FINAL REGISTRATION REPORT

Part B

Section 6

Mammalian Toxicology

Detailed summary of the risk assessment

Product code: **102000025743**

Product name(s): **Foramsulfuron + Thiencarbazone-methyl**

(Active substance(s)) **OD 80 (50+30 g/L)**

Central Zone

Zonal Rapporteur Member State: Poland

CORE ASSESSMENT

(Re-Authorisation)

Applicant: **Bayer Crop Science Division**

Submission date: **31/08/2020**

MS Finalisation date: **06/2021; 12/2021**

Version history

When	What
31/08/2020	Original Bayer Crop Science document (Regulation 1107/2009 - Art. 43) Foramsulfuron
06/2021	Assessment by the expert
December 2021	Final version prepared by zRMS after Commenting period

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6 Mammalian Toxicology (KCP 7)

Thiencarbazone-methyl (non renewed active ingredient)
In agreement with the Guidance Document on the Renewal of Authorisations according to Article 43 of Regulation (EC) No 1107/2009 (SANCO/2010/13170), for products containing two or more active substances and when the 1st substance is renewed, there is no need to evaluate data related to the 2nd substance.
Thiencarbazone-methyl (TCM) is the active ingredient not being renewed and therefore data pertaining to TCM should not be evaluated in this application unless they are required for mixture toxicity risk assessment.

6.1 Summary

Table 6.1-1: Information on FSN+TCM OD 80 (50+30) *

Product name and code	Conviso One FSN+TCM OD 80 (50+30)
Formulation type	OD
Active substance(s) (incl. content)	Foramsulfuron 50 g/L Thiencarbazone-methyl 30 g/L
Function	Herbicide
Product already evaluated as the 'representative formulation' during the approval of the active substance(s)	No
Product previously evaluated in another MS according to Uniform Principles	Yes Poland, Austria, Belgium, Czech Republic, Hungary, Ireland, Romania, UK, The Netherlands

* Information on the detailed composition of **FSN+TCM OD 80 (50+30)** can be found in the confidential dRR Part C.

Justified proposals for classification and labelling
According to the criteria given in Regulation (EC) No 1272/2008 of the European Parliament and of the Council of 16 December 2008, the following classification and labelling with regard to toxicological data is proposed for the preparation:

Table 6.1-2: Justified proposals for classification and labelling for FSN+TCM OD 80 (50+30) according to Regulation (EC) No 1272/2008

Hazard class(es), categories:	Aspiration hazard: Cat. 1 Skin irritation: Cat.2 Skin sensitisation: Cat. 1 Serious eye damage: Cat. 1 Acute toxicity: Cat. 4 Carc.2
Hazard pictograms or Code(s) for hazard pictogram(s):	GHS08, GHS07, GHS05
Signal word:	Danger
Hazard statement(s):	H304 May be fatal if swallowed and enters airways H315 Causes skin irritation H317 May cause an allergic skin reaction H318 Causes serious eye damage H332 Harmful if inhaled H351 Suspected of causing cancer
Precautionary statement(s):	P261 P280 P331 P301 + P310 P305+P351 + P338 P308+P313 P501
Additional labelling phrases:	To avoid risks to man and the environment, comply with the instructions for use. [EUH401]

Table 6.1-3: Summary of risk assessment for operators, workers, bystanders and residents for FSN+TCM OD 80 (50+30)

	Result	PPE / Risk mitigation measures
Operators	Acceptable	Gloves during mixing/loading
Workers	Acceptable	None
Bystanders	Acceptable	None
Residents	Acceptable	None

No unacceptable risk for operators, workers, bystanders and residents was identified when the product is used as intended and provided that the PPE/ risk mitigation measures stated in Table 6.1-3 are applied.

Table 6.1-4 Critical uses and overall conclusion of exposure assessment

1	2	3	4	5	6	7	8	9	10			
Use-No.*	**Crops and situation (e.g. growth stage of crop)**	**F, Fn, Fpn G, Gn, Gpn or I ****	**Application**		**Application rate**		**PHI (d)**	**Remarks:** **(e.g. safener/synergist (L/ha))** **critical gap for operator, worker, bystander or resident exposure based on [Exposure model]**	**Acceptability of exposure assessment**			
			Method / Kind **(incl. application technique *****	**Max. number (min. interval between applications)** **a) per use** **b) per crop/ season**	**Max. application rate kg as/ha** **a) a.s. 1** **b) a.s. 2**	**Water L/ha** **min / max**			**Operator**	**Worker**	**Bystander**	**Residents**
29	Sugar beet	F	Spraying,	1 ; 1	a) 0.050	80 - 300	n.a.	EFSA Guidance				

1	2	3	4	5	6	7	8	9	10
NLD	Fodder beet (BBCH 10-18)		LCTM		b) 0.030				

* Use number(s) in accordance with the list of all intended GAPs in Part B, Section 0 should be given in column 1
** F: professional field use, Fn: non-professional field use, Fpn: professional and non-professional field use, G: professional greenhouse use, Gn: non-professional greenhouse use, Gpn: professional and non-professional greenhouse use, I: indoor application
*** e.g. LC: low crops, HC: high crop, TM: tractor-mounted, HH: hand-held

Explanation for column 10 "Acceptability of exposure assessment"

A	Exposure acceptable without PPE / risk mitigation measures
R	Further refinement and/or risk mitigation measures required
N	Exposure not acceptable/ Evaluation not possible

Data gaps

No data gaps

Noticed data gaps are:

6.2 Toxicological Information on Active Substance(s)

Information regarding classification of the active substances and on EU endpoints and critical areas of concern identified during the EU review are given in Table 6.2-1.

Table 6.2-1: Information on active substance(s)

	Foramsulfuron	**Thiencarbazone-methyl**
Common Name	Common name: foramsulfuron	Common name: thiencarbazone
CAS-No.	CAS No: 173159-57-4	CAS No: 317815-83-1
Classification and proposed labelling		
With regard to toxicological endpoints (according to the criteria in Reg. 1272/2008, as amended)	~~None~~ H351 ECHA Committee for Risk Assessment RAC Adopted 18 March 2021: "In conclusion, RAC agrees with the DS that classification as Carc. 2, H351 is warranted for foramsulfuron."	None
Additional C&L proposal	None	None
Agreed EU endpoints		
AOEL systemic	0.1 mg/kg bw/d rabbit developmental (including correction for limited oral/absorption/bioavailability 20 %), safety factor of 500)	0.12 mg/kg bw/d 90 days rat (corrected for 50 % oral absorption, safety factor of 100)
Reference	EFSA Journal 2016; 14(3):4421	EFSA Journal 2013; 11(7):3270
Conditions to take into account/critical areas of concern with regard to toxicology		
Review Report/EFSA Conclusion for active substance	ECHA Committee for Risk Assessment RAC Adopted 18 March 2021	None

6.3 Toxicological Evaluation of Plant Protection Product

A summary of the toxicological evaluation for **FSN+TCM OD 80** is given in the following tables. Full summaries of studies on the product that have not been previously considered within an EU peer review process are described in detail in Appendix 2.

Table 6.3-1: Summary of evaluation of the studies on acute toxicity including irritancy and skin sensitisation for FSN+TCM OD 80

Type of test, species, model system (Guideline)	Result	Acceptability	Classification (acc. to the criteria in Reg. 1272/2008)	Reference
LD_{50} oral, rat (OECD 423)	LD_{50} > 2000 mg/kg bw	Yes	None	xxx (2013) M-453344-01-1 Not EU peer reviewed Appendix 2
LD_{50} dermal, rat (OECD 402)	LD_{50} > 2000 mg/kg bw	Yes	None	xxx (2013) M-453346-01-1 Not EU peer reviewed Appendix 2
LC_{50} inhalation, rat (OECD 403)	LC_{50}> 5.22 mg/L air	Yes	**H332 Category 4**	xxx (2013) M-461014-01-1 Not EU peer reviewed Appendix 2
Skin irritation, male rabbit (OECD 404)	Irritant	Yes	**H315 cat. 2**	xxx (2013) M-456379-01-1 Not EU peer reviewed Appendix 2
Eye irritation, male rabbit (OECD 405)	Severely irritant	Yes	**H318 cat. 1**	xxx (2013) M-453831-01-1 Not EU peer reviewed Appendix 2
Skin sensitisation, female mouse (OECD 429) LLNA	Sensitising	Yes	**H317 cat. 1B**	xxx, (2013) M-456378-01-1 Not EU peer reviewed Appendix 2
Supplementary studies for combinations of plant protection products	No data – not required			

The product Conviso One was submitted at zonal level in 2015 for the first registration in the 3 regulatory zones. As of today, Bayer CropScience did not conduct any additional toxicological studies. The acute toxicological package, as presented in the above table, was already reviewed in the 3 zones to support the 1st registration (France (zRMS South), Lithuania (zRMS North), Germany (zRMS Central).

The acute toxicological data package was conducted to meet regulatory requirements for outside EU countries (the product is registered in Chile, New Zealand and under evaluation in Japan).

Table 6.3-2: Additional toxicological information relevant for classification/labelling of FSN+TCM OD 80

	Substance (Concentration in product, % w/w)	**Classification of the substance (acc. to the criteria in Reg. 1272/2008)**	**Reference**	**Classification of product (acc. to the criteria in Reg. 1272/2008)**
Toxicological properties of non-active substance(s) (relevant for classification of product)	Butanedioic acid, 2-sulfo-, 1,4-bis(2-ethylhexyl) ester, sodium salt (1:1) CAS N°577-11-7 (> 1 – < 10 % w/w) Solvent naphtha (petroleum) light arom CAS N°64742-95-6 (577-11-7) (> 1 – < 5 % w/w)	H315: causes skin irritation H318: causes eye irritation STOT SE 3, H335 and H336 (respiratory and narcotic effects) Asp Tox cat 1, H304	Supplier MSDS	The acute skin and eye irritation studies trigger classification: H315: causes skin irritation H318: causes eye irritation **(H304 relevant since more than 10% in total with the co-formulant Solvent naphta)** STOT SE 3, H335 and H336 (not relevant since less than 20%)
Toxicological properties of non-active substance(s) (relevant for classification of product)	Poly(oxy-1,2-ethanediyl), α-isotridecyl-ω-methoxy CAS N°345642-79-7 (≤ 10% w/w)	H317: May cause allergic skin reaction H318: causes eye irritation	Supplier MSDS	The acute skin sensitization and eye irritation studies trigger classification: H317: May cause allergic skin reaction H318: causes eye irritation
Toxicological properties of non-active substance(s) (relevant for classification of product)	Benzenesulfonic acid, dodecyl-, calcium salt, 1-hexanol, 2-ethyl ((≤5% w/w)) CAS N°104-76-7 (26264-06-2, 104-76-7) (< 5 % w/w)	H315: causes skin irritation H318: causes eye irritation H332 : Harmful if inhaled STOT SE 3, H335	Supplier MSDS	The acute skin, eye irritation and inhalation studies trigger classification: H315: causes skin irritation H318: causes eye irritation H332 : Harmful if inhaled STOT SE 3, H335 (not relevant since less than 20%)
Toxicological properties of non-active substance(s) (relevant for classification of product)	Solvent naphtha (petroleum) heavy arom CAS N°64742-94-5 (> 20% w/w)	H304: May be fatal if swallowed and enters airways	Supplier MSDS	H304: May be fatal if swallowed and enters airways
Further toxicological information	No data – not required			

* Please use concentration range or concentration limit (e.g. 1-10 % or > 1 %) as provided in MSDS.
** Material safety data sheet by the applicant

6.4 Toxicological Evaluation of Groundwater Metabolites

There are no foramsulfuron metabolites with the potential to reach the groundwater in concentrations above 0.1 µg/L.

The only thiencarbazone-methyl metabolite with the potential to reach the groundwater in concentration above 0.1 µg/L is BYH 18636-carboxylic acid. The relevance assessment of the metabolite is reported in Part B, Section 10 Core.

6.4.1 Metabolite of thiencarbazone-methyl: BYH 18636-carboxylic acid

An overview of the results of the accepted toxicological studies for groundwater metabolite BYH 18636-carboxylic acid is given in the following table.

Table 6.4-1: Summary of the results of toxicity studies for metabolite BYH 18636-carboxylic acid

Type of test, species (Guideline)	Result	Acceptability	Reference*
In vitro genotoxicity – Bacterial assay for gene mutation (OECD 471)	non-mutagenic with or without S9 mix	Yes	Wirnitzer U., 2004, M-092854-02-2 EU peer reviewed
In vitro genotoxicity – Test for clastogenicity in mammalian cells (OECD 473)	not clastogenic for mammalian cells *in vitro*	Yes	Herbold B, 2005, M-250256-02-2 EU peer reviewed
In vitro genotoxicity – Test for gene mutation in mammalian cells (OECD 476)	non-mutagenic in the V79/HPRT forward mutation assay, both with and without metabolic activation	Yes	Herbold B, 2005, M-251094-01-2 EU peer reviewed
In vitro genotoxicity - micronucleus test (OECD 487)	Non-mutagenic for lymphocyte cells *in vitro*	Yes	Naumann, S., 2018, M-630020-01-1 Not EU peer reviewed Appendix 2
Acute oral toxicity in the rat (OECD 423)	LD_{50} cut-off of BYH 18636-carboxylic acid was ≥ 5 000 mg /kg bw (category 5 / unclassified of the GHS)	Yes	xxx., 2006, M-269981-01-2 EU peer reviewed
90-day tixicity study in the rat (OECD 408)	The NOEL = 972 and 1170 mg/kg/day in males and females respectively.	Yes	xxx., 2007, M-282943-01-2 EU peer reviewed

* indicates that a study was reviewed at EU level

The relevance of metabolite BYH 18636-carboxylic acid was evaluated as part of the European review for EU approval (Annex I inclusion, Directive 91/414/EC) of the active substance thiencarbazone-methyl. The metabolite was considered to be non-relevant. Detailed data and assessment are found in the EU DAR (2012) of thiencarbazone-methyl, and the corresponding EFSA peer review conclusion (EFSA Journal 2013; 11(7):3270).

All toxicological studies on this metabolite, except the *in vitro* micronucleus test, have previously been

considered within an EU peer review process. Only the studies not EU peer reviewed are summarised in detail in Appendix 2.

6.5 Dermal Absorption (KCP 7.3)

A summary of the dermal absorption rates for the active substances in FSN+ TCM OD 80 are presented in the following table.

Table 6.5-1: Dermal absorption rates for active substances in FSN+ TCM OD 80

	Foramsulfuron		**Thiencarbazone- methyl**	
	Value	**Reference**	**Value**	**Reference**
Concentrate	70 %	EFSA Guidance on dermal Absorption	0.1 %	EFSA Guidance on dermal Absorption
Dilution	70 %	EFSA Guidance on dermal Absorption	2.8 % (0.075 g a.s./L)	EFSA Guidance on dermal Absorption

6.5.1 Justification for proposed values – Foramsulfuron

No data on dermal absorption for foramsulfuron in FSN+ TCM OD 80 is available. Justifications for default values according to Guidance on Dermal Absorption (EFSA Journal 2017; 15(6):4873) are presented in the following table.

Table 6.5-2: Default dermal absorption rates for foramsulfuron

	Value	**Justification for value**	**Acceptability of justification**
Concentrate	70%	Concentration of a.s. is <50 g a.s./L	Acceptable
Dilution	70%	Concentration of a.s. is <50 g a.s./L	Acceptable

6.5.2 Justification for proposed values – Thiencarbazone-methyl

Proposed dermal absorption rates for thiencarbazone-methyl are based on a dermal absorption study on the formulation FSN+ TCM OD 80. The study results are summarized in the following table. A full summary of the study on dermal absorption of thiencarbazone-methyl/ FSN+ TCM OD 80 that have not previously been evaluated within an EU peer review process is described in detail in Appendix 2.
The results of the experiments with FSN+ TCM OD 80 are applicable for the risk assessment of the present application.

Table 6.5-3: Summary of the results of submitted dermal absorption studies for thiencarbazone-methyl

Test	Concentrate (30g a.s./L)	Dilution (0.075 g a.s./L)	Formulation in study	Acceptability of study	Justification provided on representativity of study formulation for current product	Acceptability of justification	Reference*
In vitro (human)	0.1 %	2.8 %	FSN+ TCM OD 80	Yes	Not required	Justification accepted. Endpoint can be used for current product	Bernal, J., 2015 M-537205-01-1 Not EU peer reviewed Appendix 2

* indicates that a study was reviewed at EU level

6.6 Exposure Assessment of Plant Protection Product (KCP 7.2)

Table 6.6-1: Product information and toxicological reference values used for the exposure assessment

Product	FSN+ TCM OD 80	
Formulation type	Oil Dispersion OD	
Active substance(s) (incl. content)	**Foramsulfuron (FSN)** 50 g/L	**Thiencarbazone-metyl (TCM)** 30 g/L
$AOEL_{systemic}$ (RVNAS)	0.1 mg/kg bw/d	0.12 mg/kg bw/d
Inhalation absorption	100%	100%
Oral absorption	20%	50%
Dermal absorption	Concentrate: 70% Dilution: 70% *For more information please refer to chapter 6.5*	Concentrate: 0.1% Dilution: 2.8% *For more information please refer to chapter 6.5*

6.6.1 Selection of critical use(s) and justification

The critical GAP used for the exposure assessment of the plant protection product is shown in Table 6.1-4. A list of all intended uses within the zone is given in Part B, Section 0.

6.6.2 Operator exposure (KCP 7.2.1)

No acute non-dietary risk assessment is included in this submission. Lack of scientific guidance or methodology is an acceptable reason for waiving according to Guidance of the European Commission1. The absence of such guidance on derivation of an appropriate reference dose ("AAOEL") was recognized by

- the European Food Safety Authority[2], and
- the European Commission Standing Committee[3].

Therefore, this waiver is presented in line with the Guidance of the European Commission.

This applies for the same degree with regard to acute operator exposure estimates.

6.6.2.1 Estimation of operator exposure

A summary of the exposure models used for the estimation of operator exposure to the active substance(s) during application of FSN+TCM OD 80 according to the critical use(s) is presented in the following table. Detailed calculations are presented in Appendix 3.

Table 6.6-2: Exposure models for intended uses

Critical use(s)	1 x 1 L product/ha for root and tuber vegetables (sugar beet)
Model(s)	*Guidance on the assessment of exposure of operators, workers, residents and bystanders in risk assessment for plant protection products; EFSA Journal 2014;12(10):3874*

The outcome of the estimation is presented in the following table(s).

Table 6.6-3: Estimated operator exposure, <u>foramsulfuron</u>, root and tuber vegetables (sugar beet)

Model data	Level of PPE	Total absorbed dose (mg/kg/day)	% of systemic AOEL[1] (RVNAS)
Outdoor, Downward spraying, Vehicle-mounted Application rate: 0.05 kg a.s./ha			
EFSA Operator Model (75th quantile regression) Body weight: 60 kg	no PPE[2]	0.121	120
	with PPE[3]	0.00397	**3.97**

1 AOEL (RVNAS) of FSN: 0.1 mg/kg bw/day
2 no PPE: Work wear - arms, body and legs covered
3 with PPE: Work wear - arms, body and legs covered. In addtion gloves during mixing and loading and when handling contaminated surfaces during application.

[1] Guidance Document for applicants on preparing dossiers for the approval of a chemical new active substance and for the renewal of approval of a chemical active substance according to Regulation (EU) No 283/2013 and Regulation (EU) No 284/2013. SANCO/10181/2013, May 2013
[2] Guidance on the assessment of exposure of operators, workers, residents and bystanders in risk assessment for plant protection products. EFSA Journal 2014;12(10):3874)
[3] Guidance on the assessment of exposure of operators, workers, residents and bystanders in risk assessment for plant protection products. SANTE-10832-2015

Table 6.6-4: Estimated operator exposure, thiencarbazone-methyl, root and tuber vegetables (sugar beet)

Model data	Level of PPE	Total absorbed dose (mg/kg/day)	% of systemic AOEL[1] (RVNAS)
Outdoor, Downward spraying, Vehicle-mounted Application rate: 0.03 kg a.s./ha			
EFSA Operator Model (75th quantile regression) Body weight: 60 kg	no PPE[2]	0.000311	<1
	with PPE[3]	0.000122	**<1**

[1] AOEL (RVNAS) of TCM: 0.12 mg/kg bw/day
[2] no PPE: Work wear - arms, body and legs covered
[3] with PPE: Work wear - arms, body and legs covered. In addtion gloves during mixing and loading and when handling contaminated surfaces during application.

For details on the calculations please refer to Appendix 3 of this document.

Comment:
According to the EFSA calculation, it can be concluded that the risk for operator is acceptable with the use work wear (arms, body and legs covered) + gloves at M/L and A.
Implication for labelling: P280: Wear protective gloves.

6.6.3 Measurement of operator exposure

Since the operator exposure estimations carried out indicated that the Acceptable Operator Exposure Level (AOEL/RVNAS) will not be exceeded under conditions of intended uses and considering above mentioned personal protective equipment (PPE), a study to provide measurements of operator exposure was not necessary and was therefore not performed.

6.6.4 Worker exposure (KCP 7.2.3)

6.6.4.1 Estimation of worker exposure

A summary of the exposure models used for the estimation of worker exposure to the active substance(s) after entry into a previously treated area or handling a crop treated with FSN+TCM OD 80 is presented in the following table. Detailed calculations are presented in Appendix 3.

Table 6.6-5: Exposure models for intended uses

Critical use(s)	1 x 1 L product/ha for root and tuber vegetables (sugar beet)
Model	*Guidance on the assessment of exposure of operators, workers, residents and bystanders in risk assessment for plant protection products; EFSA Journal 2014;12(10):3874*

The following table shows the crop groups with their respective transfer coefficients (TC) and task duration relevant for the estimation of worker exposure after the intended use of FSN+TCM OD 80. Worker exposures for all intended uses within the zone/ EU given in Part B, Section 0 are covered by that.

Table 6.6-6: Relevant parameters used for the worker exposure assessment

Crop / Crop Group	Active substance	Application rate (kg a.s./ha)	Nº of applications	Interval (Days)	TC[1] (cm²/hour)	Task Duration (hours)
Root and tuber vegetables (sugar beet, fodder beet)	FSN	0.05	1	365	1400	2
	TCM	0.03				

[1] TC = transfer coefficients assuming arms, body and legs covered (workwear; bare hands)

The outcome of the estimation is presented in the following tables.

Table 6.6-7: Estimated worker exposure for re-entry in root and tuber vegetables (sugar beet)

Model data	Active substance	Application rate (kg a.s./ha)	Total absorbed dose[2] (mg/kg/day)	% of systemic AOEL[1] (RVNAS)
EFSA Worker Model Body weight: 60 kg DFR: 3 µg/cm²/kg a.s./ha	FSN	0.05	0.0049	**4.9**
	TCM	0.03	0.000118	**<1**

[1]AOEL (RVNAS) of FSN: 0.1 mg/kg bw/day,
TCM: 0.12 mg/kg bw/day.
[2]Assuming arms, body and legs covered (workwear; bare hands)
For details on the calculations please refer to Appendix 3 of this document.

Comment:
Worker exposure estimations carried out indicated that the AOEL will not exceeded under conditions of intended uses, and then no risk for worker

6.6.4.2 Refinement of generic DFR value (KCP 7.2)

Since the default value of 3 µg/cm² of foliage/kg a.s. applied/ha has been used, no refinement of DFR is necessary.

6.6.4.3 Measurement of worker exposure

Since the worker exposure estimations carried out indicated that the Acceptable Operator Exposure Level (AOEL/RVNAS) will not be exceeded under conditions of intended uses a study to provide measurements of worker exposure was not necessary and was therefore not performed.

6.6.5 Bystander and resident exposure (KCP 7.2.2)

No acute non-dietary risk assessment is included in this submission. Lack of scientific guidance or methodology is an acceptable reason for waiving according to Guidance of the European Commission[4]. The absence of such guidance on derivation of an appropriate reference dose ("AAOEL") was recognized by

- the European Food Safety Authority[5], and
- the European Commission Standing Committee[6].

Therefore, this waiver is presented in line with the Guidance of the European Commission.

According to EFSA longer term exposure of bystanders is covered by the resident scenario.

6.6.5.1 Estimation of bystander and resident exposure

A summary of the exposure models used for the estimation of resident exposure to the active substance(s) during application of FSN+TCM OD 80 according to the critical use(s) is presented in the following table. Detailed calculations are presented in Appendix 3.

Table 6.6-8: Exposure models for intended uses

Critical use(s)	1 x 1 L product/ha for root and tuber vegetables (sugar beet)
Model	*Guidance on the assessment of exposure of operators, workers, residents and bystanders in risk assessment for plant protection products; EFSA Journal 2014;12(10):3874*

Regarding the resident exposure to direct drift, exposure calculations are performed for ground boom sprayer (for low crops) and broadcast air assisted applications (for high crops) separately, when relevant. The outcome of the estimation is presented in the following table(s).

[4] Guidance Document for applicants on preparing dossiers for the approval of a chemical new active substance and for the renewal of approval of a chemical active substance according to Regulation (EU) No 283/2013 and Regulation (EU) No 284/2013. SANCO/10181/2013, May 2013

[5] Guidance on the assessment of exposure of operators, workers, residents and bystanders in risk assessment for plant protection products. EFSA Journal 2014;12(10):3874)

[6] Guidance on the assessment of exposure of operators, workers, residents and bystanders in risk assessment for plant protection products. SANTE-10832-2015

Table 6.6-9: Estimated bystander and resident exposure, foramsulfuron, root and tuber vegetables (sugar beet)

	Adult[2]			Child[2]		
Outdoor, Downward spraying, Vehicle-mounted Application rate: 1 x 0.05 kg a.s./ha, 365 days interval, Minimum water volume: 80 L/ha						
Routes of exposure	**75th centile** (mg/kg bw/day)	**in % of AOEL[1] (RVNAS)**	**Mean** (mg/kg bw/day)	**75th centile** (mg/kg bw/day)	**in % of AOEL[1] (RVNAS)**	**Mean** (mg/kg bw/day)
Spray drift[3]	0.00281	2.81	0.00134	0.0117	12	0.00647
Vapour	0.00023	<1	0.00023	0.00107	1.07	0.00107
Surface deposits	0.000238	<1	0.000175	0.000518	<1	0.000379
Entry into treated crops	0.00328	3.28	0.00262	0.00591	5.91	0.00471
	Sum of all pathways: in % of AOEL (RVNAS)		4.36	**Sum of all pathways:** in % of AOEL (RVNAS)		13

1 AOEL (RVNAS) of FSN: 0.1 mg/kg bw/day
2 Considered bodyweight: adult = 60 kg, child = 10 kg
3 Exposure at 2-3 m distance

Table 6.6-10: Estimated bystander and resident exposure, thiencarbazone-methyl, root and tuber vegetables (sugar beet)

	Adult[2]			Child[2]		
Outdoor, Downward spraying, Vehicle-mounted Application rate: 1 x 0.03 kg a.s./ha, 365 days interval, Minimum water volume: 80 L/ha						
Routes of exposure	**75th centile** (mg/kg bw/day)	**in % of AOEL[1] (RVNAS)**	**Mean** (mg/kg bw/day)	**75th centile** (mg/kg bw/day)	**in % of AOEL[1] (RVNAS)**	**Mean** (mg/kg bw/day)
Spray drift[3]	0.0000729	<1	0.0000326	0.00031	<1	0.000161
Vapour	0.00023	<1	0.00023	0.00107	<1	0.00107
Surface deposits	0.00000613	<1	0.00000419	0.0000253	<1	0.0000179
Entry into treated crops	0.0000844	<1	0.0000628	0.000152	<1	0.000113
	Sum of all pathways: in % of AOEL (RVNAS)		<1	**Sum of all pathways:** in % of AOEL (RVNAS)		1.14

1 AOEL (RVNAS) of TCM: 0.12 mg/kg bw/day
2 Considered bodyweight: adult = 60 kg, child = 10 kg
3 Exposure at 2-3 m distance

For details on the calculations please refer to Appendix 3 of this document.

Comment:
The performed estimates of the exposure of bystanders / residents (adult &child) have shown that the AOEL will not be exceeded under the specified conditions of use and maintaining the buffer zone 2-3 m

6.6.5.2 Measurement of bystander and/or resident exposure

Since the bystander/resident exposure estimations carried out indicated that the Acceptable Operator Exposure Level (AOEL/RVNAS) will not be exceeded under conditions of intended uses a study to provide measurements of bystander/resident exposure to spray drift, vapour, surface deposits or entry into treated crops was not necessary and was therefore not performed.

6.6.6 Combined exposure

The product is a mixture of two active substances therefore a combined exposure assessment is provided.

6.6.6.1 Exposure Assessment of the active substances (foramsulfuron, thiencarbazone-methyl) in FSN+TCM OD 80

Note: The combined toxicological effect of these active substances has not been investigated with regard to repeated dose toxicity.
At the first tier, combined exposure is calculated as the sum of the component exposures without regard to the mode of action or mechanism/target of toxicity. Initially, the individual Hazard Quotients (HQ) are calculated for all active substances in the PPP by assessing the exposure according to appropriate models and dividing the individual exposure levels by the respective systemic AOEL/RVNAS. This is equivalent to the predicted exposure as % of systemic AOEL/RVNAS to decimal. The Hazard Index (HI) is the sum of the individual HQs.

Table 6.6-11: Acute risk assessment from combined exposure

Application scenario	Active Substance	Estimated exposure / AOEL (RVNAS) (HQ)[3]
Operators, with PPE. For details please refer to 6.6.2. Only the worst case scenario is presented	Foramsulfuron	0.040
	Thiencarbazone-methyl	0.001
	Cumulative risk Operators (HI)[2]	**0.041**
Workers For details please refer to 6.6.4. Only the worst case scenario is presented	Foramsulfuron	0.049
	Thiencarbazone-methyl	0.00098
	Cumulative risk Workers (HI)[2]	**0.05**
Resident – Adult[1] For details please refer to 6.6.5. Only the worst case scenario is presented	Foramsulfuron	0.044
	Thiencarbazone-methyl	0.0027
	Cumulative risk Resident – Adult (HI)[2]	**0.047**
Resident – Child[1] For details please refer to 6.6.5. Only the worst case scenario is presented	Foramsulfuron	0.13
	Thiencarbazone-methyl	0.011
	Cumulative risk Resident – Child (HI)[2]	**0.14**

[1] The higher exposure value either from the 75th percentile of each of the four pathways (spray drift, vapour, surface deposits, entry into treated crops) or the sum of the mean exposure values is taken into consideration
[2] HI =Hazard Index
[3] HQ = Hazard Quotient

The Hazard Index is < 1. Thus combined exposure to all active substances in FSN+TCM OD 80 is not expected to present a risk for operators, workers, bystanders and residents.
No further refinement of the assessment is required.

Appendix 1 Lists of data considered in support of the evaluation

Tables considered not relevant can be deleted as appropriate.

MS to blacken authors of vertebrate studies in the version made available to third parties/public.

List of data submitted by the applicant and relied on

Data Point	**Author(s)**	**Year**	**Title** **Company Report No.** **Source** **GLP or GEP status** **published or not**	**Vertebrate study Y/N**	**Owner**
KCP 7.1.1 / 01	xxx	2013	Foramsulfuron + thiencarbazone-methyl OD 80 (50+30 g/L) - Acute oral toxicity study in rats Report No.: 13/014-001P, Edition Number: M-453344-01-1 xxx GLP/GEP: Yes unpublished	Yes	Bayer
KCP 7.1.2 / 01	xxx	2013	Foramsulfuron + thiencarbazone-methyl OD 80 (50+30 g/L) - Acute dermal toxicity study in rats Report No.: 13/014-002P, Edition Number: M-453346-01-1 xxx GLP/GEP: Yes unpublished	Yes	Bayer
KCP 7.1.3 / 01	xxx	2013	Acute inhalation toxicity study (nose-only) in the rat with FSN+TCM OD 50+30 G Report No.: 13/014-004P, Edition Number: M-461014-01-1 xxx GLP/GEP: Yes unpublished	Yes	Bayer
KCP 7.1.4 / 01	xxx	2013	Foramsulfuron + thiencarbazone-methyl OD 80 (50+30 g/L) - Acute skin irritation study in rabbits Report No.: 13/014-006N, Edition Number: M-456379-01-1 xxxx GLP/GEP: Yes unpublished	Yes	Bayer

Data Point	**Author(s)**	**Year**	**Title** **Company Report No.** **Source** **GLP or GEP status** **published or not**	**Vertebrate study Y/N**	**Owner**
KCP 7.1.5 / 01	xxx	2013	Foramsulfuron + thiencarbazone-methyl OD 80 (50+30 g/L) - Acute eye irritation study in rabbits - FSN+TCM OD 50+30 G Report No.: 13/014-005N, Edition Number: M-453831-01-1 xxx GLP/GEP: Yes unpublished	Yes	Bayer
KCP 7.1.6 / 01	xxx	2013	Foramsulfuron + thiencarbazone-methyl OD 50+30 g/L - Local lymph node assay in the mouse Report No.: 13/014-037E, Edition Number: M-456378-01-1 xxx GLP/GEP: Yes unpublished	Yes	Bayer
KCP 7.3 / 01	Bernal, J.	2015	In-vitro human skin penetration of 14C-thiencarbazone-methyl in the thiencarbazone-methyl and foramsulfuron OD 80 formulation (specification no 102000025743) Report No.: S15-01966, Edition Number: M-537205-01-1 Eurofins Agroscience Services, Chem SAS, Vergèze, France GLP/GEP: Yes unpublished	No	Bayer
KCA 5.8.1 / 01	xxx	1995	Hoe 092944; substance technical (Code: Hoe 092944 00 ZD99 0001) Testing for acute oral toxicity in the male and female Wistar rat Report No.: A49161, Edition Number: M-138232-02-1 xxx ... amended: 1995-04-20 GLP/GEP: Yes unpublished	Yes	Bayer
KCA 5.8.1 / 02	xxx	1995	TBS-1203: Acute oral toxicity study in male mice Report No.: A55629, Edition Number: M-139539-01-1 xxx GLP/GEP: No unpublished	Yes	

Data Point	Author(s)	Year	Title Company Report No. Source GLP or GEP status published or not	Vertebrate study Y/N	Owner
KCA 5.8.1 / 03	Stammberger, I.	1992	Hoe 092944 - substance, technical (Code: Hoe 092944 00 ZD99 0001) Study of the mutagenic potential in strains of Salmonella typhimurium (Ames Test) and Escherichia coli Report No.: A48871, Edition Number: M-137963-01-1 Hoechst AG, Frankfurt am Main, Germany GLP/GEP: Yes unpublished	No	Bayer
KCA 5.8.1 / 04	Spruth, B.	2017	Mutagenicity study of AE F092944 in the Salmonella typhimurium reverse mutation assay (in vitro) Report No.: 35401, Edition Number: M-644749-01-1 LPT Laboratory of Pharmacology and Toxicology GmbH & Co. KG, Hamburg, Germany GLP/GEP: Yes unpublished	No	Bayer
KCA 5.8.1 / 05	Anon.	2015	AE F092944 - Derek Nexus report Report No.: M-685932-01-1 xxx GLP/GEP: No unpublished	Yes	Bayer
KCA 5.8.1 / 06	xxx	2019	Amidosulfuron - In silico assessment of the metabolite AE F092944 Report No.: M-654051-01-1 xxx GLP/GEP: n.a. unpublished	Yes	Bayer
KCA 5.8.1 / 07	Naumann, S.	2018	BYH18636-carboxylic acid (BCS-AT36039, AE 1394083): Micronucleus test in human lymphocytes In vitro Report No.: 1889000, Edition Number: M-630020-01-1 Envigo CRS GmbH, Rossdorf, Germany GLP/GEP: Yes unpublished	No	Bayer

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

Please note that all data mentioned as part of DAR, RAR, or EFSA journals are considered as relied upon.

Bayer is the owner of the data package peer-reviewed for the EU approval of the active substance **thiencarbazone-methyl.**

Data protection will be requested when relevant at MS level in the Part A

Thiencarbazone-methyl
The following studies are considered as already evaluated at EU peer review as they were submitted during the EU approval process of thiencarbazone-methyl (OECD Joint Review Project - Section B.6: Toxicology and metabolism - Part A: Evaluation and Assessment of the data submitted).

Data Point	**Author(s)**	**Year**	**Title** **Company Report No.** **Source** **GLP or GEP status** **published or not**	**Vertebrate study Y/N**	**Owner**
KIIA 5.8 /01 (DAR)	Wirnitzer, U.	2006	BYH 18636-carboxylic acid (project: BYH 18636) - Salmonella/microsome test - Plate incorporation and preincubation method - 1st amendment to toxicology report AT01522 of September 22, 2004 Report No.: AT01522A, Edition Number: M-092854-02-2 Bayer HealthCare AG, Wuppertal, Germany GLP/GEP: Yes, unpublished	No	Bayer
KIIA 5.8 /02 (DAR)	Herbold, B.	2006	BYH 18636-carboxylic acid (Project: BYH 18636) - In vitro chromosome aberration test with chinese hamster V79 cells Report No.: M-250256-02-2 Bayer HealthCare AG, Wuppertal, Germany GLP/GEP: Yes, unpublished	No	Bayer
KIIA 5.8 /03 (DAR)	Herbold, B.	2006	BYH 18636-carboxylic acid (Project: BYH 18636) - V79/HPRT-test in vitro for the detection of induced forward mutations Report No.: AT02038, Edition Number: M-251094-01-2 Bayer AG, Wuppertal, Germany GLP/GEP: Yes, unpublished	No	Bayer

Data Point	**Author(s)**	**Year**	**Title** **Company Report No.** **Source** **GLP or GEP status** **published or not**	**Vertebrate study Y/N**	**Owner**
KIIA 5.8 /04 (DAR)	xxx	2006	BYH 18636-carboxylic acid (AE 1394083) - Acute toxicity in the rat after oral administration Report No.: AT02902, Edition Number: M-269981-01-2 xxx GLP/GEP: Yes, unpublished	Yes	Bayer
KIIA 5.8 /05 (DAR)	xxx	2007	BYH 18636-carboxylic acid - 90-day toxicity study in the rat by dietary administration Report No.: SA 06035, Edition Number: M-282943-01-2 xxx GLP/GEP: Yes, unpublished	Yes	Bayer

The following tables are to be completed by MS

List of data submitted by the applicant and not relied on

Data point	Author(s)	Year	Title Company Report No. Source (where different from company) GLP or GEP status Published or not	Vertebrate study Y/N	Owner

List of data relied on not submitted by the applicant but necessary for evaluation

Data point	Author(s)	Year	Title Company Report No. Source (where different from company) GLP or GEP status Published or not	Vertebrate study Y/N	Owner

Appendix 2 Detailed evaluation of the studies relied upon

A 2.1 Statement on bridging possibilities

None.

A 2.2 Acute oral toxicity (KCP 7.1.1)

Comments of zRMS:	**Under the experimental conditions, the oral LD50 of FSN+TCM OD80 is higher than 2000 mg/kg bw in rats.** **Thus, no classification is required according to Regulation (EC) No. 1272/2008** **See Core Assessment 2015**

According to the Regulation (EC) No. 1272/2008 Annex 3.1.3.6.2.1 the classification of the mixture may be estimated with a calculation method.

The formulation FSN+TCM OD80 doesn't contain ingredients relevant for calculation of an oral ATE-mix, therefore no classification for this endpoint is requested. For details please refer to Part C.

In addition, for a country outside of Europe, an acute oral toxicity study was conducted with the formulation itself which revealed a LD_{50} greater than 2000 mg/kg bw and no classification requested.

Reference:	**KCP 7.1.1/01**
Title:	Foramsulfuron + thiencarbazone-methyl OD 80 (50+30 g/L) - Acute oral toxicity study in rats
Report:	xxx,; 2013; 13/014-001P; M-453344-01-1
Authority registration No:	
Guideline(s):	OECD Guidelines for Testing of Chemicals No. 423. Acute Oral Toxicity – Acute Toxic Class Method. Adopted: 17th December 2001 COMMISSION REGULATION (EC) NO 440/2008 OF 30 MAY 2008, B.1.TRIS EPA Health Effects Test Guidelines (OPPTS 870.1100), United States, EPA 712-C-98-190 (1998)
Deviations:	none
GLP/GEP:	yes
Acceptability:	Acceptable
Duplication (if vertebrate study):	No

Materials and methods

Test material (Lot/Batch No.)	Foramsulfuron + thiencarbazone –methyl OD 80 (50+30 g/L) FSN+TCM OD 80 batch number: 2012-005269
Species	CRL:(WI) rats
No. of animals (group size)	3 female rats
Dose(s)	2000 mg/kg bw
Exposure	Once by gavage
Vehicle/Dilution	None

Post exposure observation period	14 days
Remarks	None

Results and discussions

Table A 1: Results of acute oral toxicity study in rats of FSN+TCM OD80

Dose (mg/kg bw)	Toxicological results *	Duration of signs	Time of death	LD50 (mg/kg bw) (14 days)
Female rats (1st round)				
2000	0/0/3	--	--	> 2000
Female rats (2nd round)				
2000	0/0/3	--	--	> 2000

* Number of animals which died/number of animals with clinical signs/number of animals used

Table A 2: Summary of findings of acute oral toxicity study in rats of FSN+TCM OD80

Mortality:	No mortality occurred.
Clinical signs:	No clinical signs of toxicity were observed.
Body weight:	Body weight gain was considered to be normal.
Macroscopic examination:	The necropsies performed at the end of the study revealed no apparent findings.

Conclusion

Under the experimental conditions, the oral LD50 of FSN+TCM OD80 is higher than 2000 mg/kg bw in rats. Thus, no classification is required according to Regulation (EC) No. 1272/2008.

A 2.3 Acute percutaneous (dermal) toxicity (KCP 7.1.2)

Comments of zRMS:	**Under the experimental conditions, the dermal LD_{50} of FSN+TCM OD 80 is higher than 2000 mg/kg bw in rats.** **Thus, no classification is required according to Regulation (EC) No. 1272/2008.** **See Core Assessment 2015**

According to the Regulation (EC) No. 1272/2008 Annex 3.1.3.6.2.1 the classification of the mixture may be estimated with a calculation method.

The formulation FSN+TCM OD80 doesn't contain ingredients relevant for calculation of a dermal ATE-mix, therefore no classification for this endpoint is requested. For details please refer to Part C.

In addition, for a country outside of Europe, an acute dermal toxicity study was conducted with the formulation itself which revealed a LD_{50} greater than 2000 mg/kg bw and no classification requested.

Reference:	**KCP 7.1.2/01**
Title:	Foramsulfuron + thiencarbazone-methyl OD 80 (50+30 g/L) - Acute dermal toxicity study in rats
Report:	xxx; 2013; 13/014-002P; M-453346-01-1
Authority registration No:	
Guideline(s):	OECD 402 (1987) EPA OPPTS 870.1200 (1998) EC 440/2008 (2008)
Deviations:	none
GLP/GEP:	yes
Acceptability:	Acceptable
Duplication (if vertebrate study):	No

Materials and methods

Test material (Lot/Batch No.)	Foramsulfuron + thiencarbazone –methyl OD 80 (50+30 g/L) FSN+TCM OD 80 batch number: 2012-005269
Species	Rat, CRL/(WI) rats
No. of animals (group size)	5 rats/sex
Dose(s)	2000 mg/kg bw
Exposure	24 hours (dermal, semi-occlusive)
Vehicle/Dilution	None
Post exposure observation period	14 days
Remarks	None

Results and discussions

Table A 3: Results of acute dermal toxicity study in rats of FSN+TCM OD 80

Dose (mg/kg bw)	Toxicological results *	Duration of signs	Time of death	LD50 (mg/kg bw) (14 days)
Male rats				
2000	0/0/5	--	--	> 2000
Female rats				
2000	0/0/5	--	--	> 2000

* Number of animals which died/number of animals with clinical signs/number of animals used

Table A 4: Summary of findings of acute dermal toxicity study in rats of FSN+TCM OD 80

Mortality:	No mortality occurred.
Clinical signs:	No clinical signs of toxicity were observed. Local dermal signs: After treatment erythema (score 1 or 2) was noted in all animals and oedema (score 1) was observed in three animals from day 1 to day 3. Callus then scab was observed in 10/10 animals which was reversible by the end of the 14 day observation period in 9/10 animals.
Body weight:	Body weight gain was considered to be normal.

Macroscopic examination:	The necropsies performed at the end of the study revealed no apparent findings. The single scab, 0.5 cm x 1 cm in size, at the site of application observed in one female animal could be considered as incidental, procedure related macroscopic findings.

Conclusion

Under the experimental conditions, the dermal LD_{50} of FSN+TCM OD 80 is higher than 2000 mg/kg bw in rats. Thus, no classification is required according to Regulation (EC) No. 1272/2008.

A 2.4 Acute inhalation toxicity (KCP 7.1.3)

Comments of zRMS:	**Under the experimental conditions, the inhalation LC_{50} of FSN+TCM OD 80 is > 5.22 mg/L air in male rats (no classification), and > 4.91 mg/L air in female rats (acute toxicity, category 4, dust and mist).** **Thus, Acute Tox.4/H332 classification is required according to Regulation (EC) No. 1272/2008.** **See Core Assessment 2015**

According to the Regulation (EC) No. 1272/2008 Annex 3.1.3.6.2.1 the classification of the mixture may be estimated with a calculation method.

The formulation FSN+TCM OD 80 contains ingredients relevant for calculation of an inhalation ATEmix (vapor) of 1375 mg/L, which does not request a classification for acute inhalation toxicity (threshold 20 mg/L). For details please refer to Part C.

However, for a country outside of Europe, an acute inhalation toxicity study was conducted with the formulation itself which revealed a LC_{50} > 5.22 mg/L air in male rats (no classification), and > 4.91 mg/L air in female rats (acute toxicity, category 4, dust and mist). In order to provide a harmonized MSDS under CLP/GHS for the current formulation the result of the acute inhalation toxicity study needs to be taken into account.

Reference:	**KCP 7.1.3/01**
Title:	Acute inhalation toxicity study (nose-only) in the rat with FSN+TCM OD 50+30 G
Report:	xxx; 2013; 13/014-004P; M-461014-01-1
Authority registration No:	
Guideline(s):	OECD 403 (2009) EPA OPPTS 870.1300 (1998) EC 440/2008, B.2 (2008)
Deviations:	not specified
GLP/GEP:	yes
Acceptability:	Acceptability
Duplication (if vertebrate study):	No

Materials and methods

Test material (Lot/Batch No.)	Foramsulfuron + thiencarbazone –methyl OD 80 (50+30 g/L) FSN+TCM OD 80 batch number: 2012-005269
Species	Rat, CRL/(WI) rats
No. of animals (group size)	Sighting exposure - Group 0.1 (1female and 1 male) Main study – Group 1 (5 females and 5 males) Main study – Group 2 (5 females) Main study – Group 3 (5 females)

Concentration(s)	Sighting exposure - Group 0.1 (5.18 mg/L) Main study – Group 1 (5.22 mg/L) Main study – Group 2 (3.99 mg/L) Main study – Group 3 (3.40 mg/L)
Exposure	4 hours (nose only)
Vehicle/Dilution	None
Post exposure observation period	14 days
Remarks	None

Results and discussions

Table A 5: Concentration(s) and exposure conditions

Group number	Nominal conc. (mg/L air)	Mean achievable conc. (mg/L air)	MMAD * (µm)	GSD ** (µm)
0.1	73.48	5.18	3.87	1.96
1	71.82	5.22	3.88	1.98
2	44.83	3.99	3.81	1.86
3	40.83	3.40	3.46	1.89

* MMAD = Mass Median Aerodynamic Diameter
** GSD = Geometric Standard Deviation

Table A 6: Results of acute inhalation toxicity study in rats of FSN+TCM OD80

Mean achieved concentration (mg/L air)	Toxicological results *	Duration of signs	Time of death	LC_{50} (mg/L air) (14 days)
Male rats				
Group 0.1 5.18	0/1/1	until the end of the observation period	at final necropsy	> 5.18
Group 1 5.22	2/5/5	Symptoms free at day 11	N°64: death at day 1 N°75: death at day 2 The others : death at final necropsy	>5.22
Female rats				
Group 0.1 5.18	0/1/1	until the end of the observation period	at final necropsy	> 5.18
Group 1 5.22	3/5/5	until the end of the observation period	N°85: death at day 9 N°86: death at day 2 N°91: death at day 2 The others : death at final necropsy	<5.22
Group 2 3.99	1/5/5	N°284 and 291: until the end of the observation period N°282: symptoms free at day 13	N°288: death at day 2 The others: death at final necropsy	>3.99

Mean achieved concentration (mg/L air)	Toxicological results *	Duration of signs	Time of death	LC_{50} (mg/L air) (14 days)
Group 3 3.40	0/5/5	until the end of the observation period	death at final necropsy	>3.40

* Number of animals which died/number of animals with clinical signs/number of animals used

Table A 7: Summary of findings of acute inhalation toxicity study in rats of FSN+TCM OD 80

Mortality:	Yes, mortality occurred at day 1 and 2 for 6 animals over 22. A single four hours nose-only exposure of FSN+TCM+ OD 50+30 G to Wistar CRL:WI rats led to the death of 6 animals between Days 1-8 during the Main study. Affected rats included 1/5 and 5/10 rats dosed at 3.99 mg/L and 5.22 mg/L, respectively. Potentially test item-related gross changes were observed in the lungs, thymus and/or fur at the perinasal/perioral areas. In surviving animals, no test item-related macroscopic findings were seen at the termination on Day 14.
Clinical signs:	Yes, wet fur and fur staining were commonly recorded in exposed animals on the day of exposure and several days after exposure. These observations were considered to be related to the restraint and exposure procedures and, were considered not to be test item related. *Sighting exposure – Group 0.1 (1♂+1♀):* Slight to severe laboured and noisy respiration, decreased activity were recorded for the animals on day of exposure. In addition, gasping respiration, sneezing, hunched posture, weak and wasted conditions, fur loss on nose were noted for the exposed animals during two weeks recovery period. *Main study – Group 1 (5♂+5♀):* The same clinical signs were recorded in Group 1 exposed at the same aerosol concentration. Laboured, gasping and noisy respiration, activity decreased were noted on day of exposure; sneezing, hunched posture, weak and wasted conditions, fur loss on nose were recorded during the further two weeks observation period. Two males and three females were found dead on Day 1, 2 and 8, respectively. *Main study – Group 2 (5♀):* Laboured, gasping and noisy respiration, activity decreased were noted in exposed animals on day of exposure; sneezing, hunched posture, weak and wasted conditions were recorded during the further two weeks of the observation period. One animal was found dead on Day 1. *Main study – Group 3 (5♀):* The following clinical signs were noted for the exposed animals on day of exposure: laboured and noisy respiration, activity decreased. In addition, sneezing, gasping respiration, hunched posture, weak and wasted conditions, fur loss on nose were recorded during the observation period.
Body weight:	Following exposure, bodyweight loss was observed in all animals. Due to the severe clinical signs in some animals from each dose groups slight to moderate bodyweight loss was recorded during the first week of the observation period.
Macroscopic examination:	In animals dead at days 1 and 2: potentially test item-related gross changes were observed in the lungs, thymus and/or fur at the perinasal/perioral areas. Dark/red discoloration and/or non-collapsing of the lungs were found in 5/5 animals dosed at 5.22 mg/L. Enlarged and red discoloured lungs were observed in one female exposed to 3.99 mg/L and one female rat dosed at 5.22 mg/L. Red liquid material at the perinasal/perioral for areas was noted in 6/6 found dead animals. In addition, red discoloured thymus was seen in 2/5 found dead rats exposed to 5.22 mg/L. These changes were considered to be potentially related to die administration of the test item. In surviving animals, no test item-related macroscopic findings were seen at the termination on Day 14.

Conclusion

Under the experimental conditions, the inhalation LC_{50} of FSN+TCM OD 80 is > 5.22 mg/L air in male rats (no classification), and > 4.91 mg/L air in female rats (acute toxicity, category 4, dust and mist).

Thus, H332 classification is required according to Regulation (EC) No. 1272/2008.

A 2.5 Skin irritation (KCP 7.1.4)

Comments of zRMS:	**Under the experimental conditions, FSN+TCM OD80 is a skin irritant, category 2.** **Thus, Skin Irrit.2/H315 classification is required according to Regulation (EC) No. 1272/2008.** **See Core Assessment 2015**

The skin irritating properties were evaluated according to Commission Regulation (EC) No 1272/2008, Annex I table 3.2.3, for classification of mixtures.

In the current formulation the overall content of skin corrosive category 1 ingredients is 0 %, and the overall content of skin irritant category 2 ingredients is 12%, which is below the generic concentration limit of ≥ 10 % for classification.

Therefore, the current formulation is classified for skin irritation. For details please refer to Part C.

In addition for a country outside of Europe, a skin irritation study conducted with the formulation itself confirmed that classification for skin irritation is warranted, Cat 2, H315, according to Regulation (EC) No. 1272/2008.

Reference:	**KCP 7.1.4/01**
Title:	Foramsulfuron + thiencarbazone-methyl OD 80 (50+30 g/L) - Acute skin irritation study in rabbits
Report:	xxx; 2013; 13/014-006N; M-456379-01-1
Authority registration No:	
Guideline(s):	OECD GUIDELINES FOR TESTING OF CHEMICALS 404 (24th April 2002) OECD: Paris, Commission Regulation (EC) No 440/2008, B.4 (L 142, 30 May 2008); OPPTS 870.2500 (EPA 712-C-98-196) August 1998
Deviations:	not specified
GLP/GEP:	yes
Acceptability:	
Duplication (if vertebrate study):	No

Materials and methods

Test material (Lot/Batch No.)	Foramsulfuron + thiencarbazone –methyl OD 80 (50+30 g/L) FSN+TCM OD 80 batch number: 2012-005269
Species	Rabbit, New Zealand White
No. of animals (group size)	3 males
Initial test using one animal	Yes
Exposure	0.5 mL (4 hours, semi-occlusive)
Vehicle/Dilution	None
Post exposure observation period	14 days
Remarks	None

Results and discussions

Table A 8: Skin irritation of FSN+TCM OD 80

Animal No.		Scores after treatment *				Mean scores (24-72 h)	Reversible (day)
		1 h	24 h	48 h	72 h		
01904	Erythema Oedema	1 1	2 1	2 1	2 1	2.0 1.0	No
01931	Erythema Oedema	1 1	2 1	2 1	2 1	2.0 1.0	No
01917	Erythema Oedema	1 1	2 1	2 1	2 1	2.0 1.0	No

* scores in the range of 1 to 2.

Skin irritation Scores-Mean values after 24, 48 and 72 hours of FSN+TCM OD80

Animal number	Sex	Erythema	N	Oedema	N	Primary Skin Irritation Index
01904	Male	2.00	3	1.00	3	3
01931	Male	2.00	3	1.00	3	
01917	Male	2.00	3	1.00	3	
Mean score		2.00		1.00		
N= number of available data points						

Clinical signs:	No clinical signs of systemic toxicity were observed in the animals during the study and no mortality occurred. The body weights of all rabbits were considered to be within the normal range of variability.

Conclusion
Under the experimental conditions, FSN+TCM OD80 is a skin irritant, category 2. Thus, H315 classification is required according to Regulation (EC) No. 1272/2008.

A 2.6 Eye irritation (KCP 7.1.5)

Comments of zRMS:	**Under the experimental conditions, FSN+TCM OD 80 is an eye irritant, category 1.** **Thus, Eye Dam.1/H318 classification is required according to Regulation (EC) No. 1272/2008.** **See Core Assessment 2015**

The eye irritating properties were evaluated according to Commission Regulation (EC) No 1272/2008, Annex I table 3.2.3, for classification of mixtures.

In the current formulation the overall content of ingredients classified for eye effects category 1 is 22 % and thereby above the generic concentration limit of ≥ 3% for classification for eye effects category 1. For details please refer to Part C.

In addition, an in vitro eye irritation study was conducted with the current formulation. According to this in vitro eye irritation test the formulation should be classified for eye irritation/corrosivity, Category 1, H318, according to Regulation (EC) No. 1272/2008.

Reference:	**KCP 7.1.5/01**
Title:	Foramsulfuron + thiencarbazone-methyl OD 80 (50+30 g/L) - Acute eye irritation study in rabbits - FSN+TCM OD 50+30 G
Report:	xxx; 2013; 13/014-005N; M-453831-01-1
Authority registration No:	
Guideline(s):	OECD Test Guideline 405 (02nd October 2012) EPA OPPTS 870.2400 (1998) EC No 440/2008, B.5 (2008)
Deviations:	not specified
GLP/GEP:	yes
Acceptability:	
Duplication (if vertebrate study):	No

Materials and methods

Test material (Lot/Batch No.)	Foramsulfuron + thiencarbazone –methyl OD 80 (50+30 g/L) FSN+TCM OD 80 batch number: 2012-005269
Species	Rabbit, New Zealand White
No. of animals (group size)	1 male
Initial test using one animal	Yes
Exposure	0.1 mL (single instillation in conjunctival sac)
Irrigation (time point)	The treated eye of test animal was rinsed with physiological saline solution after the 1 hour observation, due to the irritation scores of more than 1.
Vehicle/Dilution	None
Post exposure observation period	24, 48, 72, 7 days, 14 days and 21 days
Remarks	None

Results and discussions

Table A 9: Eye irritation of FSN+TCM OD80

Animal No.	Effects	Scores after treatment *				Mean scores (24-72 h)	Reversible (day)
		1 h	24 h	48 h	72 h		
9825	Corneal opacity	1	1	1	1	1	Not reversible
	Iritis	0	0	0	0	0	Not applicable
	Redness conjunctivae	1	2	2	2	2	Not reversible
	Chemosis conjunctivae	2	2	2	2	2	Reversible at day 21
	Discharge	3	3	3	3	3	Reversible at day 21

- scores remain stable after treatment : 1 for cornea opacity, 2 for chemosis and 3 for iritis, scores range of1 to 2 for redness of conjunctivae.

Clinical signs:	No clinical signs of toxicity were observed.

Conclusion

Under the experimental conditions, FSN+TCM OD 80 is an eye irritant, category 1. Thus, H318 classification is required according to Regulation (EC) No. 1272/2008.

A 2.7 Skin sensitisation (KCP 7.1.6)

Comments of zRMS:	**Under the experimental conditions, FSN+TCM OD80 is a skin sensitizer category 1B.** **Thus,Skin Sens.1B/ H317 classification is required according to Regulation (EC) No. 1272/2008.** **See Core Assessment 2015**

The skin sensitising properties were evaluated according to Commission Regulation (EC) No 1272/2008, Annex I table 3.4.5, for classification of mixtures.

The current formulation contains one ingredient at 10% classified for sensitization therefore classification of the mixture for skin sensitization is requested. For details please refer to Part C.

In addition, a Local Lymph Node Assay was conducted with the formulation itself for a country outside of Europe which revealed a positive response requiring classification for skin sensitisation according to Regulation (EC) No. 1272/2008, Category 1, H317.

Reference:	**KCP 7.1.6/01**
Title:	Foramsulfuron + thiencarbazone-methyl OD 50+30 g/L - Local lymph node assay in the mouse
Report:	xxx; 2013; 13/014-037E; M-456378-01-1
Authority registration No:	
Guideline(s):	OECD Guidelines for Testing of Chemicals No. 429., Skin Sensitisation: Local Lymph Node Assay Adopted: 22 July 2010; Commission Regulation (EC) No 440/2008 of 30 May 2008, B.42., Skin Sensitisation: Local Lymph Node Assay (Official Journal L 142, 31/05/2008)
Deviations:	not specified
GLP/GEP:	yes
Acceptability:	Acceptability
Duplication (if vertebrate study):	No

Materials and methods

Test material (Lot/Batch No.)	Foramsulfuron + thiencarbazone –methyl OD 80 (50+30 g/L) FSN+TCM OD 80 batch number: 2012-005269
Species	Mouse, CBA/J Rj strain
No. of animals (group size)	4 females/group 6 groups : 4 treated groups, one positive control group, and one negative control group.
Range finding:	Yes, two preliminary tests were performed. Preliminary test I: 100% (undiluted), 50% and 25% (w/v) in 1% Pluronic Preliminary test II: 5%, 2.5% and 1% (w/v) in 1% Pluronic.
Exposure (concentration(s), no. of applications)	test item (4 groups): 10%, 5%, 2.5% and 1% in 1% Pluronic Positive control : 25% HCA in 1% Pluronic Negative control : 1% Pluronic During the assay each mouse was topically dosed on the dorsal surface of each ear with 25 µL of the appropriate formulation applied using a pipette. Each animal was dosed once a day for three consecutive days (Days 1, 2 and 3). There was no treatment on Days

	4, 5 and 6.
Vehicle	1% Pluronic
Pre treatment prior to topical application	No
Reliability check	The positive control group animals were treated with 25 % (w/v) HCA solution in a relevant vehicle (1% Pluronic) concurrent to the test item groups. The positive control substance was chosen according to the OECD guideline [1]. To minimise animal use, the positive control animals were part of a concurrent study using the same vehicle. No mortality, cutaneous reactions or signs of toxicity were observed in the positive control group. A significant lymphoproliferative response (stimulation index value of 8.6) was noted for α-Hexylcinnamaldehyde in this experiment. The results of the positive control group demonstrated the appropriate performance of the assay. Furthermore, the DPN values observed for the negative (vehicle) and positive control substances in this experiment were within the historical control range.
Remarks	None

Results and discussions

Table A 10: Results of skin sensitisation study of FSN+TCM OD 80

	No. of animals	**Concentration (%)**	**DPM / group**	**Stimulation index (SI)**
FSN+TCM OD80	4	10	3164	4.8
	4	5	1170	1.7
	4	2.5	887	1.3
	4	1	798	1.2
Test Vehicle Control Group	4	1% Pluronic	687	1.0
Positive control	4	25% (w/v) HCA in 1% Pluronic	5617	8.6

Clinical signs:	No mortality or systemic toxicity was observed during the study. No treatment related effects were observed on animal body weights in any treated groups. There were no indications of any irritancy at the site of application.

Conclusion

Under the experimental conditions, FSN+TCM OD80 is a skin sensitizer category 1B. Thus, H317 classification is required according to Regulation (EC) No. 1272/2008.

A 2.8 Supplementary studies for combinations of plant protection products (KCP 7.1.7)

None.

A 2.9 Data on co-formulants (KCP 7.4)

A 2.9.1 Material safety data sheet for each co- formulant

Information regarding material safety data sheets of the co-formulants can be found in the confidential dossier of this submission (Registration Report - Part C).

A 2.9.2 Available toxicological data for each co-formulant

Available toxicological data for each co-formulant can be found in the confidential dossier of this submission (Registration Report - Part C).

A 2.10 Studies on dermal absorption (KCP 7.3)

Comparative dermal absorption, *in vitro* using rat and human skin

Comments of zRMS:	Comment on study; acceptable or not; deficiencies, corrections, according to recent guidelines or not, used in evaluation or only as additional information

Reference:	**KCP 7.3/01**
Title:	In-vitro human skin penetration of 14C-thiencarbazone-methyl in the thiencarbazone-methyl and foramsulfuron OD 80 formulation (specification no 102000025743)
Report:	Bernal, J.; 2015; S15-01966; M-537205-01-1
Authority registration No:	
Guideline(s):	OECD Guideline for the testing of Chemicals Skin Absorption In Vitro Method Guideline 428 (April 2004); OECD Environmental Health and Safety Publication Series on testing and Assessment No 28, Guidance Document for the Conduct of Skin Absorption Studies (March 2004); EFSA Panel on Plant Protection Products and their Residues (PPR): Guidance on Dermal Absorption, EFSA Journal 2012: 10(4): 2665
Deviations:	none
GLP/GEP:	yes
Acceptability:	
Duplication (if vertebrate study):	

Material and methods

Human skin: Source: Alphenyx, Marsaille, France and Banque de Tissu, Lyon or Tissue solutions, Montpellier, France.
Number and sex: 4 donors, 2 male and 2 female.
Anatomical region: Abdomen.
Thickness: 312 to 400 µm.

Test Material:

Non-radiolabelled: Batch: BCOO5877-18-2.
Purity = 99%.

Radiolabelled: [thiophene-4-^{14}C]-thiencarbazone-methyl
Batch: KML 9931.
Specific activity: 105.14 µCi/mg.
Radiopurity of the formulation: >99%.

Formulation: The formulation used in this experiment was the thiencarbazone-methyl + foramsulfuron OD 80 formulation (specification number 102000025743) containing thiencarbazone-methyl at a concentration of 30 g/L. It was used at two nominal concentrations of thiencarbazone-methyl: neat, 30 g/L and 0.075 g/L.

Test system: A flow-through diffusion cell system was used to study the absorption of the test substance (exposure area of 1 cm^2 skin). A diffusion cell consisted of a donor chamber and a receptor chamber between which the skin was positioned. The receptor fluid used in this study was PBS 0.01M pH 7.4. The skin surface temperature was maintained at 32°C ± 1°C, with a fixed water bath integrated in the dynamic system (close to the normal skin temperature). The receptor fluid was pumped through the receptor chamber at a rate of 1 mL/h.

Skin integrity: Before dose application, the integrity of the skin samples was assessed by measuring the trans-epidermal water loss (TEWL) from the stratum corneum. The skin integrity was evaluated before use by measuring the TEWL. The absence of water on the skin was controlled using a Tewameter which allows measurement of water evaporation from skin surfaces based on the diffusion principle and expresses the results digitally in $g/m^2/h$. The measurement was carried out away from any heating source and air stream after at least 1 hour stabilisation. The human skin was included in the study if the TEWL was ≤ 4 $g/m^2/h$.

Treatment: The dose preparation was applied to the split-thickness skin sample with a positive displacement pipette at the rate of approximately 10 $\mu L/cm^2$. The specific activity of 6 aliquots of thiencarbazone-methyl and the homogeneity of the test items were checked on the day of preparation, before and during application. The homogeneity of the test items before the application was acceptable if the obtained CV was < 5%. The specific activity of the test items obtained during the application was used to calculate the recovery. The coefficient of variation between this series of samples was stated as a measure of variability of the application system.

Sampling: The receptor fluid passing through the receptor chamber was collected in glass vials held in a fraction collector. The receptor fluid was collected in one vial per time point and per cell at 1h, 2h, 3h, 4h, 5h, 6h, 7h, 8h, 10h, 12h, 15h, 18h, 21h and 24h post the start of application. At 8 hours post-application, the skin was swabbed with 10% v/v Tween 80 in water using cotton buds and then with 9 x 1 mL of UHQ water. The washing solution was added to the skin surface then removed using a pipette and was collected for analysis. Then, skin surface was carefully dried with three cotton-buds in order to remove and retain the non-absorbed dose. At the end of the study (24 hours after application), the treated skin and the skin adjacent to the treatment site (surrounding swabs) were swabbed. Each skin sample was tape-stripped to remove the stratum corneum. The strips were performed using adhesive scotch tape Magic 3M®. In order to standardise stripping, a weight of 150 g/cm^2 was placed top of the Scotch tape for 10 s before taking off. A maximum of 15 strips were performed until the slightly shiny layer below the *stratum corneum* was visible, corresponding to the viable epidermis (presumed to be the region around the *stratum spinosum*). All strips were ana-

lysed separately. The first two strips are considered in the calculation as material likely to be lost to the external environment due to desquamation of the superficial external layers of the skin surface.

Radioassay Samples were analysed for radiolabel content by scintillation counter. Calculations were performed using Excel 2010 directly from the raw data obtained with the scintillation counter. The software runs calculations using 7 decimal points, but in general less numbers are printed on the raw data sheets. Conversion of the counts per minute (cpm) to disintegrations per minute (dpm) was performed directly by the microprocessor in the instrument using a quench curve of the appropriate scintillation cocktail stored in the instrument database.

Findings:

Thiencarbazone-methyl was demonstrated to be sufficiently soluble in the receptor fluid to avoid any risk of back diffusion.

Measurements of the homogeneity of the two concentrations of formulation applied indicated that it was acceptable.

The study results are presented in Table A11.

Table A11: Mean distribution of radioactivity at 24 hours after dose application of [^{14}C]- thiencarbazone-methyl in an OD 80 formulation at the rates of 30 g/L and 0.075 g/L to human skin samples.

Results expressed in terms of percentage of applied radioactivity.

	Distribution of radioactivity (% dose)			
Dose Levels	Neat formulation: High dose (30 g/L)		Dilution: Low dose (0.075 g/L)	
Species	Human (n=5, K N° = 1.2)		Human (n=6, K N° = 1)	
	Mean	SD	Mean	SD
SURFACE COMPARTMENT				
Dislodgeable (8h)	101.4	1.29	93.14	2.83
Surface Dose (1st two tape-strips)	0.11	0.10	1.86	0.88
Total % non-absorbed	**101.5**	**1.24**	**94.99**	**2.15**
SKIN COMPARTMENT				
Skin [b]	0.06	0.02	1.24	0.71
Stratum corneum [c]	0.06	0.04	1.73	1.03
Total % at dose site	**0.12**	**0.05**	**2.97**	**1.08**
RECEPTOR COMPARTMENT				
Total % directly absorbed [d]	0.01	0.01	0.68	0.44
STUDY: Total % Potentially Absorbable [e]	0.12	0.04	3.65	1.50
TOTAL % RECOVERY	**101.7**	**1.21**	**98.64**	**0.94**
Evaluation according to EFSA Guidance				
Absorption >75% within half of study duration	Yes (exclude SC values)		Yes (exclude SC values)	
Recovery <95%	No correction needed		No correction needed	
Total % Potentially Absorbable adjusted according to EFSA (2017)	Mean %skin+%directly absorbed + SD*1.2		Mean %skin+%directly absorbed + SD*1	
	0.1		**2.8**	

[a]: sum of radioactivity found in swabs at termination and in surrounding swabs.
[b]: sum of radioactivity found in skin after tape-stripping procedure and in surrounding skin.
[c]: tape-strips excluding numbers 1 & 2 which are considered to be non-absorbed dose.
[d]: sum of radioactivity found in receptor fluid (0-24h), receptor fluid terminal and receptor chamber.
[e]: total % directly absorbed + total % at dose site
SD: standard deviation
n: number of skin cells used for calculation
In the above table, the presented means do not always calculate exactly from the presented individual data. This is due to rounding-up differences resulting from the use of the spreadsheet program.

Conclusion:
The dermal penetration through human dermatomed skin of [^{14}C]-thiencarbazone-methyl in the OD 80 formulation was investigated at two concentrations corresponding to the neat product (30 g /L) and a representative dilution of 0.075 g/L.

Concentrate

The mean percentage of thiencarbazone-methyl in the OD 80 formulation that was considered to be potentially absorbable (directly absorbed plus total remaining at dose site) over a period of 24 hours for the neat formulation was 0.12% for the human skin. Applying the EFSA guidance (2017) this value adjusts to 0.1%.

Low Dose level (Spray dilution)

The mean percentage of thiencarbazone-methyl in the OD 80 formulation that was considered to be potentially absorbable *(directly absorbed plus total remaining at dose site)* over a period of 24 hours for the low dose rate was 3.65% for human skin. Applying the new EFSA guidance (2017) this value adjusts to 2.8%.

Comment:

The following dermal absorption value can be proposed for use in the non-dietary risk assessments for [^{14}C]-thiencarbazone-methyl in the FSN+TCM OD 80 formulation: 0.1% for the neat formulation (30 g/L) and 2.8% for the low dose (0.075 g/L).

A 2.11 Other/Special Studies

The following section aims at providing further toxicological information of the foramsulfuron metabolite AE F092944 in relation with the residue section

Comments of zRMS:	**Acceptable**

Reference:	**KCA 5.8.1/01**
Title:	Hoe 092944; substance technical (Code: Hoe 092944 00 ZD99 0001) Testing for acute oral toxicity in the male and female Wistar rat
Report:	xxx; 1995; A49161; M-138232-02-1
Authority registration No:	Acceptable
Guideline(s):	OECD: 401 (1987); USEPA (=EPA): § 81-1 (1984)
Deviations:	--
GLP/GEP:	yes
Acceptability:	Acceptability
Duplication (if vertebrate study):	No

Reference:	**KCA 5.8.1/02**
Title:	TBS-1203: Acute oral toxicity study in male mice
Report:	xxx.; 1995; A55629; M-139539-01-1
Authority registration No:	
Guideline(s):	--
Deviations:	--
GLP/GEP:	no
Acceptability:	Acceptability
Duplication (if vertebrate study):	No

Reference:	**KCA 5.8.1/03**
Title:	Hoe 092944 - substance, technical (Code: Hoe 092944 00 ZD99 0001) Study of the mutagenic potential in strains of Salmonella typhimurium (Ames Test) and Escherichia coli
Report:	Stammberger, I.; 1992; A48871; M-137963-01-1
Authority registration No:	
Guideline(s):	--
Deviations:	--
GLP/GEP:	yes
Acceptability:	Acceptability
Duplication (if vertebrate study):	

Reference:	**KCA 5.8.1/04**
Title:	Mutagenicity study of AE F092944 in the Salmonella typhimurium reverse mutation assay (in vitro)
Report:	Spruth, B.; 2017; 35401; M-644749-01-1
Authority registration No:	
Guideline(s):	Regulation (EC) No. 440/2008 method B.13/14 and OECD Guideline 471
Deviations:	None
GLP/GEP:	yes
Acceptability:	Acceptability
Duplication (if vertebrate study):	

Reference:	**KCA 5.8.1/05**
Title:	AE F092944 - Derek Nexus report
Report:	Anon.; 2015; M-685932-01-1
Authority registration No:	
Guideline(s):	None
Deviations:	None
GLP/GEP:	no
Acceptability:	Acceptability
Duplication (if vertebrate study):	No

Reference:	**KCA 5.8.1/06**
Title:	Amidosulfuron - In silico assessment of the metabolite AE F092944
Report:	xxx.; 2019; M-654051-01-1
Authority registration No:	
Guideline(s):	none
Deviations:	--
GLP/GEP:	not applicable
Acceptability:	Acceptability
Duplication (if vertebrate study):	No

Reference:	**Refer to Part C – Confidential document**
Title:	Request for information on the batches of foramsulfuron used in toxicology studies (Position paper)
Report:	xxx.; 2003; C026175; M-210912-01-1
Authority registration No:	Acceptable
Guideline(s):	--
Deviations:	--
GLP/GEP:	not applicable
Acceptability:	Acceptability
Duplication (if vertebrate study):	No

AE F092944 is a small degradation product of the parent foramsulfuron containing the pyrimidine part of parent so that already due to this fact a quicker elimination and shorter systemic bioavailability can be expected and thus a lower toxicity potential. Therefore, no higher toxicity for this metabolite than for parent has to be expected. This was confirmed by toxicity data for AEF092944, position papers and a QSAR analysis.
The LD_{50} in an acute toxicity study was between 2000 and 5000 mg/kg bw and calculated as 2669 mg/kg bw (M-138232-02-1), which together with the LD_{50} of > 2000 mg/kg bw in male mice (M-139539-01-1) confirmed a low acute toxic potential of this metabolite. Two Ames tests (M-137963-01-1; M-644749-01-1) were negative, so that based on this there is no evidence of a mutagenic potential.

A QSAR analysis by DEREK analysis (2015, M-685932-01-1) confirmed that the toxicity profile of AE F092944 was similar to that of the parent. The DEREK analysis gave alerts for foramsulfuron of bladder urothelial hyperplasia, hepatotoxicity, phototoxicity and skin sensitization, which, however, were not confirmed by the experimental data. These alerts are hence not relevant and similar alerts which were given for some of the metabolites are also not regarded as relevant. Therefore, the DEREK analysis did not give results for AE F092944 which would raise concerns. Also another QSAR analysis of AE F092944 as metabolite of another parent compound, amidosulfuron, with Derek Nexus, Leadscope and Toxtree models (xxx, 2019, M-654051-01-1) did not indicate a higher toxicity than that of this parent.

Furthermore, AE F092944 was included as impurity in many foramsulfuron batches which were tested in apical toxicology studies. A summary is given in a position paper (B. Mallyon, 2003, M-210912-01-1) in which the concentrations of AE F092944 in different batches which were used in toxicology studies are given. They ranged from 0.1 % to 0.4 % in 4 batches used in toxicology studies.

Thus, AE F092944 was included in batches used in apical studies, like acute toxicity, irritation, sensitization and genotoxicity tests, reproduction and developmental toxicity studies and in rat, dog and mouse long-term studies. For example, the batch used for the mouse oncogenicity study contained 0.4 % AE F092944. With the highest dose of 1136 mg/kg bw/day (males and females combined), a dose of 4.5 mg/kg bw of AE F092944 was tested in this lifetime study along with the active. Since the highest dose did not cause any adverse effects, AE F92944 at approximately 4.5 mg/kg bw/day over lifetime is without adverse effect. The lowest NOAEL would come from the rabbit developmental toxicity study with a ma-

ternal-toxic NOAEL of 50 and a developmental NOAEL of 500 mg/kg bw which would result in AE F092944 NOAELs of 0.1 and 1.0 mg/kg bw, respectively.

Overall, therefore it can be concluded that AE F092944 has no higher toxic potential than foramsulfuron and thus does not present a hazard.

Studies assessing the toxicological non relevance of the metabolite BYH 18636-carboxylic acid

Comments of zRMS:	Acceptable

Reference:	**KCA 5.8.1/07**
Title:	BYH18636-carboxylic acid (BCS-AT36039, AE 1394083): Micronucleus test in human lymphocytes In vitro
Report:	Naumann, S.; 2018; 1889000; M-630020-01-1
Authority registration No:	Acceptable
Guideline(s):	OECD Guideline for the Testing of Chemicals No. 487, In vitro Mammalian Cell Micronucleus Test, adopted 29 July 2016
Deviations:	None
GLP/GEP:	yes
Acceptability:	Acceptability
Duplication (if vertebrate study):	

Materials and methods

The test item BYH18636-carboxylic acid (BCS-AT36039, AE 1394083), dissolved in culture medium, was assessed for its potential to induce micronuclei in human lymphocytes in vitro in two independent experiments.

In each experimental group, two parallel cultures were analyzed. Per culture 1000 binucleated cells were evaluated for cytogenetic damage.

The highest applied concentration in this study (2037 µg/mL of the test item) was chosen with regard to the purity (98.2%) of the test item and with respect to the current OECD Guideline 487.
Dose selection of the cytogenetic experiment was performed considering the toxicity data in accordance with OECD Guideline 487.

Chosen treatment concentrations were:
Exp. I: 13.2, 23.2, 40.5, 70.9, 124, 217, 380, 665, 1164, 2037 µg/mL
Exp. II: 217, 380, 665, 1164, 2037 µg/mL

Results and discussions

In the absence and presence of S9 mix, no cytotoxicity was observed up to the highest applied concentration.

In both independent experiments, neither a statistically significant nor a biologically relevant increase in the number of micronucleated cells was observed after treatment with the test item.

Demecolcine (125 ng/mL), MMC (1.0 µg/mL) and CPA (17.5 µg/mL) were used as positive controls and showed distinct increases in cells with micronuclei. They induced statistically significant increases in cells with micronuclei.

Conclusion

Thus, it can be stated that under the experimental conditions reported, the test item did not induce micronuclei as determined by the *in vitro* micronucleus test in human lymphocytes.

Therefore, BYH18636-carboxylic acid (BCS-AT36039, AE 1394083) is considered to be non-mutagenic in this *in vitro* micronucleus test, when tested up to the highest required concentration.

Appendix 3 Exposure calculations

The following tables provide an overview of exposure calculations for all active substances, relevant crops and PPE scenarios as an outcome of the most updated version of the EFSA calculator.

A 3.1 Operator exposure calculations (KCP 7.2.1.1)

Table A-11: Operator exposure, foramsulfuron, root and tuber vegetables (sugar beet), no PPE / with PPE

Substance	Foramsulfuron	**Formulation =** Soluble concentrates, emulsifiable concentrate, etc.	**Application rate =** 0.05 kg a.s. /ha	**Spray dilution** = 0.625 g a.s./l	**Vapour pressure =** Low volatile substances having a vapour pressure of <5*10-3Pa
Scenario	Outdoor, Downward spraying, Vehicle-mounted			**Buffer =** 2-3 m	**Number of applications =** 1 **Application interval =** 365 days
Percentage Absorption	Dermal for product = 70%	**Dermal for in use dilution** = 70%	**Oral =** 20%	**Inhalation =** 100%	
RVNAS[1] (AOEL)	0.1 mg/kg bw/day		RVAAS[2]	not defined yet, thus no acute exposure calculations are provided	
DFR	3 µg a.s./cm² per kg a.s./ha		DT50	30 days	

Operator Model		Mixing, loading and application AOEM			
Potential exposure	Longer term systemic exposure mg/kg bw/day		0.202	% of RVNAS[1]	200%
	Acute systemic exposure mg/kg bw/day		not relevant	% of RVAAS[2]	not relevant
Mixing and Loading		**Gloves = No / Yes**	Clothing = Work wear - arms, body and legs covered	RPE = None	Soluble bags = No
Application		**Gloves = No / Yes**	Clothing = Work wear - arms, body and legs covered	RPE = None	Closed cabin = No
Exposure (Workwear) **Gloves = No**	Longer term systemic exposure mg/kg bw/day		**0.121**	% of RVNAS[1]	**120%**
	Acute systemic exposure mg/kg bw/day		not relevant	% of RVAAS[2]	not relevant
Exposure (Workwear) **Gloves = Yes**	Longer term systemic exposure mg/kg bw/day		**0.00397**	% of RVNAS[1]	**3.97%**
	Acute systemic exposure mg/kg bw/day		not relevant	% of RVAAS[2]	not relevant

[1] RVNAS = Reference Value Non Acutely toxic active Substance = AOEL

[2] RVAAS = Reference Value Acutely toxic active Substance

Table A-12: Operator exposure, thiencarbazone-methyl, root and tuber vegetables (sugar beet), no PPE / with PPE

Substance	Thiencarbazone-methyl	**Formulation =** Soluble concentrates, emulsifiable concentrate, etc.	**Application rate =** 0.03 kg a.s. /ha	**Spray dilution =** 0.375 g a.s./l	**Vapour pressure =** Low volatile substances having a vapour pressure of <5*10-3Pa
Scenario	Outdoor, Downward spraying, Vehicle-mounted			**Buffer =** 2-3 m	**Number of applications =** 1 **Application interval =** 365 days
Percentage Absorption	Dermal for product = 0.1%	**Dermal for in use dilution** = 2.8%	**Oral =** 50%	**Inhalation =** 100%	
RVNAS[1] (AOEL)	0.12 mg/kg bw/day		RVAAS[2]	not defined yet, thus no acute exposure calculations are provided	
DFR	3 µg a.s./cm² per kg a.s./ha		DT50	30 days	

Operator Model		Mixing, loading and application AOEM			
Potential exposure	Longer term systemic exposure mg/kg bw/day			% of RVNAS[1]	%
	Acute systemic exposure mg/kg bw/day		not relevant	% of RVAAS[2]	not relevant
Mixing and Loading		**Gloves = No / Yes**	Clothing = Work wear - arms, body and legs covered	RPE = None	Soluble bags = No
Application		**Gloves = No / Yes**	Clothing = Work wear - arms, body and legs covered	RPE = None	Closed cabin = No
Exposure (Workwear) **Gloves = No**	Longer term systemic exposure mg/kg bw/day		**0.000311**	% of RVNAS[1]	**<1%**
	Acute systemic exposure mg/kg bw/day		not relevant	% of RVAAS[2]	not relevant
Exposure (Workwear) **Gloves = Yes**	Longer term systemic exposure mg/kg bw/day		**0.000122**	% of RVNAS[1]	**<1%**
	Acute systemic exposure mg/kg bw/day		not relevant	% of RVAAS[2]	not relevant

1 RVNAS = Reference Value Non Acutely toxic active Substance = AOEL

2 RVAAS = Reference Value Acutely toxic active Substance

A 3.2 Worker exposure calculations (KCP 7.2.3.1)

Table A-13: Worker exposure, foramsulfuron, root and tuber vegetables (sugar beet)

Substance	Foramsulfuron	**Formulation =** Soluble concentrates, emulsifiable concentrate, etc.	**Application rate =** 0.05 kg a.s. /ha	**Spray dilution =** 0.625 g a.s./l	**Vapour pressure =** Low volatile substances having a vapour pressure of <5*10-3Pa
Scenario	Outdoor, Downward spraying, Vehicle-mounted			**Buffer =** 2-3 m	**Number of applications =** 1 **Application interval =** 365 days
Percentage Absorption	Dermal for product = 70%	**Dermal for in use dilution** = 70%	**Oral =** 20%	**Inhalation =** 100%	
RVNAS[1] (AOEL)	0.1 mg/kg bw/day		RVAAS[2]	not defined yet, thus no acute exposure calculations are provided	
DFR	3 µg a.s./cm² per kg a.s./ha		DT50	30 days	

Worker - Hand harvesting	Potential exposure mg/kg bw/day	0.0438	% of RVNAS[1]	44%
	Working clothing mg/kg bw/day	0.0049	% of RVNAS[1]	4.9%
	Working clothing and gloves mg/kg bw/day		% of RVNAS[1]	%

[1] RVNAS = Reference Value Non Acutely toxic active Substance = AOEL

[2] RVAAS = Reference Value Acutely toxic active Substance

Table A-14: Worker exposure, thiencarbazone-methyl, root and tuber vegetables (sugar beet)

Substance	Thiencarbazone-methyl	**Formulation =** Soluble concentrates, emulsifiable concentrate, etc.	**Application rate =** 0.03 kg a.s. /ha	**Spray dilution =** 0.375 g a.s./l	**Vapour pressure =** Low volatile substances having a vapour pressure of <5*10-3Pa
Scenario	Outdoor, Downward spraying, Vehicle-mounted			**Buffer =** 2-3 m	**Number of applications =** 1 **Application interval =** 365 days
Percentage Absorption	Dermal for product = 0.1%	**Dermal for in use dilution** = 2.8%	**Oral =** 50%	**Inhalation =** 100%	
RVNAS[1] (AOEL)	0.12 mg/kg bw/day		RVAAS[2]	not defined yet, thus no acute exposure calculations are provided	
DFR	3 µg a.s./cm² per kg a.s./ha		DT50	30 days	

Worker - Hand harvesting	Potential exposure mg/kg bw/day	0.00105	% of RVNAS[1]	<1%
	Working clothing mg/kg bw/day	0.000118	% of RVNAS[1]	<1%
	Working clothing and gloves mg/kg bw/day		% of RVNAS[1]	%

[1] RVNAS = Reference Value Non Acutely toxic active Substance = AOEL

[2] RVAAS = Reference Value Acutely toxic active Substance

A 3.2.1 Calculations for the active substance(s)

Please refer to A 3.

A 3.3 Bystander and resident exposure calculations (KCP 7.2.2.1)

Table A-15: Resident exposure, foramsulfuron, root and tuber vegetables (sugar beet)

Substance	Foramsulfuron	**Formulation =** Soluble concentrates, emulsifiable concentrate, etc.	**Application rate =** 0.05 kg a.s. /ha	**Spray dilution =** 0.625 g a.s./l	**Vapour pressure =** Low volatile substances having a vapour pressure of <5*10-3Pa
Scenario	Outdoor, Downward spraying, Vehicle-mounted			**Buffer =** 2-3 m	**Number of applications =** 1 **Application interval =** 365 days
Percentage Absorption	Dermal for product = 70%	**Dermal for in use dilution** = 70%	**Oral =** 20%	**Inhalation =** 100%	
RVNAS[1] (AOEL)	0.1 mg/kg bw/day		RVAAS[2]	not defined yet, thus no acute exposure calculations are provided	
DFR	3 µg a.s./cm² per kg a.s./ha		DT50	30 days	

Resident - child	Spray drift (75th percentile) mg/kg bw/day	0.0117	% of RVNAS[1]	12%
	Vapour (75th percentile) mg/kg bw/day	0.00107	% of RVNAS[1]	1.07%
	Surface deposits (75th percentile) mg/kg bw/day	0.000518	% of RVNAS[1]	<1%
	Entry into treated crops (75th percentile) mg/kg bw/day	0.00591	% of RVNAS[1]	5.91%
	All pathways (mean) mg/kg bw/day	0.0126	% of RVNAS[1]	13%
Resident - adult	Spray drift (75th percentile) mg/kg bw/day	0.00281	% of RVNAS[1]	2.81%
	Vapour (75th percentile) mg/kg bw/day	0.00023	% of RVNAS[1]	<1%
	Surface deposits (75th percentile) mg/kg bw/day	0.000238	% of RVNAS[1]	<1%
	Entry into treated crops (75th percentile) mg/kg bw/day	0.00328	% of RVNAS[1]	3.28%
	All pathways (mean) mg/kg bw/day	0.00436	% of RVNAS[1]	4.36%

1 RVNAS = Reference Value Non Acutely toxic active Substance = AOEL

2 RVAAS = Reference Value Acutely toxic active Substance

Table A-16: Resident exposure, thiencarbazone-methyl, root and tuber vegetables (sugar beet)

Substance	Thiencarbazone-methyl	**Formulation =** Soluble concentrates, emulsifiable concentrate, etc.	**Application rate =** 0.03 kg a.s. /ha	**Spray dilution =** 0.375 g a.s./l	**Vapour pressure =** Low volatile substances having a vapour pressure of <5*10-3Pa
Scenario	Outdoor, Downward spraying, Vehicle-mounted			**Buffer =** 2-3 m	**Number of applications =** 1 **Application interval =** 365 days
Percentage Absorption	Dermal for product = 0.1%	**Dermal for in use dilution** = 2.8%	**Oral =** 50%	**Inhalation =** 100%	
RVNAS[1] (AOEL)	0.12 mg/kg bw/day		RVAAS[2]	not defined yet, thus no acute exposure calculations are provided	
DFR	3 µg a.s./cm² per kg a.s./ha		DT50	30 days	

Resident - child	Spray drift (75th percentile) mg/kg bw/day	0.00029	% of RVNAS[1]	<1%
	Vapour (75th percentile) mg/kg bw/day	0.00107	% of RVNAS[1]	<1%
	Surface deposits (75th percentile) mg/kg bw/day	0.0000244	% of RVNAS[1]	<1%
	Entry into treated crops (75th percentile) mg/kg bw/day	0.000142	% of RVNAS[1]	<1%
	All pathways (mean) mg/kg bw/day	0.00136	% of RVNAS[1]	1.14%
Resident - adult	Spray drift (75th percentile) mg/kg bw/day	0.0000681	% of RVNAS[1]	<1%
	Vapour (75th percentile) mg/kg bw/day	0.00023	% of RVNAS[1]	<1%
	Surface deposits (75th percentile) mg/kg bw/day	0.00000572	% of RVNAS[1]	<1%
	Entry into treated crops (75th percentile) mg/kg bw/day	0.0000788	% of RVNAS[1]	<1%
	All pathways (mean) mg/kg bw/day	0.00033	% of RVNAS[1]	<1%

1 RVNAS = Reference Value Non Acutely toxic active Substance = AOEL
2 RVAAS = Reference Value Acutely toxic active Substance

A 3.3.1 Calculations for the active substance(s)

Please refer to A 3.

Appendix 4 Detailed evaluation of exposure and/or DFR studies relied upon (KCP 7.2, KCP 7.2.1.1, KCP 7.2.2.1, KCP 7.2.3.1)

No studies available.