/L}$ . A further assessment in Step 5 is required.

#### 10.4.5 STEP 5: Refined risk assessment

IN-E9260 has a  $\text{PEC}_{\text{gw}}$  between  $0.75 \mu\text{g/L}$  and  $10 \mu\text{g/L}$ . A refined assessment of the potential toxicological significance including the selected ADI is presented here.

The estimated safety margin including potential exposure via other routes besides drinking water for IN-E9260 are all below the ADI. Potential drinking water exposure assuming a maximum water concentration of  $1.913 \mu\text{g/L}$  (rounded to  $2 \mu\text{g/L}$  in drinking water calculations) are 0.3% of ADI (infant), ~~0.2~~ 0.166% of ADI (child), and ~~0.07~~ 0.06% of ADI (adult). Potential consumer exposure via other routes besides drinking water are based on a highly conservative approach assuming IN-E9260 residues present on all crops in the EFSA dietary model at the same LOQ levels as the parent and has the same ADI as rimsulfuron. Based on the EFSA PRIMO (rev 3.1), the highest Theoretical Maximum Daily Intake (TMDI) is 2% of the ADI for the Netherlands toddler. A detailed consumer risk assessment is provided in the Core Part B, Section 7.

##### Justification for the selected ADI:

IN-E9260 ADI:  $0.1 \text{ mg/kg bw/day}$  – same as parent: Rimsulfuron (EFSA, 2005):

##### Infant:

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

$$\begin{aligned} &= 2 \mu\text{g/L PEC}_{\text{gw}} \times 0.75 \text{ L water/day} \div 5 \text{ kg body weight} \\ &= 0.3 \mu\text{g/kg bw/day} \equiv 0.0003 \text{ mg/kg bw/day} \\ &= (0.0003 \text{ mg/kg bw/day} \div 0.1 \text{ mg/kg bw/day}) \times 100\% = 0.3\% \text{ of the ADI} \end{aligned}$$

##### Child:

Calculation of risk (% ADI) for ~~10~~ 12-kg child (consuming 1.0 L/day):

$$\begin{aligned} &= 2 \mu\text{g/L PEC}_{\text{gw}} \times 1.0 \text{ L water/day} \div ~~10~~ 12 \text{ kg body weight} \\ &= ~~0.2~~ 0.166 \mu\text{g/kg bw/day} \equiv ~~0.0002~~ 0.000166 \text{ mg/kg bw/day} \\ &= (~~0.0002~~ 0.000166 \text{ mg/kg bw/day} \div 0.1 \text{ mg/kg bw/day}) \times 100\% = ~~0.2~~ 0.166\% \text{ of the ADI} \end{aligned}$$

##### Adult:

Calculation of risk (% ADI) for ~~60~~ 70-kg adult (consuming 2.0 L/day):

$$\begin{aligned} &= 2 \mu\text{g/L PEC}_{\text{gw}} \times 2.0 \text{ L water/day} \div ~~60~~ 70 \text{ kg body weight} \\ &= ~~0.07~~ 0.06 \mu\text{g/kg bw/day} \equiv ~~0.00007~~ 0.00006 \text{ mg/kg bw/day} \\ &= (~~0.00007~~ 0.00006 \text{ mg/kg bw/day} \div 0.1 \text{ mg/kg bw/day}) \times 100\% = ~~0.07~~ 0.06\% \text{ of the ADI} \end{aligned}$$

In conclusion, a conservative refined risk assessment for the IN-E9260 metabolite of rimsulfuron shows that there would be no risk to consumers from predicted groundwater concentrations, even potentially up to  $2 \mu\text{g/L}$ .

## 10.5 Relevance assessment of IN-L9225

### Summary:

The relevance of the groundwater metabolite IN-L9225 has already been assessed and the assessment agreed at EU level (see EFSA Journal 2015;13(7):4201), but the relevance assessment is not applicable for the GAP and groundwater scenarios considered in this dRR. Therefore, the assessment and conclusions are presented here (see Table 10.1-4). IN-L9225 is not considered relevant according to the criteria laid down in the EC guidance document SANCO/221/2000 –rev.10. A summary of the relevance assessment is given in Table 10.5-1 and the corresponding studies are listed in the corresponding sections.

**Table 10.5-1: Summary of the relevance assessment for IN-L9225**

Table 10.5-1. Summary of the Relevance Assessment for AN-17225				
	Assessment step		Result of assessment	
	STEP 1		Metabolite of no concern?	No
Quantification of groundwater contamination	STEP 2		Max PEC <sub>gw</sub>	0.110 µg/L
			Based on	PEARL/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	<i>In silico</i> modeling predicts slightly more toxic for acute oral toxicity, but <i>in vivo</i> studies resulted in LD <sub>50</sub> >2000 mg/kg bw. <i>In silico</i> modeling also did not identify carcinogenic or reproductive toxicity potential.
			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	PEC <sub>gw</sub> was 0.110 µg/L (see the Core Part B, Section 8). Assuming 2 L of water consumption, the exposure would be of 0.220 µg/L, which is below the TTC of 1.5 µg/L.
	STEP 5		Refined risk assessment	N/A*
			Predicted exposure (% of ADI)	N/A*
			ADI based on	N/A*

\* N/A: not applicable

### 10.5.1 STEP 1: Exclusion of degradation products of no concern

IN-L9225 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<sub>gw</sub> calculations after leaching from soil for IN-L9225 were performed (see the Core Part B, Section 8). The uses for which concentrations of IN-L9225 were considered to exceed 0.1 µg/L are

listed in Table 10.5-1. Details are given in the Core Part B, Section 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 IN-L9225 does not have comparable target activity as the parent active compound as indicated in Thifensulfuron methyl EFSA Conclusion, 2015. IN-L9225 is considered not relevant and is further evaluated in Stage 2.

#### **10.5.3.2 STEP 3, Stage 2: screening for genotoxicity**

IN-L9225 was screened for genotoxic activity by the following data package of *in vitro* genotoxicity studies which are summarized in Thifensulfuron methyl RAR, Volume 3, Annex B.6, March 2015: Ames test (Myhre, 2011), gene mutation test with mammalian cells (Clarke, 2011), and a chromosome aberration test (IN-L9225). IN-L9225 was non-genotoxic as shown by a negative Ames test, negative gene mutation test with mammalian cells, and negative chromosome aberration test. Additional testing was also performed by the thifensulfuron methyl task force which are also summarized in Thifensulfuron methyl RAR, Volume 3, Annex B.6, March 2015. Specifically, an Ames test (Donath, 2011) and an *in vitro* micronucleus test (May, 2012) also produced negative results for genotoxicity. IN-L9225 is considered not relevant and is further evaluated in Stage 3.

#### **10.5.3.3 STEP 3, Stage 3: screening for toxicity**

Thifensulfuron methyl, the parent to IN-L9225, is not classified for any toxicity. IN-L9225 has been tested for toxicity, which is summarized in the Thifensulfuron methyl RAR, Volume 3, Annex B.6, March 2015. Briefly, acute oral testing (2011) demonstrated an LD<sub>50</sub> >2000 mg/kg bw. *In silico* toxicity was also evaluated using the OECD tool QSAR tool box (Kelly *et al.*, 2011). Results indicated that IN-L9225 is of moderate acute oral toxicity and lacks bacterial genotoxicity, carcinogenicity, and reprotoxicity potential.

### **10.5.4 STEP 4: Exposure assessment – threshold of concern approach**

IN-L9225 was not considered relevant in the hazard assessment of Step 3. The PEC<sub>gw</sub> for IN-L9225 was <0.75 µg/L. There is no consumer exposure via other routes. IN-L9225 is not considered to exceed the toxicological threshold of concern as defined in EC guidance document SANCO/221/2000 –rev.10.

### **10.5.5 STEP 5: Refined risk assessment**

The European Commission has established that metabolites, such as IN-L9225, that pass Step 3 and are below a threshold concentration of 0.75 µg/L in drinking water (or 0.02 µg/kg bw/day), need no further assessments.

## 10.6 Relevance assessment of IN-L9223

### Summary:

The relevance of the groundwater metabolite IN-L9223 has already been assessed and the assessment agreed at EU level (see EFSA Journal 2015;13(7):4201), and the relevance assessment is applicable as well for the GAP and groundwater scenarios considered in this dRR (*i.e.*, the conclusions reached at Step 4 and 5 of the relevance assessment made at the EU-level are valid also with regard to the  $PEC_{gw}$  calculated for the GAP and groundwater scenarios considered in this dRR). IN-L9223 is not considered relevant according to the criteria laid down in the EC guidance document SANCO/221/2000 –rev.10. A summary of the relevance assessment is given in Table 10.6-1 and the corresponding studies are listed in the corresponding sections.

**Table 10.6-1: 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 $PEC_{gw}$	0.831 $\mu\text{g/L}$
			Based on	PEARL/Thiva scenario
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	Not genotoxic or carcinogenic, but <i>in silico</i> modeling predicts oral toxicity may be greater than parent.
			Classification of parent	Not classified
			Classification of metabolite	Not classified
Consumer health risk assessment	STEP 4		Estimated consumer exposure via drinking water and other sources; threshold of concern approach	$PEC_{gw}$ was 0.831 $\mu\text{g/L}$ (see the Core Part B, Section 8). Assuming 2 L of water consumption, the exposure would be of 1.662 $\mu\text{g/L}$ , which is above the TTC of 1.5 $\mu\text{g/L}$ .
	STEP 5		Refined risk assessment	Acceptable
			Predicted exposure (% of ADI)	1.5% of ADI (Infant); <del>1.0</del> 0.8% of ADI (Child); <del>0.3</del> 0.2% of ADI (Adult)
			ADI based on	Based on parent: Thifensulfuron methyl ADI = 0.01 mg/kg bw/day

### 10.6.1 STEP 1: Exclusion of degradation products of no concern

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.

### 10.6.2 STEP 2: Quantification of potential groundwater contamination

$PEC_{gw}$  calculations after leaching from soil for IN-L9223 were performed (see in the Core Part B,

Section 8). The uses for which concentrations of IN-L9223 were considered to exceed 0.1 µg/L are listed in Table 10.6-1. Details are given in the Core Part B, Section 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 IN-L9223 does not have comparable target activity as the parent active compound as shown as indicated in Thifensulfuron methyl EFSA conclusion, 2015. IN-L9223 is considered not relevant and is further evaluated in Stage 2.

#### **10.6.3.2 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, March 2015.

Furthermore, IN-L9223 is a rat metabolite observed in the metabolism study conducted with thifensulfuron methyl, and therefore, has been intrinsically tested during the development of the toxicity database for thifensulfuron methyl. Genotoxicity studies have been conducted with thifensulfuron methyl, which was concluded to be not genotoxic (Thifensulfuron methyl RAR, Volume 3, Annex B.6, March 2015). Therefore, the results of the genotoxicity studies conducted with thifensulfuron methyl can be used to support the absence of potential genotoxicity of the groundwater metabolite IN-L9223. Therefore, based on the results of the genotoxicity studies conducted with IN-L9223 s, the weight of evidence indicates that IN-L9223 is not genotoxic.

IN-L9223 is considered not relevant and is further evaluated in Step 3, screening for toxicity.

#### **10.6.3.3 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, March 2015. 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<sub>50</sub> value for IN-L9223 to be 800 mg/kg (Thifensulfuron methyl RAR, Volume 3, Annex B.6, March 2015).

Based on the lack of hazard identification, IN-L9223 is not considered relevant and is further evaluated in Step 4.

### **10.6.4 STEP 4: Exposure assessment – threshold of concern approach**

The potential exposure to IN-L9223 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**

IN-L9223 has a PEC<sub>gw</sub> 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 estimated safety margin including potential exposure via other routes besides drinking water for IN-L9223 are all below the ADI. Potential drinking water exposure assuming a maximum water concentration of 0.831 µg/L (rounded to 1 µg/L in drinking water calculations) are 1.5% of ADI (infant), ± 0.8% of ADI (child), 0.3 0.2% of ADI (adult). Potential consumer exposure via other routes besides drinking water are based on a highly conservative approach assuming IN-L9223 residues present on all crops in the EFSA dietary model at the same LOQ levels as the parent and has same ADI as thifensulfuron methyl. Based on the EFSA PRIMO (rev 3.1), the highest Theoretical Maximum Daily Intake (TMDI) is 12% of the ADI for the Netherlands toddler. A detailed consumer risk assessment is provided in the Core Part B, Section 7.

#### **Justification for the selected ADI:**

IN-L9223 ADI: 0.01 mg/kg bw/day – same as parent: Thifensulfuron methyl (EFSA, 2015):

##### **Infant:**

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

$$\begin{aligned} &= 1 \mu\text{g/L PEC}_{\text{gw}} \times 0.75 \text{ L water/day} \div 5 \text{ kg body weight} \\ &= 0.15 \mu\text{g/kg bw/day} \equiv 0.00015 \text{ mg/kg bw/day} \\ &= (0.00015 \text{ mg/kg bw/day} \div 0.01 \text{ mg/kg bw/day}) \times 100\% = 1.5\% \text{ of the ADI} \end{aligned}$$

##### **Child:**

Calculation of risk (% ADI) for 12-kg child (consuming 1.0 L/day):

$$\begin{aligned} &= 1 \mu\text{g/L PEC}_{\text{gw}} \times 1.0 \text{ L water/day} \div 12 \text{ kg body weight} \\ &= 0.08 \mu\text{g/kg bw/day} \equiv 0.00008 \text{ mg/kg bw/day} \\ &= (0.00008 \text{ mg/kg bw/day} \div 0.01 \text{ mg/kg bw/day}) \times 100\% = 0.8\% \text{ of the ADI} \end{aligned}$$

##### **Adult:**

Calculation of risk (% ADI) for 70-kg adult (consuming 2.0 L/day):

$$\begin{aligned} &= 1 \mu\text{g/L PEC}_{\text{gw}} \times 2.0 \text{ L water/day} \div 70 \text{ kg body weight} \\ &= 0.02 \mu\text{g/kg bw/day} \equiv 0.00002 \text{ mg/kg bw/day} \\ &= (0.00002 \text{ mg/kg bw/day} \div 0.01 \text{ mg/kg bw/day}) \times 100\% = 0.2\% \text{ of the ADI} \end{aligned}$$

In conclusion, a conservative refined risk assessment for the IN-L9223 metabolite of thifensulfuron methyl shows that there would be no risk to consumers from predicted groundwater concentrations, even potentially up to 1 µg/L.

## **10.7 Relevance assessment of IN-JZ789**

### **Summary:**

The relevance of the groundwater metabolite IN-JZ789 has already been assessed and the assessment agreed at EU level (see EFSA Journal 2015;13(7):4201), and the relevance assessment is applicable as well for the GAP and groundwater scenarios considered in this dRR (i.e., the conclusions reached at Step 4 and 5 of the relevance assessment made at the EU-level are valid also with regard to the  $\text{PEC}_{\text{gw}}$  calculated for the GAP and groundwater scenarios considered in this dRR). IN-JZ789 is not considered relevant according to the criteria laid down in the EC guidance document SANCO/221/2000 –rev.10. A summary of the relevance assessment is given in

Table 10.7-1 and the corresponding studies are listed in the corresponding sections.

**Table 10.7-1: 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 <sub>gw</sub>	0.328 µg/L
			Based on	PEARL/Hamburg Scenario
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	Based on structure similarity reference values of the parent and IN-L9225
			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	PEC <sub>gw</sub> was 0.328 µg/L (see the Core Part B, Section 8). Assuming 2 L of water consumption, the exposure would be of 0.648 µg/L, which is below the TTC of 1.5 µg/L.
	STEP 5		Refined risk assessment	N/A*
			Predicted exposure (% of ADI)	N/A*
			ADI based on	N/A*

\* N/A: not applicable

### 10.7.1 STEP 1: Exclusion of degradation products of no concern

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.

### 10.7.2 STEP 2: Quantification of potential groundwater contamination

PEC<sub>gw</sub> calculations after leaching from soil for IN-JZ789 were performed (see Core Part B, Section 8). The uses for which concentrations of IN-JZ789 were considered to exceed 0.1 µg/L are listed in

Table 10.7-1. Details are given in Core Part B, Section 8.

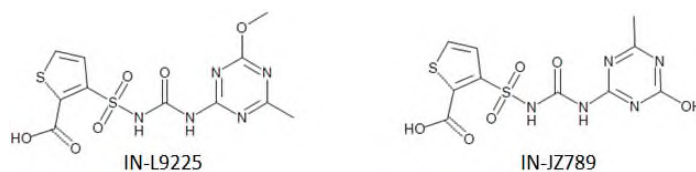
### 10.7.3 STEP 3: Hazard assessment – identification of relevant metabolites

#### 10.7.3.1 STEP 3, Stage 1: screening for biological activity

The biological activity of IN-JZ789 does not have comparable target activity as the parent active compound as shown in biological screening data (DuPont-43667, summarised in dRR Part B, Section 9 (Ecotoxicology)). IN-JZ789 is considered not relevant and is further evaluated in Stage 2.

#### 10.7.3.2 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)). DGV0081 and DGV0082 are summarised in the Thifensulfuron methyl RAR, Volume 3, Annex B.6, March 2015. IN-JZ789 is structurally related to rat metabolite IN-L9225.



A single oxygen atom differentiates IN-L9225 (ether moiety) from IN-JZ789 (methyl moiety).

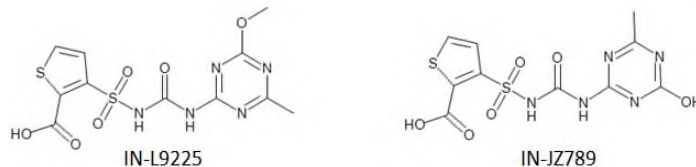
Since IN-JZ789 is structurally similar to the rat metabolite IN-L9225, which was negative for genotoxicity in a battery of *in vitro* studies (as discussed above), these data add further support to the weight of evidence that IN-JZ789 is not genotoxic.

Therefore, based on the results of the genotoxicity studies, the structural similarity to rat metabolite IN-L9225, the weight of evidence indicates that IN-JZ789 is not genotoxic.

IN-JZ789 is considered not relevant and is further evaluated in Step 3, screening for toxicity.

#### 10.7.3.3 STEP 3, Stage 3: screening for toxicity

Thifensulfuron methyl, the parent to IN-L9225, is not classified for any toxicity. However, IN-JZ789 is structurally related to rat metabolite IN-L9225.



A single oxygen atom differentiates IN-L9225 (ether moiety) from IN-JZ789 (methyl moiety).

Therefore, the acute toxicity data available for IN-L9225 may be used as a surrogate for IN-JZ789. The oral LD<sub>50</sub> value for IN-L9225 was >2000 mg/kg in female rats (EU TSM Task Force report no. 206 TIM, summarised in Thifensulfuron methyl RAR, Volume 3, Annex B.6, March 2015). Based on the acute oral LD<sub>50</sub> 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.

#### **10.7.4 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 IN-JZ789 was  $<0.75 \mu\text{g/L}$ . There is no consumer exposure via other routes. IN-JZ789 is not considered to exceed the toxicological threshold of concern as defined in EC guidance document SANCO/221/2000 –rev.10.

#### **10.7.5 STEP 5: Refined risk assessment**

The European Commission has established that metabolites, such as IN-JZ789, that pass Step 3 and are below a threshold concentration of  $0.75 \mu\text{g/L}$  in drinking water (or  $0.02 \mu\text{g/kg bw/day}$ ), need no further assessments.

## Appendix 1 Lists of data considered in support of the evaluation

### List of data submitted by the applicant and relied on – all documents

No studies submitted.

### List of data submitted by the applicant and relied on – vertebrate studies

No vertebrate studies submitted.

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

No studies previously submitted and relied upon.

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

No vertebrate studies previously submitted.

### 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
-	-	-	-	-	-