Committee for Risk Assessment

RAC

Annex 1

Background document

to the Opinion proposing harmonised classification and labelling at EU level of

Foramsulfuron (ISO); 2-{[(4,6-dimethoxypyrimidin-2-yl)carbamoyl]sulfamoyl}-4-formamido-N,N-dimethylbenzamide; 1-(4,6-dimethoxypyrimidin-2-yl)-3-(2-dimethylcarbamoyl-5-formamidophenylsulfonyl)urea

EC Number: -
CAS Number: 173159-57-4

CLH-O-0000006964-62-01/F

The background document is a compilation of information considered relevant by the dossier submitter or by RAC for the proposed classification. It includes the proposal of the dossier submitter and the conclusion of RAC. It is based on the official CLH report submitted to public consultation. RAC has not changed the text of this CLH report but inserted text which is specifically marked as 'RAC evaluation'. Only the RAC text reflects the view of RAC.

Adopted

18 March 2021

CLH report

Proposal for Harmonised Classification and Labelling

Based on Regulation (EC) No 1272/2008 (CLP Regulation),
Annex VI, Part 2

International Chemical Identification:

foramsulfuron (ISO); 2-{[(4,6-dimethoxypyrimidin-2-yl)carbamoyl]sulfamoyl}-4-formamido-N,N-dimethylbenzamide; 1-(4,6-dimethoxypyrimidin-2-yl)-3-(2-dimethylcarbamoyl-5-formamidophenylsulfonyl)urea

EC Number:

CAS Number: **173159-57-4**

Index Number:

Contact details for dossier submitter: **Finnish competent authority**
Finnish Safety and Chemical Agency (Tukes), Finland

Version number: 2 **Date: 10.02.2020**

ANNEX 1 - BACKGROUND DOCUMENT TO RAC OPINION ON FORAMSULFURON (ISO); 2-{[(4,6-DIMETHOXYPYRIMIDIN-2-YL)CARBAMOYL]SULFAMOYL}-4-FORMAMIDO-N,N-DIMETHYLBENZAMIDE; 1-(4,6-DIMETHOXYPYRIMIDIN-2-YL)-3-(2-DIMETHYLCARBAMOYL-5-FORMAMIDOPHENYLSULFONYL)UREA

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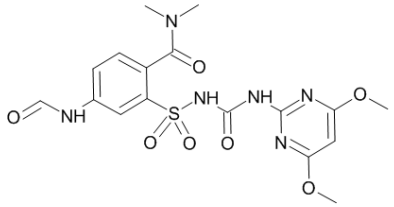
1 IDENTITY OF THE SUBSTANCE

1.1 Name and other identifiers of the substance

Table 1: Substance identity and information related to molecular and structural formula of the substance

Name(s) in the IUPAC nomenclature or other international chemical name(s)	1-(4,6-dimethoxypyrimidin-2-yl)-3-[2-(dimethylcarbamoyl)-5-formamidophenylsulfonyl]urea (IUPAC) 2-[[[[(4,6-dimethoxy-2-pyrimidinyl)amino]carbonyl]amino]sulfonyl]-4-(formylamino)-N,N-dimethylbenzamide (CA)
Other names (usual name, trade name, abbreviation)	Foramsulfuron Benzamide, 2-[[[[(4,6-dimethoxy-2-pyrimidinyl)amino]carbonyl]amino]sulfonyl]-4-(formylamino)-N,N-dimethyl-
ISO common name (if available and appropriate)	Foramsulfuron (ISO accepted)
EC number (if available and appropriate)	
EC name (if available and appropriate)	
CAS number (if available)	173159-57-4
Other identity code (if available)	CIPAC number: 659
Molecular formula	$C_{17}H_{20}N_6O_7S$
Structural formula	
SMILES notation (if available)	O=C(Nc1nc(cc(OC)n1)OC)NS(=O)(=O)c1cc(NC=O)ccc1C(=O)N(C)C
Molecular weight or molecular weight range	452.44 g/mol
Information on optical activity and typical ratio of (stereo) isomers (if applicable and appropriate)	
Description of the manufacturing process and identity of the source (for UVCB substances only)	
Degree of purity (%) (if relevant for the entry in Annex VI)	min. 97.3%

1.2 Composition of the substance

Table 2: Constituents (non-confidential information)

Constituent (Name and numerical identifier)	Concentration range (% w/w minimum and maximum in multi-constituent substances)	Current CLH in Annex VI Table 3.1 (CLP)	Current self-classification and labelling (CLP)
Foramsulfuron (CAS: 173159-57-4)	min. 97.3%	Currently not included in Annex VI	Aquatic Chronic 3, H412

Table 3: Impurities (non-confidential information) if relevant for the classification of the substance

Impurity (Name and numerical identifier)	Concentration range (% w/w minimum and maximum)	Current CLH in Annex VI Table 3.1 (CLP)	Current self-classification and labelling (CLP)	The impurity contributes to the classification and labelling
-	-	-	-	-

Table 4: Additives (non-confidential information) if relevant for the classification of the substance

Additive (Name and numerical identifier)	Function	Concentration range (% w/w minimum and maximum)	Current CLH in Annex VI Table 3.1 (CLP)	Current self-classification and labelling (CLP)	The additive contributes to the classification and labelling
-	-	-	-	-	-

Table 5: Test substances (non-confidential information) (this table is optional)

Identification of test substance	Purity	Impurities and additives (identity, %, classification if available)	Other information	The study(ies) in which the test substance is used
-	-	-	-	-

2 PROPOSED HARMONISED CLASSIFICATION AND LABELLING

2.1 Proposed harmonised classification and labelling according to the CLP criteria

Table 6:

	Index No	International Chemical Identification	EC No	CAS No	Classification		Labelling			Specific Conc. Limits, M-factors	Notes
					Hazard Class and Category Code(s)	Hazard statement Code(s)	Pictogram, Signal Word Code(s)	Hazard statement Code(s)	Suppl. Hazard statement Code(s)		
Current Annex VI entry	not yet listed in Annex VI										
Dossier submitters proposal		foramsulfuron (ISO); 2-{[(4,6-dimethoxypyrimidin-2-yl)carbamoyl]sulfamoyl}-4-formamido-N,N-dimethylbenzamide; 1-(4,6-dimethoxypyrimidin-2-yl)-3-(2-dimethylcarbamoyl-5-formamidophenylsulfonyl)urea	-	173159-57-4	Carc. 2 Aquatic Acute 1 Aquatic Chronic 1	H351 H400 H410	GHS08 GHS09 Wng	H351 H410		M=1000 M=100	
Resulting Annex VI entry if		foramsulfuron (ISO); 2-{[(4,6-dimethoxypyrimidi	-	173159-57-4	Carc. 2 Aquatic Acute 1 Aquatic Chronic 1	H351 H400	GHS08 GHS09Wng	H351 H410		M=1000	

agreed by RAC and COM		n-2-yl)carbamoyl]sulfamoyl}-4-formamido-N,N-dimethylbenzamide; 1-(4,6-dimethoxypyrimidin-2-yl)-3-(2-dimethylcarbamoyl-5-formamidophenylsulfonyl)urea				H410				M=100	

Table 7: Reason for not proposing harmonised classification and status under public consultation

Hazard class	Reason for no classification	Within the scope of public consultation
Explosives	data conclusive but not sufficient for classification	Yes
Flammable gases (including chemically unstable gases)	hazard class not applicable	No
Oxidising gases	hazard class not applicable	No
Gases under pressure	hazard class not applicable	No
Flammable liquids	hazard class not applicable	No
Flammable solids	data conclusive but not sufficient for classification	Yes
Self-reactive substances	data conclusive but not sufficient for classification	Yes
Pyrophoric liquids	hazard class not applicable	No
Pyrophoric solids	data conclusive but not sufficient for classification	Yes
Self-heating substances	data conclusive but not sufficient for classification	Yes
Substances which in contact with water emit flammable gases	data conclusive but not sufficient for classification	Yes
Oxidising liquids	hazard class not applicable	No
Oxidising solids	data lacking	Yes
Organic peroxides	hazard class not applicable	No
Corrosive to metals	data conclusive but not sufficient for classification	Yes
Acute toxicity via oral route	data conclusive but not sufficient for classification	Yes
Acute toxicity via dermal route	data conclusive but not sufficient for classification	Yes
Acute toxicity via inhalation route	data conclusive but not sufficient for classification	Yes
Skin corrosion/irritation	data conclusive but not sufficient for classification	Yes
Serious eye damage/eye irritation	data conclusive but not sufficient for classification	Yes
Respiratory sensitisation	data lacking	No
Skin sensitisation	data conclusive but not sufficient for classification	Yes
Germ cell mutagenicity	data conclusive but not sufficient for classification	Yes
Carcinogenicity	harmonised classification proposed	Yes
Reproductive toxicity	data conclusive but not sufficient for classification	Yes
Specific target organ toxicity-single exposure	data conclusive but not sufficient for classification	Yes
Specific target organ toxicity-repeated exposure	data conclusive but not sufficient for classification	Yes

Hazard class	Reason for no classification	Within the scope of public consultation
Aspiration hazard	data conclusive but not sufficient for classification	Yes
Hazardous to the aquatic environment	harmonised classification proposed	Yes
Hazardous to the ozone layer	data conclusive but not sufficient for classification	Yes

3 HISTORY OF THE PREVIOUS CLASSIFICATION AND LABELLING

For foramsulfuron there is no harmonized classification available, as the substance is not listed in Annex VI of Regulation (EC) No 1272/2008 (CLP regulation).

RAC general comment
Foramsulfuron is a sulfonylurea herbicide. There is no existing entry in Annex VI of CLP regulation.

4 JUSTIFICATION THAT ACTION IS NEEDED AT COMMUNITY LEVEL

[A.] There is no requirement for justification that action is needed at Community level as foramsulfuron in an active substance in plant protection products.

5 IDENTIFIED USES

Foramsulfuron is a sulfonyl-urea herbicide mainly used in corn and sugarbeet. Foramsulfuron, when applied post emergence, is effective in controlling most annual and perennial grasses occurring in corn and sugarbeet, such as *Echinocloa crus-galli; Poa annua, Lolium spp. Agropyron repens* and others. It also controls a broad spectrum of broad-leaved weeds including *Ambrosia spp, Solanum nigrum, Stellaria media* and many other weeds of agricultural significance. Foramsulfuron is an inhibitor of acetolactate synthase.

6 DATA SOURCES

The Renewal Assessment Report (2016) of foramsulfuron under Regulation (EC) 1107/2009 was used as the main data source for the CLH report of foramsulfuron. In addition, full study reports which have been submitted for renewal under 1107/2009 and open literature publications have been used.

7 PHYSICOCHEMICAL PROPERTIES

Table 8: Summary of physicochemical properties

Property	Value	Reference	Comment (e.g. measured or estimated)
Physical state at 20°C and 101,3 kPa	Solid Active substance, pure: Powder with agglomerates Active substance as manufactured: white powder	KCA 2.3 /07; 2013;	observed
Melting/freezing point	The melting point was found to be 194 °C (coupled with decomposition).	KCA 2.1 /01; 2000;	measured
Boiling point	Not measurable, decomposition above 190 °C.	KCA 2.1 /01; 2000;	measured
Relative density	D = 1.44 at 25.5 °C	KCA 2.14 /01; 2000;	measured
Vapour pressure	4.2 x 10^{-11} Pa for 20 °C 1.3 x 10^{-10} Pa for 25 °C	KCA 2.2 /01; 1997;	measured
Surface tension	σ = 65.1 mN/m at 20 °C	KCA 2.12 /01; 2000;	measured
Water solubility	pH 4.90 37.2 mg/L at 20°C pH 6.91 3293 mg/L at 20°C pH 8.05 94577 mg/L at 20°C	KCA 2.5 /01; 1997;	measured
Partition coefficient n-octanol/water	Unbuffered distilled water (pH 5.42-5.71) (20 °C): Pow log Pow 4.01 0.60 Buffered water (20 °C): Pow log Pow pH 2 27.5 1.44 pH 7 0.166 -0.78 pH 9 0.0106 -1.97	KCA 2.7 /01; 1997;	measured
Flash point	Not applicable. The active substance is a solid; its melting point is > 40 °C.		
Flammability	Not highly flammable in the sense of EC Guideline A.10.	KCA 2.9 /03; 2013;	measured

Property	**Value**	**Reference**	**Comment (e.g. measured or estimated)**
Explosive properties	Not explosive in the sense of EC guideline A.14.	KCA 2.11 /03; 2013;	measured
Self-ignition temperature	No self-ignition temperature was observed until the maximum temperature of 400 °C.	KCA 2.9 /04; 2013;	measured
Oxidising properties	No oxidizing properties in the sense of EC guideline A.17.	KCA 2.13 /02; 2013;	measured
Granulometry	% size mm 5.05 > 1.190 76.49 1.190 - 0.500 14.27 0.500 - 0.250 3.59 0.250-0.106 0.50 0.106-0.053 0.26 < 0.053	2001;	measured, local Brazilian study
Solubility in organic solvents and identity of relevant degradation products	[g/L at 20 °C] acetone 1.925 acetonitrile 1.111 1,2-dichloroethane 0.185 ethyl acetate 0.362 heptane < 0.010 methanol 1.660 p-xylene <0.010	KCA 2.6 /01; 1997;	measured
Dissociation constant	at 21.5 °C: pKa = 4.60	KCA 2.8 /01; 1997;	measured
Viscosity	Not applicable. The active substance is a solid; its melting point is > 40 °C.		
Spectra (UV/VIS, IR, NMR, MS), molar extinction at relevant wavelengths, optical purity	UV (methanol, neutral) Wavelength molar extinction [nm] [L x mol-1 x cm-1] 202 42363 219 31939 252 33298 291 3245 methanol / NaOH (90/10)(v/v) [NaOH] = 0.1 mol/L 250 38732 291 3747	KCA 2.4 /02; 2000;	measured

8 EVALUATION OF PHYSICAL HAZARDS

8.1 Explosives

Table 9: Summary table of studies on explosive properties

Method	Results	Remarks	Reference
OECD 113 (1981) Differential scanning calorimetry (DSC)	Not explosive	-	KCA 2.11 /03;

8.1.1 Short summary and overall relevance of the information provided on explosive properties

The screening measurements done with DSC (OECD 113) showed a maximum heat of decomposition energy of 397 J/g.

8.1.2 Comparison with the CLP criteria

There are no chemical groups associated with explosive properties present in the molecule according to the given examples of groups in Table A6.1 in Appendix 6 of the UN RTDG, Manual of Tests and Criteria. Additionally, the exothermic decomposition energy is below 500 J/g. The substance does not meet the criteria for classification for this hazard class.

8.1.3 Conclusion on classification and labelling for explosive properties

Data conclusive but not sufficient for classification.

8.2 Flammable gases (including chemically unstable gases)

Table 10: Summary table of studies on flammable gases (including chemically unstable gases)

Method	Results	Remarks	Reference
not applicable	-	-	-

Short summary and overall relevance of the provided information on flammable gases (including chemically unstable gases)

Hazard class not applicable: The substance is a solid.

8.2.1 Comparison with the CLP criteria

Hazard class not applicable: The substance is a solid.

8.2.2 Conclusion on classification and labelling for flammable gases

Hazard class not applicable.

8.3 Oxidising gases

Table 11: Summary table of studies on oxidising gases

Method	Results	Remarks	Reference
not applicable	-	-	-

8.3.1 Short summary and overall relevance of the provided information on oxidising gases

Hazard class not applicable: The substance is a solid.

8.3.2 Comparison with the CLP criteria

Hazard class not applicable: The substance is a solid.

8.3.3 Conclusion on classification and labelling for oxidising gases

Hazard class not applicable.

8.4 Gases under pressure

Table 12: Summary table of studies on gases under pressure

Method	Results	Remarks	Reference
not applicable	-	-	-

8.4.1 Short summary and overall relevance of the provided information on gases under pressure

Hazard class not applicable: The substance is a solid.

8.4.2 Comparison with the CLP criteria

Hazard class not applicable: The substance is a solid.

8.4.3 Conclusion on classification and labelling for gases under pressure

Hazard class not applicable.

8.5 Flammable liquids

Table 13: Summary table of studies on flammable liquids

Method	Results	Remarks	Reference
not applicable	-	-	-

8.5.1 Short summary and overall relevance of the provided information on flammable liquids

Hazard class not applicable: The substance is a solid.

8.5.2 Comparison with the CLP criteria

Hazard class not applicable: The substance is a solid.

8.5.3 Conclusion on classification and labelling for flammable liquids

Hazard class not applicable.

8.6 Flammable solids

Table 14: Summary table of studies on flammable solids

Method	Results	Remarks	Reference
EC A.10	Not a highly flammable solid	-	KCA 2.9 /03; 2013;

8.6.1 Short summary and overall relevance of the provided information on flammable solids

One study has been performed according to the (EC) No 440/2008 A.10 guideline. The preliminary sreening test described in the EC A.10 differs from the screening test described in Part III, sub-section 33.2.1.4.3.1, of the UN RTDG, Manual of Tests and Criteria, by the longer test period.

The test item melted when ignited and burning was observed above the molten test item. The test item extinguished shortly after the ignition flame was removed. The burning extinguished during the initial burning phase and as a consequence the main test had not to be performed.

8.6.2 Comparison with the CLP criteria

The substance ignites but does not propagate combustion either by burning with flame or smouldering along 200 mm of the powder train wthin the 2 minute test period. The substance should not be classified as a flammable solid and no further testing is required accorging to the screening test described in Part III, sub-section 33.2.1.4.3.1, of the UN RTDG, Manual of Tests and Criteria. The substance does not meet the criteria for classification for this hazard class.

8.6.3 Conclusion on classification and labelling for flammable solids

Data conclusive but not sufficient for classification.

8.7 Self-reactive substances

Table 15: Summary table of studies on self-reactivity

Method	Results	Remarks	Reference
UN H.4	Not a self-reactive substance	-	2019;

8.7.1 Short summary and overall relevance of the provided information on self-reactive substances

Based on a DSC measurement the test method H.4 “Heat accumulation storage test” decribed in the UN RTDG, Manual of Tests and Criteria, has been performed as the heat release was > 300 J/g and the exothermic onset was below 200 °C.

The heat loss of the used Dewar-vessel was 36.0 mW/kg·K and the test volume 400 ml. The oven temperature was raised to 81 °C. The sample temperature was monitored for 10 days. The sample temperature did not rise above the test chamber temperature. There was no sign of self-reactive behaviour. The SADT for a 50 kg package is greater than 81 °C.

8.7.2 Comparison with the CLP criteria

The SADT for a 50 kg package is greater than 75 °C. The substance does not meet the criteria for classification for this hazard class.

8.7.3 Conclusion on classification and labelling for self-reactive substances

Data conclusive but not sufficient for classification.

8.8 Pyrophoric liquids

Table 16: Summary table of studies on pyrophoric liquids

Method	Results	Remarks	Reference
not applicable	-	-	-

8.8.1 Short summary and overall relevance of the provided information on pyrophoric liquids

Hazard class not applicable: The substance is a solid.

8.8.2 Comparison with the CLP criteria

Hazard class not applicable: The substance is a solid.

8.8.3 Conclusion on classification and labelling for pyrophoric liquids

Hazard class not applicable.

8.9 Pyrophoric solids

Table 17: Summary table of studies on pyrophoric solids

Method	Results	Remarks	Reference
Data waived	Not a pyrophoric solid	-	-

8.9.1 Short summary and overall relevance of the provided information on pyrophoric solids

Based on experience in manufacture and handling the substance does not ignite spontaneously on coming into contact with air at normal temperatures. Thus, the study does not need to be conducted according to CLP Annex I, 2.10.4.

8.9.2 Comparison with the CLP criteria

Experience in manufacture and handling shows that the substance does not ignite spontaneously on coming into contact with air at normal temperatures. The substance does not meet the criteria for classification for this hazard class.

8.9.3 Conclusion on classification and labelling for pyrophoric solids

Data conclusive but not sufficient for classification.

8.10 Self-heating substances

Table 18: Summary table of studies on self-heating substances

Method	Results	Remarks	Reference
UN N.4	Not a self-heating substance	-	2019;

8.10.1 Short summary and overall relevance of the provided information on self-heating substances

One study has been performed to assess the self-heating properties of Foramsulfuron. The test followed the method UN N.4 “Test method for self-heating substances” decribed in the UN RTDG, Manual of Tests and Criteria.

The oven temperature was raised to the prescribed 140 °C and kept it for at least 24 hours. The sample temperature followed the oven temperature and there was no sign of self-ignition.

8.10.2 Comparison with the CLP criteria

The sample temperature did not exceed the oven temperature by 60 K and spontaneous ignition did not occur. The substance does not meet the criteria for classification for this hazard class.

8.10.3 Conclusion on classification and labelling for self-heating substances

Data conclusive but not sufficient for classification.

8.11 Substances which in contact with water emit flammable gases

Table 19: Summary table of studies on substances which in contact with water emit flammable gases

Method	Results	Remarks	Reference
Data waived	-	-	-

8.11.1 Short summary and overall relevance of the provided information on substances which in contact with water emit flammable gases

Based on the chemical structure of the substance and the experience in manufacture and handling the substance does not react with water. Thus, a study does not need to be conducted according to CLP Annex I, 2.12.4.1.

8.11.2 Comparison with the CLP criteria

The chemical structure of the substance does not contain metals or metalloids. Also experience in production and handling shows that the substance does not react with water. The substance does not meet the criteria for classification for this hazard class.

8.11.3 Conclusion on classification and labelling for substances which in contact with water emit flammable gases

Data conclusive but not sufficient for classification.

8.12 Oxidising liquids

Table 20: Summary table of studies on oxidising liquids

Method	Results	Remarks	Reference
not applicable	-	-	-

8.12.1 Short summary and overall relevance of the provided information on oxidising liquids

Hazard class not applicable: The substance is a solid.

8.12.2 Comparison with the CLP criteria

Hazard class not applicable: The substance is a solid.

8.12.3 Conclusion on classification and labelling for oxidising liquids

Hazard class not applicable.

8.13 Oxidising solids

Table 21: Summary table of studies on oxidising solids

Method	Results	Remarks	Reference
EC A.17	No oxidizing properties according to EC A.17	-	KCA 2.13 /02; 2013;

8.13.1 Short summary and overall relevance of the provided information on oxidising solids

In the standardized main test as described in the (EC) No 440/2008, A.17 (cellulose as combustible material; barium nitrate as reference), the substance burned slower compared to the reference mixture and thus it is concluded that the test item has no oxidizing properties according to EC A.17.

8.13.2 Comparison with the CLP criteria

The test was performed according to EC A.17 which is not in line with CLP criteria. The substance contains oxygen chemically bonded to other than carbon or hydrogen and therefore the waiving criteria in section 2.13.4.1 of CLP Annex I are not met.

8.13.3 Conclusion on classification and labelling for oxidising solids

No classification due to lack of data.

8.14 Organic peroxides

Table 22: Summary table of studies on organic peroxides

Method	Results	Remarks	Reference
not applicable	-	-	-

8.14.1 Short summary and overall relevance of the provided information on organic peroxides

Hazard class not applicable: The substance is not a peroxide.

8.14.2 Comparison with the CLP criteria

Hazard class not applicable: The substance is not a peroxide.

8.14.3 Conclusion on classification and labelling for organic peroxides

Hazard class not applicable.

8.15 Corrosive to metals

Table 23: Summary table of studies on the hazard class corrosive to metals

Method	Results	Remarks	Reference
Expert opinion	Not metal-corrosive in the sense of UN RTDG, Manual of Tests and Criteria	-	2019;

8.15.1 Short summary and overall relevance of the provided information on the hazard class corrosive to metals

The standardized test UN C.1 described in the UN RTDG, Manual of Tests and Criteria, applies to substances that are liquid. Foramsulfuron is a solid that shows a melting point clearly above the test conditions and thus it cannot be liquid during performing the UN C.1. As a consequence the test cannot be performed.

The chemical structure contains no elements which are known to have corrosive properties to metal.

Foramsulfuron has no metal-corrosive properties in the sense of UN RTDG, Manual of Tests and Criteria, provided it is not hygroscopic.

8.15.2 Comparison with the CLP criteria

The substance is a solid having a melting point higher than 55 °C (which is the test temperature required in UN Test C.1). The substance does not meet the criteria for classification for this hazard class.

8.15.3 Conclusion on classification and labelling for corrosive to metals

Data conclusive but not sufficient for classification.

RAC evaluation of physical hazards

Summary of the Dossier Submitter's proposal

The active substance foramsulfuron is manufactured as a white solid (powder). Therefore, physico-chemical hazards related to gases and liquids were considered not applicable to foramsulfuron.

Explosives

Based on a screening measurement done with differential scanning calorimetry (OECD TG 113), the maximum heat of exothermic decomposition energy was 397 J/g, which is below 500 J/g proposed in CLP. Moreover, the Dossier Submitter (DS) pointed out that the molecule did not contain chemical groups that were associated with explosive properties based on the examples of such groups given in Table A6.1 in Appendix 6 of the UNRTDG, Manual of Tests and Criteria. Therefore, no classification was proposed by the DS.

Flammable solids

One study on flammability (EC No. 440/2008 A.10 guideline) showed that foramsulfuron is not a highly flammable solid. The substance ignites but does not propagate combustion either by burning with flame or smouldering along 200 mm of the powder train within the 2-minute test period. Thus, no further test was considered necessary according to the screening test described in Part III, sub-section 33.2.1.4.3.1, of the UNRTDG, Manual of Tests and Criteria. No classification was proposed by the DS.

Self-reactive substances

Based on a heat accumulation storage test (UN H.4), the substance was not considered as a self-reactive substance. Heat release was > 300 J/g and the exothermic onset was below 200 °C. The Self-Accelerating Decomposition Temperature (SADT) for a 50 kg package was greater than 75 °C. No classification was proposed by the DS.

Pyrophosphoric solids

Based on the experience in manufacturing and handling of the substance, foramsulfuron does not ignite spontaneously when coming into contact with air at normal temperatures. Thus, the study does not need to be conducted according to CLP Annex I, 2.10.4 and no classification was proposed by the DS.

Self-heating substances

Based on the test method UN N.4 "test method for self-heating substances", described in the UN RTDG, the oven temperature was raised to 140°C and kept there at least for 24h. The sample temperature followed the oven temperature and there were no signs of self-ignition. The sample temperature did not exceed the oven temperature by 60 K and spontaneous ignition did not occur. On this basis, no classification was proposed by the DS.

Substances which in contact with water emit flammable gases

No data were available. As the substance does not contain metals or metalloids and, based on the experience in manufacturing and handling showing that the substance does not react with water, no classification was proposed by the DS.

Oxidising solids

In a test performed as described in the (EC) No 440/2008, A.17 (cellulose as combustible material; barium nitrate as reference), the substance burned slower compared to the reference mixture. Although the test item had no oxidizing properties according to EC A.17., this test was considered by the DS to not be in line with the CLP criteria. Therefore, no acceptable study was submitted to evaluate the oxidising properties of solid foramsulfuron. The substance contains oxygen chemically bonded to other than carbon or hydrogen. A test should have been available as the waiving criteria in section 2.13.4.1 of CLP Annex I are not met. As a conclusion, the DS proposed no classification due to lack of data.

Corrosive to metals

No study was available to evaluate the corrosivity to metals of foramsulfuron. As foramsulfuron is a solid and has a melting point higher than 55 °C, the substance does not meet the criteria for classification for this hazard class, according to the DS. Moreover, the DS highlighted that the chemical structure contains no elements which are known to have corrosive properties to metals and it is not hygroscopic.

Comments received during consultation

One industry representative supported the DS's proposal.

Assessment and comparison with the classification criteria

RAC concludes that **with one exception (see below), the reported physico-chemical properties of foramsulfuron do not warrant classification** using the criteria set out in the CLP Regulation.

For oxidising solids, RAC agrees that no classification is warranted based on lack of data.

9 TOXICOKINETICS (ABSORPTION, METABOLISM, DISTRIBUTION AND ELIMINATION)

Table 24: Summary table of toxicokinetic studies

Method	Results	Remarks	Reference
OECD TG 417, 1984 GLP Preliminary toxicokinetic study:	Rapid absorption and elimination following the administration of 10 and	Deviations: Animal group sizes were smaller than required in OECD	KCA 5.1.1/01, 1999

Method	Results	Remarks	Reference
2 rats of each sex were dosed orally by gavage with [^{14}C-phenyl]- or [^{14}Cpyrimidyl]- radiolabelled at 10 mg/kg bw. A further animal of each sex was dosed with phenyl-labelled foramsulfuron at 1000 mg/kg bw. An additional animal of each sex was dosed with either 10 or 1000 mg phenyl-labelled foramsulfuron/ kg bw and the blood pharmacokinetic parameters at each dose level were examined. Samples were taken at 0.5, 1, 2, 4, 6, 8, 12, 16, 20, 24, 30, 48, and 72 hours. After examining the results of this study, further animals were dosed at 10 or 1000 mg/kg bw and sacrificed at 1 hour after dosing, when the blood levels of radioactivity were expected to be at a maximum.	1000 mg/kg bw in both sexes. At both dose levels the maximum blood concentration (Cmax) occurred at approx. 1 hour after dosing. The majority of radioactivity was excreted within 24 hours at 10 mg/kg bw (94.6% and 70.1% for rats dosed with pyrimidyl- or phenyl-labelled foramsulfuron, respectively). At the higher dose of 1000 mg/kg bw, excretion of the majority of the dose (92.7%) was found in the 0-48 hour excreta. The major route of excretion was via the faeces (87%) of the dose at 10 mg/kg bw (approx. 10% in urine), and approx. 92% from rats dosed at 1000 mg/kg bw (4% in urine). The concentration of radioactive residues in the tissues at necropsy was low, the only tissue to contain radioactive residues above the limit of detection was the liver of rats dosed with pyrimidyl-labelled foramsulfuron (mean of 0.038 μg eq./g tissue).	TG 417	
OECD TG 417, 1984 GLP <u>Absorption, distribution, elimination</u> following oral dosing at 10 and 1000 mg/kg bw: Five male and five female rats were dosed orally by gavage with [14C-phenyl]-radiolabelled as a single oral gavage dose of 10 or 1000 mg/kg	Foramsulfuron was poorly absorbed with mean values of 5.7% of the dose in the urine of male and female rats at the low dose within 72 h, and 1.5% at the high dose. In the faeces, approx. 90% and 96% of the radiolabel were recovered 72 h after the low and high dose, respectively. Elimination was rapid,		KCA 5.1.1/02, 1999

Method	Results	Remarks	Reference
bw. Urine and faeces were collected for 0 to 72 hours after the final dose.	with a mean of 91.5% of the dose being found in the 0 to 24-hour excreta at both dose levels.		
OECD TG 417, 1984 GLP Absorption and excretion following oral administration to bile duct cannulated rats: Four male rats were dosed orally by gavage with [U-14C-phenyl]-foramsulfuron at 10 mg/kg bw. All animals were fasted overnight prior to dosing. Bile, urine, faeces, cage washings and debris were sampled over a 48-hour time course.	Foramsulfuron was poorly absorbed with a mean of 75.6% of the dose in the faeces. Biliary excretion was not a major route of elimination with about 25% of the absorbed dose, while the largest portion of the absorbed dose was excreted via the urine.		1998 Amended: 2000-03-01 KCA 5.1.1 /03;
OECD TG 417, 1984 GLP Tissue distribution and clearance: Male and female rats were dosed orally with [14C-phenyl]-foramsulfuron at 10 or 1000 mg/kg bw. For each dose group, 3 animals/sex were sacrificed at 0.5, 1, 4, 12 and 30 hours after dose administration. At necropsy, whole blood, major organs and samples of selected tissues were taken and analysed for radioactivity.	Foramsulfuron was well distributed throughout the tissues after 10 or 1000 mg/kg bw, but was rapidly cleared from the tissues with an elimination half-life in the plasma of 5.4–18.5 hours at the low dose and of 2.4–2.9 hours at the high dose. The maximum tissue concentrations were observed at 1–4 hours at the low dose and 4–12 hours at the high dose. At the high dose level, relatively high tissue levels of radioactivity were determined in the eyes, adrenals, thyroid and female gonads.		KCA 5.1.1 /04, 1999
OECD TG 417, 1984 GLP Metabolism Rats (4/sex) were given a single oral	Foramsulfuron was shown to undergo limited metabolism		KCA 5.1.1 /05, 1999

Method	Results	Remarks	Reference
dose of 10 or 1000 mg/kg bw [14Cphenyl]- foramsulfuron. A second group of 2 rats/sex received 10 mg/kg bw [^{14}C-pyrimidyl]-radiolabelled foramsulfuron. Urine and faeces were collected for 24 or 72 hours after the final dose.	there were minor qualitative differences seen in the metabolism of foramsulfuron depending on the position of the radiolabel. In rats administered the phenyl-label at the 10 mg/kg dose level, the principal metabolite besides parent to be recovered in the faeces with 8.4-8.7% AD was N,N-dimethyl-2-sulfamoyl-4-formylamino¬benzamide (= AE F153745), formed by the cleavage of foramsulfuron's sulfonylurea bridge. The remainder of the metabolites for both labels were polar compounds, no single component of which exceeded 0.2%. The major metabolites in urine were AE F153745 (2.3% AD; phenyl-label only) and N,N-dimethyl-2-[3-(4,6-dimethoxypyrimidin-2-yl)-ureidosulfonyl]-4-amino-benzamide (= AE F130619, 0.8-2.6% AD) formed by cleavage of the formyl group. The remainder of the metabolites (approx. 9% in the case of pyrimidyl-labelled foramsulfuron) was comprised of unidentified polar components, each of which was present at less than 4% of the dose.		
OECD TG 417, 1984 GLP Absorption, distribution and elimination – repeat oral dose (10 mg/kg bw): Groups of 3 male and 3 female rats were given 10 mg [14C-phenyl]-radiolabelled foramsulfuron/kg bw	The route and rate of excretion after 14 daily doses of foramsulfuron was found to be similar to that seen following a single oral dose. The concentrations of radioactivity in tissues are shown in Table 26. Tissue levels 24h after a single dose were generally very low, with the liver	Deviations of the guideline: Only low-dose (10mg/kg bw) groups included. Dose of 1000 mg/kg bw, recommended in the test guideline for substances of low toxicity was not included in the study.	KCA 5.1.1 /06, 1999

Method	Results	Remarks	Reference
for up to 14 days. Groups were killed 24 hours after 1, 9 or 14 daily doses. Samples of adrenals, blood, bone, brain, eyes, heart, kidneys, liver, lungs, muscle, ovaries, plasma, renal fat, skin, spleen, testes, thyroid and carcass (inclusive of the gastrointestinal tract) were removed and analysed on the level of radioactive residues. A further group of 3 rats/sex were fasted overnight before receiving the final 14th dose (the other groups were not fasted) and transferred to individual allglass metabolism cages after final dosing. Urine and faeces of these animals were collected over the next 48 h.	(both sexes) and the kidney (females only) to show clearly higher concentrations than in plasma. For most of the tissues, repeated-dose treatment over 14 days resulted in increased residue levels. These increases did not exceed 3-fold with the exception of the following male tissues: brain (20x increase), testes (15x), thyroid (10x), and heart (6.5x). Only residue concentrations in liver (both sexes) and testes were clearly higher than in plasma. At 48 h after administration of the 14th dose, the only tissue to show clearly higher levels than those determined in plasma was the liver.		
[Pyrimidine-2-^{14}C]Foramsulfuron: <u>Metabolic Stability and Profiling in Liver Microsomes from Rats and Humans for Inter-Species Comparison:</u> The comparative metabolism of [pyrimidine-2-^{14}C]-foramsulfuron was investigated in animal in-vitro systems by incubating the test item separately with liver microsomes from male Wistar rats (pool of 200 individuals) and humans (pool of 50 donors from both genders) in the presence of NADPH cofactor at 37 ± 1°C.	14C-Foramsulfuron was found to be stable after incubation with rat and human liver microsomes. No detectable metabolites were found after the 1 hour incubation period. The results suggest that phase I metabolism is not involved in the biotransformation of foramsulfuron in rat and human liver microsomes.	Non-guideline study. In vitro metabolism study is a data requirement according to the Commission Regulation (EU) No. 283/2013.	KCA 5.1.2 /01, 2013

The absorption, distribution, metabolism and excretion, including plasma and blood pharmacokinetics of foramsulfuron has been investigated in the Sprague-Dawley rat following a nominal single oral gavage dose of 10 or 1000 mg/kg bw and following 14 daily oral doses of 10 mg/kg bw. There were no significant differences in the excretion profile of the phenyl- or pyrimidyl-labelled foramsulfuron and a very low level of metabolism of the compound. In view of these results [14C-phenyl]- foramsulfuron was used for the majority of the studies, although [14C-pyrimidyl]-foramsulfuron was also dosed as part of the determination of the metabolism.

Absorption

Following oral administration of foramsulfuron at a single dose of 10 mg/kg bw in bile-duct cannulated rats, 12.7% of the radiolabel was recovered in urine, 4.2% in bile and 2.3% in the cage wash within 48 h. Furthermore, 1.5% of the administered radiolabelled dose was detected in the residual carcass, which included the gastrointestinal tract and tissues. On this basis, the fraction of the administered radiolabel (10 mg/kg bw) absorbed within 48 h from the gastrointestinal tract is approximately 20%.

Distribution

Radioactivity was distributed into almost all tissues within 30 min after administration of a single dose of radiolabelled foramsulfuron. At 30 hours after administration of the low dose (10 mg/kg bw), highest residue levels were detected in liver and kidney; by 72 h, levels of all tissues were near or below the limit of detection. At the high-dose level (1000 mg/kg bw) comparibly high concentrations were determined at the 30-h timepoint in the thyroid (69–79 µg eq./g), adrenals (36–61 µg eq./g), female gonads (13 µg eq./g), eyes (~7.4 µg eq./g) and liver (3.8–6.8 µg eq./g), while the residue levels in the other tissues were below the limit of detection. All tissue residue levels were below 0.5 mg eq./g tissue at the 72-h timepoint with the exception of the spleen, heart and renal fat in males (0.7–1.6 mg eq./g) and liver and spleen of females (0.5 mg eq./g).

The maximum tissue concentrations were observed at 1– 4 hours at the low dose and 4–12 hours at the high dose. A summary of the pharmacokinetic parameters for plasma, of the mean tissue concentrations is Table 25.

Table 25: Toxicokinetic parameters of foramsulfuron after single oral administration to rats

Toxicokinetic parameters	**10 mg/kg bw**		**1000 mg/kg bw**	
	Male	**Female**	**Male**	**Female**
Plasma C_{max} (µg/g)	0.903	0.691	11.57	14.81
Plasma T_{max} (h)	0.5	1.0	4.0	4.0
$t_{½}$ elim (h)	18.46	5.437	2.407	2.865
Range (h)	12–30	4–30	4–12	4–12
AUC_{0-t} (µg.h/g)	5.028	4.305	84.66	101.6
$AUC_{0-\alpha}$ (µg.h/g)	5.800	4.384	88.68	110.4

Potential for accumulation

Upon repeated administration of radiolbelled foramsulfuron at 10mg/kg bw/d, increases of residue concentration levels resulted in most tissues over the 14-d treatment period. These increases did not exceed 3-fold with the exception of the following male tissues: brain (20x increase), testes (15x), thyroid (10x), and heart (6.5x). The level of the radioactive residues in the tissues throughout the study was

generally below 0.1 µg equivalent/g. The liver was the only tissue exhibiting clearly increased radiolabel concentrations compared to plasma at both timepoints of investigation (24 and 48 h). This finding is considered to reflect redistribution of the radiolabel prior to biliary/renal excretion and should not be interpretated as an indication of an accumulation potential of foramsulfuron A shortcoming of the study is that high dose, 1000 mg/kg, recommended in the guideline, was not used.

Elimination

Foramsulfuron was rapidly eliminated from the body following absorption. The elimination half-life in the plasma was 5.4–18.5 h at the low dose and 2.4–2.8 h at the high dose level. A mean of 96% of the dose was present in the 0-48 hour excreta at both dose levels. Faecal excretion predominated with only 5.6% of the low dose and 1.4% of the high dose being found in the urine. There was no significant sex difference in the route of excretion and no excretion of radiolabelled carbon dioxide, demonstrating the stability of the position of the radiolabel. Repeat dosing at 10 mg/kg bw/day for 14 days had no significant effect on the excretion profile.

Table 26 Concentrations of radioactive residues in rat tissues 72 h following single oral administration

Tissue	**Concentration of radioactive residues (as µg eq./g tissue)**							
	Dose of 10 mg/kg bw				**Dose of 1000 mg/kg bw**			
	Males		**Females**		**Males**		**Females**	
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
Adrenal	0.001	0.001	0.001	0.000	0.309	0.112	0.196	0.047
Blood	0.001	0.000	BLQ		0.101	0.020	0.097	0.030
Bone	BLQ		BLQ	-	0.130	0.027	0.146	0.070
Brain	BLQ		BLQ		0.152	0.048	0.131	0.025
Carcass	BLQ		BLQ		0.032	0.038	0.094	0.110
Eyes	0.001	0.000	0.001	0.001	0.005	0.010	BLQ	
Heart	BLQ		BLQ		0.813	0.406	0.459	0.058
Kidney	BLQ		BLQ		0.006	0.013	0.007	0.014
Liver	0.002	0.000	0.002	0.000	0.480	0.117	0.510	0.161
Lung	BLQ		BLQ		0.004	0.008	0.005	0.010
Muscle	0.003	0.001	0.002	0.000	0.182	0.016	0.180	0.037
Ovaries			0.001	0.000			0.264	0.185
Plasma	BLQ		BLQ		0.036	0.029	0.018	0.028
Renal fat	0.001	0.001	0.001	0.000	0.653	0.237	0.485	0.218
Skin	0.001	0.000	BLQ		0.104	0.114	0.116	0.064
Spleen	BLQ		BLQ		1.608	0.859	0.551	0.258
Testes	BLQ				0.293	0.110		
Thyroid	BLQ		BLQ		BLQ		BLQ	

BLQ = Below the Limit of Quantification.
SD = Standard Deviation

After 74 h, the dose level 1000 mg/kg of mean concentrations of radioactive residues were generally very low with the exception of the spleen, heart and renal fat in males (0.653-1.608 µg eq./g) and liver and spleen of females (0.510-0.551 µg eq./g).

Table 27 Concentration of radioactivity in tissues and body fluids of rats after repeated oral administration (10 mg/d for 14 d) of foramsulfuron

Tissue	Concentration in male rats (µg eq./g tissue)				Concentration in female rats (µg eq./g tissue)			
	24 h after receiving			48 h after receiving	24 h after receiving			48 h after receiving
	1 dose	9 doses	14 doses	14 doses	1 dose	9 doses	14 doses	14 doses
Adrenal	0.001	0.001	0.003	0.010	0.002	0.004	0.003	0.002
Blood	0.012	0.009	0.012	0.087	0.012	0.011	0.014	0.010
Bone	0.009	0.013	0.012	0.031	0.009	0.033	0.019	0.014
Brain	0.001	0.000	0.020	0.003	0.003	0.001	0.008	0.001
Eyes	0.002	0.002	0.003	0.007	0.002	0.003	0.005	0.001
Heart	0.002	0.000	0.013	0.035	0.004	0.002	0.019	0.008
Kidney	0.021	0.017	0.027	0.120	0.048	0.022	0.026	0.020
Liver	0.079	0.182	0.222	1.232	0.114	0.184	0.280	0.187
Lung	0.008	0.004	0.019	0.046	0.006	0.006	0.022	0.051
Muscle	0.018	0.006	0.008	0.026	0.011	0.015	0.014	0.004
Ovaries	-		-	-	0.003	0.005	0.003	0.003
Plasma	0.017	0.014	0.019	0.147	0.015	0.016	0.021	0.015
Renal fat	0.004	0.003	0.012	0.020	0.019	0.008	0.013	0.006
Skin*	0.022	0.014	0.042	0.046	0.026	0.043	0.166	0.025
Spleen	0.004	0.008	0.009	0.025	0.005	0.006	0.016	0.013
Testes	0.005	0.005	0.073	0.021	-		-	-
Thyroid	0.002	0.004	0.020	0.033	0.001	0.005	0.002	0.022

* These results may be affected by contamination from urine during housing.

Table 28 Concentrations of foramsulfuron residues in the tissues of male rats following 14 daily oral doses.

Tissue	Conc. 24 hours after a single dose (C14 µg/g)	Conc. 24 hours after 14 doses residue conc. (C14 µg/g)	Ratio C14/C14 single
Adrenal	0.001	0.003	3.00
Blood	0.012	0.012	1.00
Bone	0.009	0.012	1.33
Brain	0.001	0.020	20.00
Eyes	0,002	0,003	1.50
Heart	0.002	0.013	6.50
Kidney	0.021	0.027	1.29
Lungs	0.008	0.019	2.38

Muscle	0.018	0.008	0.44
Plasma	0.017	0.019	1.12
Renal fat	0.004	0.012	3.00
Skin *	0.022	0.042	1.91
Spleen	0.004	0.009	2.25
Testes	0.005	0.073	14.60
Thyroid	0.002	0.020	10.00

*These results may be affected by contamination from urine during housing

Table 29 Concentration of foramsulfuron residues in the tissues of female rats following 14 daily oral doses.

Tissue	**Conc. 24 hours after a single dose (C14 µg/g)**	**Conc. 24 hours after 14 doses residue conc. (C14 µg/g)**	**Ratio C14/C14 single**
Adrenal	0.002	0.003	1.50
Blood	0.012	0.014	1.167
Bone	0.009	0.019	2.11
Brain	0.003	0.008	2.667
Eyes	0.002	0.005	2.500
Heart	0.004	0.019	4.75
Kidney	0.048	0.026	0.54
Lungs	0.006	0.022	3.67
Muscle	0.011	0.014	1.27
Ovaries	0.003	0.003	1.00
Plasma	0.015	0.021	1.400
Renal fat	0.019	0.013	0.68
Skin *	0.026	0.166	6.385
Spleen	0.005	0.016	3.200
Thyroid	0.001	0.002	2.00

*These results may be affected by contamination from urine during housing

Metabolism

The metabolism of foramsulfuron has been determined in the rat following dosing at 10 or 1000 mg/kg bw. The main excretion product was unchanged foramsulfuron excreted mainly in the faeces. There were two metabolic pathways identified, deformylation to give the amine AE F130619 (= N,Ndimethyl-2-[3-(4,6-dimethoxypyrimidin-2-yl)-ureidosulfonyl]-4-aminobenzamide), and cleavage of the

sulfonylurea bridge to produce AE F153745 (= N,N-dimethyl-2-sulfamoyl-4-formylaminobenzamide), both of which were excreted as minor metabolites. In addition a number of minor (< 4% of dose) polar metabolites from both the phenyl- and pyrimidyl-labelled compound were also excreted but not identified. These results support the decision to use only phenyl-labelled foramsulfuron for the majority of the studies as the minor metabolites associated only with the pyrimidine ring were found to be polar and would therefore be readily excreted.

10 EVALUATION OF HEALTH HAZARDS

Acute toxicity

10.1 Acute toxicity - oral route

Table 30: Summary table of animal studies on acute oral toxicity

Method, guideline, deviations if any	Species, strain, sex, no/group	Test substance,	Dose levels, duration of exposure	Value LD_{50}	Reference
OECD TG 401 (1987) Oral GLP	Sprague-Dawley rat 5 males + 5 females	Foramsulfuron, (purity: 98.4 % (w/w))	5000 mg/kg bw Single oral dose by gavage	LD_{50}: > 5000 mg/kg bw	dRAR B.6.2.1. 1997

10.1.1 Short summary and overall relevance of the provided information on acute oral toxicity

Material and Methods

A group of five male and five female Sprague-Dawley rats was given foramsulfuron (purity: 98.4 % (w/w)) formulated at a concentration of 50 % w/v in 1 % w/v aqueous methylcellulose and administered at a dose volume of 10 ml/kg bw as a single oral dose by gavage of 5000 mg/kg bw of active substance following overnight fasting. Animals were observed soon after dosing and at frequent intervals for the remainder of Day 1 (day of dosing). Thereafter they were observed twice daily for 15 days. Individual body weights were recorded just prior to dosing and once weekly thereafter. All animals were sacrificed and examined externally and internally (abdominal and thoracic cavities) for macroscopic abnormalities on Day 15.

Results

There were no deaths during the study. Treatment-related clinical signs seen in all the animals included piloerection (seen within 5 minutes of dosing), hunched posture and white, soft to liquid faeces. Recovery was complete in all cases by day 4. A slightly low body weight gain was recorded on day 15 for all males and 3/5 females. No abnormalities were detected in any animal at the necropsy on day 15.

10.1.2 Comparison with the CLP criteria

Foramsulfuron does not fulfil criteria for acute oral classification, as the LD_{50} is beyond the range of values for category 4 ($300 < LD_{50} \leq 2000$ mg/kg bw) with an LD_{50} of > 5000 mg/kg bw.

10.1.3 Conclusion on classification and labelling for acute oral toxicity

The data on the acute oral toxicity potential of foramsulfuron is conclusive. Based on the oral LD_{50} of > 5000 mg/kg bw, an acute oral toxicity classification is not warranted according to CLP Regulation (EC) No 1272/2008.

10.2 Acute toxicity - dermal route

Table 31: Summary table of animal studies on acute dermal toxicity

Method, guideline, deviations if any	Species, strain, sex, no/group	Test substance,	Dose levels duration of exposure	Value LD_{50}	Reference
OECD TG 402 (1987) Dermal GLP	Sprague-Dawley rat, 5 males + 5 females	Foramsulfuron, (purity: 98.4 % (w/w))	2000 mg/kg bw Single occlusive 24-h dermal application	LD_{50}: > 2000 mg/kg bw	dRAR B.6.2.2, 1997

10.2.1 Short summary and overall relevance of the provided information on acute dermal toxicity

Material and Methods

A group of five male and five female Sprague-Dawley rats was given a single occlusive 24-h dermal application of 2000 mg/kg bw of active substance at the maximum practical concentration of 75 % w/v in 1 % w/v aqueous methylcellulose. At the end of the exposure period, the dressing was removed and the treated area of skin washed with warm water to remove any remaining test substance, then blotted dry.

Animals were observed after dosing and at frequent intervals on the remainder of Day 1 (day of dosing). On subsequent days they were observed twice. Any mortalities and local or systemic symptoms of toxicity were recorded during a 14-day observation period. Body weights were recorded immediately prior to dosing and at weekly intervals thereafter. All animals were sacrificed on Day 15 and examined externally and internally (abdominal and thoracic cavities) for macroscopic abnormalities.

Results

No deaths occurred during the study and no signs of systemic reaction to the treatment were seen. Transient slight irritation (grade 1 for erythema and oedema) was seen on Day 2 alone in 2/10 animals at the application site following the removal of the dressings. These reactions had disappeared by the following day. No other dermal reactions were observed in any other animals throughout the study.

10.2.2 Comparison with the CLP criteria

Foramsulfuron does not fulfil any criteria for acute dermal classification, as the LD_{50} is beyond the range of values for category 4 ($1000 < LD_{50} \leq 2000$ mg/kg bw).

10.2.3 Conclusion on classification and labelling for acute dermal toxicity

The data on the acute dermal toxicity of foramsulfuron is conclusive. Based on the LD_{50} value of > 2000 mg/kg bw, classification of foramsulfuron is not warranted according to CLP Regulation (EC) No 1272/2008.

10.3 Acute toxicity - inhalation route

Table 32: Summary table of animal studies on acute inhalation toxicity

Method, guideline, deviations if any	Species, strain, sex, no/group	Test substance, , form and particle size (MMAD)	Dose levels, duration of exposure	Value LC_{50}	Reference
OECD TG 403 (1981/2009) Inhalation GLP	Sprague-Dawley rat 5 males + 5 females	Foramsulfuron (purity: 93.7 % (w/w) after milling) MMAD: 2 µm < 4 µm: 79.9 %	5.04 mg/L Exposure by inhalation for 4 hours (nose-only)	LC_{50}: > 5.04 mg/L	dRAR B.6.2.3, 1998

10.3.1 Short summary and overall relevance of the provided information on acute inhalation toxicity

Material and Methods

A group of five male and five female Sprague-Dawley rats were exposed by inhalation for 4 h using a nose-only system to an achieved dust aerosol atmosphere of 5.04 mg/L. The dust atmosphere was generated by a Wright's dust feed mechanism and the chamber atmosphere was equilibrated prior to exposure of the animals. Before the start of the study, test material atmospheres were generated within the exposure chamber by varying the amount of input in order to achieve the optimum atmospheric conditions.

The mean achieved chemically analysed atmospheric concentration of foramsulfuron was 5.04 mg/L. The nominal (gravimetric) atmosphere concentration was 9.7 mg/L. By particle size analysis of the atmosphere drawn from the animals' breathing zone, the mass median aerodynamic diameter of the particles (MMAD) was 2.0 µm (79.9 % particles <4 µm) and the geometric standard deviation was 0.44 µm.

Animals were observed for mortality and clinical signs at hourly intervals during exposure, immediately on removal from the restraining tubes at the end of exposure, one hour after termination of exposure and once daily thereafter for 14 days post exposure, then sacrificed and necropsied. Individual body weights were recorded prior to treatment on the day of exposure and at weekly intervals thereafter.

Results

There was no mortality. During the exposure all animals exhibited wet fur. Increased or decreased respiratory rate was also seen occasionally. On removal from the chamber, wet fur, hunched posture, piloerection and increased respiration were commonly observed and several animals had red/brown staining around the eyes, snout or head. Wet fur was no longer seen 1 hour after completion of the exposure period and signs of increased respiratory rate and red/brown staining had diminished. On Day 1 after exposure, all animals appeared normal and no further clinical signs were observed during the study. Body weight gain was unaffected by treatment and no abnormalities were detected at necropsy.

After the study was performed, a new version of the OECD Test Guideline 403 has been adopted in September, 2009. The study practically fulfils the current data requirements.

Comparison with the CLP criteria

Acute inhalation lethal concentration of foramsulfuron to the rats was >5.04 mg/L, which did not cause mortality and was the highest achievable concentration. Foramsulfuron does not fulfil criteria for acute inhalation classification, as the LC_{50} is beyond the range of values for category 4 ($1.0 < LC_{50} \leq 5.0$ mg/L).

10.3.2 Conclusion on classification and labelling for acute inhalation toxicity

As the LC_{50} value of > 5.04 mg/L lies beyond the criteria for classification, an acute inhalation toxicity classification of foramsulfuron is not warranted according to CLP Regulation (EC) No 1272/2008.

RAC evaluation of acute toxicity

Summary of the Dossier Submitter's proposal

No classification was proposed by the DS for acute toxicity as all relevant LD_{50}/LC_{50} values were above the thresholds for classification.

Comments received during consultation

One industry representative agreed with the DS's proposal.

Assessment and comparison with the classification criteria

Acute toxicity: oral

There is one acute oral toxicity study available in rat, conducted according to OECD TG 401 (GLP-compliant). The LD_{50} values in rats were > 5000 mg/kg bw in both males and females. There were no deaths during the study.

RAC notes that the study was conducted with foramsulfuron formulated at a concentration of 50% w/v in 1% w/v aqueous methylcellulose. It is not specified in the CLH dossier if the dose levels were expressed for the 50% w/v foramsulfuron or if they were recalculated for the 100% w/v substance. Although a higher concentration could have been more toxic, the oral LD_{50} values caused by foramsulfuron at 50% were so much higher than the threshold for classification that it is not expected that a higher concentration would fulfil the CLP criteria for classification. Therefore, RAC agrees with the DS that no classification is warranted for acute toxicity via the oral route.

Acute toxicity: inhalation

In one rat study, conducted according to OECD TG 403, the acute inhalation LC_{50} value was > 5.04 mg/L/4hr (achieved dust aerosol atmosphere, after milling). There were no deaths during the study. RAC agrees with the DS that **no classification is warranted for acute toxicity by inhalation**.

Acute toxicity: dermal

In one rat study conducted according to OECD TG 402, the acute dermal LD_{50} values were > 2000 mg/kg bw in both males and females. Although the concentration of the test substance was 75% w/v in 1% w/v aqueous methylcellulose in the assay, no mortality was observed in the tested animals. RAC agrees with the DS that **no classification is warranted for acute toxicity via the dermal route**.

10.4 Skin corrosion/irritation

Table 33: Summary table of animal studies on skin corrosion/irritation

Method, guideline, deviations if any	Species, strain, sex, no/group	Test substance,	Dose levels duration of exposure	Results -Observations and time point of onset -Mean scores/animal -Reversibility	Reference
Acute skin corrosion/irritation OECD TG 404, 1992 According to GLP	Rabbit, New Zealand White 6 males	Foramsulfuron purity: 98.4% (w/w)	500 mg foramsulfuron, moistened with water. 4 hours topical semi-occlusive application. Observed 60 min, 24, 48 and 72 hours, after exposure	No adverse clinical signs No skin reactions Mean scores/ animal (24, 48 and 72 hours) Erythema: 0, 0, 0, 0, 0, 0; Oedema: 0, 0, 0, 0, 0, 0 Non-irriting to rabbit skin	dRAR B.6.2.4, 1997

Table 34: Summary table of human data on skin corrosion/irritation

Type of data/report	Test substance,	Relevant information about the study (as applicable)	Observations	Reference
No evidence for skin corrosion/irritation in humans				

Table 35: Summary table of other studies relevant for skin corrosion/irritation

Type of study/data	Test substance,	Relevant information about the study (as applicable)	Observations	Reference
Acute dermal toxicity, OECD TG 402, 1987 According to GLP	Foramsulfuron, purity: 98.4% (w/w)	Sprague-Dawley rat, five males and five females Single occlusive 24-h dermal application of 2000 mg/kg bw	Transient slight irritation (grade 1 for erythema and oedema) was seen on Day 2 alone in 2/10 animals at the application site following the removal of the dressings. These reactions had disappeared by the following day. No other dermal reactions were observed in any other animals	dRAR B.6.2.2, 1997

Type of study/data	Test substance,	Relevant information about the study (as applicable)	Observations	Reference
			throughout the study. Acute dermal LD50 > 2000 mg/kg bw	

10.4.1 Short summary and overall relevance of the provided information on skin corrosion/irritation

In the skin irritation study in rabbits, no clinical signs of toxicity and no mortality occurred. No skin reactions were observed in any of the animals throughout the observation period.

In acute dermal toxicity study in rats transient slight irritation (grade 1 for erythema and oedema) was seen on Day 2 alone in 2/10 animals at the application site following the removal of the dressings. These reactions had disappeared by the following day. No other dermal reactions were observed in any other animals throughout the study.

10.4.2 Comparison with the CLP criteria

None of the skin corrosion/irritation criteria for categories 1 or 2 are fulfilled by the data from studies with foramsulfuron.

10.4.3 Conclusion on classification and labelling for skin corrosion/irritation

No classification is warranted (conclusive but not sufficient for classification).

RAC evaluation of skin corrosion/irritation

Summary of the Dossier Submitter's proposal

Based on the results of a dermal skin irritation study in rabbits and the acute dermal toxicity study in rats, the DS proposed not to classify foramsulfuron for skin corrosion/irritation.

Comments received during consultation

One industry representative agreed with the DS's proposal.

Assessment and comparison with the classification criteria

Irritation/corrosivity was tested in an *in vivo* rabbit study, conducted according to OECD TG 404 (GLP-compliant). In this study, no dermal reactions were seen in 6 animals after 4-h exposure (foramsulfuron moistened with water) under semi-occlusive conditions.

The slight erythema noted in 2 out of 10 animals in the dermal acute toxicity study in rats was fully reversible on day 2 of the study. RAC agrees with the DS that **foramsulfuron does not meet the CLP criteria for skin corrosion/irritation and no classification is warranted**.

10.5 Serious eye damage/eye irritation

Table 36: Summary table of animal studies on serious eye damage/eye irritation

Method, guideline, deviations if any	Species, strain, sex, no/group	Test substance,	Dose levels duration of exposure	Results - Observations and time point of onset - Mean scores/animal - Reversibility	Reference
Rabbit eye irritation test OECD TG 405, 24 Feb. 1987 Accepted by RMS	New Zealand White rabbits Seven adult males	Foramsul-furon (purity: 98.4% (w/w))	Single ocular dose of 57 mg of the test substance (0.1 ml) for 1 sec under lid held together and then released, observed for three days after instillation.	Transient very slight to well defined conjunctival irritation after 1 hour which all had resolved two days after instillation	dRAR B.6.2.5, 1997

Table 37: Summary table of human data on serious eye damage/eye irritation

Type of data/report	Test substance,	Relevant information about the study (as applicable)	Observations	Reference
No data available				

Table 38: Summary table of other studies relevant for serious eye damage/eye irritation

Type of study/data	Test substance,	Relevant information about the study (as applicable)	Observations	Reference
No other studies available				

10.5.1 Short summary and overall relevance of the provided information on serious eye damage/eye irritation

Seven healthy adult male New Zealand White rabbits were used, one of which served as a screen animal, and another as a pilot animal for initial assessments for eye irritancy in accordance with animal welfare regulations. 0.1 ml (57 mg) of foramsulfuron was instilled into one eye of the screen rabbit whilst the other eye served as a control. The treated eye was then rinsed for 30 seconds with distilled water 30 seconds after instillation. The rationale for this was to prevent further animals being treated if the reaction was severe. The pilot animal was treated in exactly the same way, except that the eye was not rinsed. The next day the remaining five rabbits were treated in a similar fashion to the pilot animal. These five animals and the pilot animal comprised the main study.

All animals were observed daily for clinical signs of toxicity and mortality. Examination of the eyes of all animals was conducted 1, 24, 48 and 72 hours after instillation

No corneal opacity or iritis were observed at any time point of investigation. All six main study rabbits exhibited slight to moderate conjunctival redness, which was accompanied by slight chemosis and slight to moderate conjunctival discharge in 5 of 6 rabbits at 1 h after exposure. By 24 h after treatment, slight conjunctival redness (grade 1) without any discharge was observed in all rabbits; only one rabbit remained to have slight chemosis (grade 1). Responses had completely resolved in all rabbits 48 hours post instillation.

10.5.2 Comparison with the CLP criteria

The average score for conjunctival redness and chemosis in the animals following grading at 24, 48 and 72 hours after instillation of foramsulfuron was below 2 in all animals, thus the eye irritation criteria for category 2 are not fulfilled. Therefore, the substance is not considered to have produced eye irritation according to CLP criteria.

10.5.3 Conclusion on classification and labelling for serious eye damage/eye irritation

Since no corneal opacity or iritis were observed in any animal at any time point and as the average score for conjunctival redness and chemosis in the animals following grading at 24, 48 and 72 hours after instillation of foramsulfuron was not meeting the criteria for classification, the results are conclusive, but they do not warrant a classification for serious eye damage/eye irritation according to the CLP.

RAC evaluation of serious eye damage/irritation

Summary of the Dossier Submitter's proposal

Based on the available *in vivo* eye irritation study in rabbits, classification of foramsulfuron for serious eye damage/irritation was not proposed by the DS.

Comments received during consultation

One industry representative agreed with the DS's proposal.

Assessment and comparison with the classification criteria

An eye irritation study, conducted according to OECD TG 405 (GLP-compliant), was performed in 7 rabbits including a screen animal and a pilot animal. In a screened rabbit,

foramsulfuron was instilled into one eye that was rinsed for 30 seconds with distilled water 30 seconds after instillation. As this did not cause any severe reaction, the treated eye of the pilot animal was not rinsed. The other five animals were treated as the pilot rabbit; i.e. the treated eyes were not rinsed. The mean scores for 24-72 h in the six rabbits (eyes unrinsed) were:

- 0 in all six rabbits for corneal opacity and iritis,
- 0.33 in one rabbit and 0 in the other 5 rabbits for conjunctival chemosis,
- 0.33 in all the 6 rabbits for conjunctival redness.

All the eye effects were resolved 48h post instillation.

Based on the available *in vivo* study in rabbits, RAC agrees with the DS that **no classification for serious eye damage/irritation is warranted for foramsulfuron.**

10.6 Respiratory sensitisation

For foramsulfuron there is no relevant *in vitro*, *in vivo* or human data available for classification for this hazard class.

10.6.1 Short summary and overall relevance of the provided information on respiratory sensitisation

No data.

10.6.2 Comparison with the CLP criteria

No data.

10.6.3 Conclusion on classification and labelling for respiratory sensitisation

No data.

10.7 Skin sensitisation

Table 39: Summary table of animal studies on skin sensitisation

Method, guideline, deviations if any	Species, strain, sex, no/group	Test substance,	Dose levels duration of exposure	Results	Reference
Guinea-pig skin sensitisation (Magnusson and Kligman test) OECD TG	Guinea pigs, Dunkin/Hartley 5 control and 10 test animals for the main study, 6 for the preliminary dose range finder	Foramsul-furon (purity: 98.4 % (w/w))	Induction intra-dermal: injections: 2.5 % w/v in Alembicol D[a] Induction topical: 60% w/v in Alembicol D[a]	No skin sensitization, no dermal reactions in any test or control animal observed following challenge administration of 30 % or 60 % w/v foramsulfuron	dRAR B.6.2.6, 1997

Method, guideline, deviations if any	Species, strain, sex, no/group	Test substance,	Dose levels duration of exposure	Results	Reference
406 (1992) GLP			Challenge topical: 30, 60 % w/v in Alembicol D [a] coconut oil product		

10.7.1 Short summary and overall relevance of the provided information on skin sensitisation

The potential of the foramsulfuron to cause skin sensitation was evaluated in a Magnusson and Kligman test (the Guinea Pig Maximisation test).

In the preliminary study to the Magnusson and Kligman test in guinea pigs, a concentration of 2.5 % w/v foramsulfuron in Alembicol D (maximum concentration that could be dosed intradermally) caused well-defined erythema and oedema after 24 and 72 hours, but did not adversely affect the animals, whereas topical induction administration of 60 % w/v of the test compound in Alembicol D (maximum practical concentration) did not cause any irritation.

In the induction phase of the main study, after the intradermal injections, necrosis was seen at sites receiving Freund's Complete Adjuvant in all test and control animals. Slight erythema was seen in test animals at sites receiving 2.5 % w/v test compound in Alembicol D and in control animals receiving Alembicol D alone.

After the topical applications, slight erythema was observed in test animals following application with 60 % w/v foramsulfuron in Alembicol D and in the control guinea pigs receiving Alembicol D alone.

In the challenge phase, no dermal reactions in any test or control animal were observed following administration of either 30 % or 60 % w/v foramsulfuron. In conclusion, foramsulfuron was not a skin sensitiser in this guinea pig Magnusson and Kligman test.

10.7.2 Comparison with the CLP criteria

Substances may be allocated to one of the two sub-categories 1A or 1B using a weight of evidence approach in accordance with the criteria given in CLP and on the basis of reliable and good quality evidence from human cases or epidemiological studies and/or observations from appropriate studies in experimental animals. Classification is required when a positive response is observed in at least 30 % of the animals in a maximisation test at >1 % intradermal induction dose.

Compared with the aforementioned criteria, the animal study did not indicate a skin sensitising potential.

10.7.3 Conclusion on classification and labelling for skin sensitisation

Since for foramsulfuron no evidence of a skin sensitizing potential exists, the data available indicates that foramsulfuron does not require classification as skin sensitiser according to the CLP regulation (EC) No 1272/2008.

RAC evaluation of skin sensitisation

Summary of the Dossier Submitter's proposal

Based on the results of a Magnusson and Kligman test, in which none out of 10 tested animals showed sensitising effects, the DS concluded that foramsulfuron does not meet the CLP criteria for skin sensitisation.

Comments received during consultation

One industry representative agreed with the DS's proposal.

Assessment and comparison with the classification criteria

Male Dunkin-Hartley Guinea-pigs (n=10 in treatment group, n=5 in control group) were treated with a 2.5% intradermal induction concentration of foramsulfuron in Alembicol D. Before challenge, irritation was induced by sodium dodecyl sulphate. At challenge, a 60% concentration of foramsulfuron in Alembicol D was used. The concentrations of foramsulfuron and vehicle were based on a preliminary study. A positive control was included in this study. No dermal reactions in any test or control animal were observed.

RAC agrees with the DS that based on the negative results of the Magnusson and Kligman test, **no classification of foramsulfuron as a skin sensitiser is warranted.**

10.8 Germ cell mutagenicity

Table 40 Summary table of mutagenicity/genotoxicity tests in vitro

Method, guideline, deviations if any	Test substance,	Relevant information about the study including rationale for dose selection (as applicable)	Observations	Reference
Bacterial mutation (Ames Test) *Salmonella typhimurium* strains TA 1535, TA 1537, TA 98, TA 100,	Foramsul-furon purity 98.4% (w/w)	The test compound was toxic to all Salmonella typhimurium strains at concentrations of 20 µg/plate and above with and without metabolic activation. It was not toxic to Escherichia coli WP2uvrA.	Not mutagenic in the absence or in the presence of the metabolic activation	1996 KCA5.4.1/ 01

Method, guideline, deviations if any	**Test substance,**	**Relevant information about the study including rationale for dose selection (as applicable)**	**Observations**	**Reference**
Escherichia coli strain WP2 uvrA OECD TG 471 and TG 472, 26 May 1983 Acceptable		In the toxicity test using histidine enriched agar plates and a dilution of the tester strain TA 100 (designated TA 100 D), which was performed in parallel with the second experiment, toxicity was found at concentrations of 4 µg/plate and above in the absence of metabolic activation. No cytotoxicity was found in the presence of metabolic activation up to 100 µg/plate.		
In vitro human lymphocyte chromosome aberration test OECD TG 473, 26 May 1983, EEC, Directive 92/69/EEC (OJ No. L383A, 29.12.92), Part B, Method B.10. Acceptable	Foramsul-furon purity: 98.4% (w/w)	Human blood collected from healthy male donors was pooled and diluted with RPMI tissue culture medium containing 16.7% foetal calf serum (PAA). Three separate tests were carried out both, with and without S-9 mix. Concentrations were from 600 to 2400 µg/mL, with and without S-9 mix. Following coding, 100 metaphase figures in each culture were evaluated for aberrations. Only cells with 44 to 46 chromosomes were analysed.	Evidence of clastogenic activity without S-9 mix (just outside historical control range), but not with S-9. Positive only at the highest dose. The positive effects occurred at concentrations with some precipitation and apparently slight degree of cytotoxicity.	1997 KCA5.4.1/ 02
Chinese hamster lung V79 cell HPRT mutation test OECD 476, 4 April 1984 Acceptable	Foramsul-furon purity: 98.4% (w/w)	Since 2000 µg/mL produced a slight precipitate, the preliminary toxicity study was carried out using a dose range from 1–2000 µg/mL. In the presence or absence of S9-mix, there was no indication of toxicity up to the limit of solubility. Ethanol was used as solvent control. Two independent assays for mutation to 6-	Negative with or without the presence of metabolic activation	1996 KCA5.4.1/ 03

Method, guideline, deviations if any	Test substance,	Relevant information about the study including rationale for dose selection (as applicable)	Observations	Reference
		thioguanine resistance were performed with and without S9 mix using dose levels of 250, 500, 1000 and 2000 µg/mL. Ethyl methane sulphonate and 9,10-dimethyl-1,2-benzanthracene were used as positive controls.		

Table 41 Summary table of mutagenicity/genotoxicity tests in mammalian somatic or germ cells in vivo

Method, guideline, deviations if any	Test substance,	Relevant information about the study (as applicable)	Observations	Reference
Mouse micro-nucleus test NMRI mice OECD TG 474, adopted 1983 USEPA Subdivision F § 84-2, Nov. 1984 EU 92/69/EEC, B12 5 male and 5 female NMRI mice/dose Acceptable	Foramsul-furon purity 98.4% (w/w)	Groups of 3 x 5 male and 3 x 5 female NMRI mice were given a single oral dose by gavage of 0, 200, 1000 or 2000 mg/kg bw foramsulfuron suspended in 1% w/v aqueous methylcellulose. Another group of 5 males and 5 females was given a single gavage dose of 50 mg/kg body weight of Endoxan (cyclophosphamide) as the positive control. 5 males and 5 females from each of the test and negative control groups were sacrificed 12, 24 and 48 hours after dosing, all positive control animals were sacrificed 24 hours post-dosing.	Negative, there were no statistically significant increases in micronucleated polychromatic erythrocytes in animals treated with foram-sulfuron. A slightly reduced ratio of polychromatic to normochromatic erythrocytes at 2000 mg/kg bw after 12 and 48 hours is regarded as indication of bone marrow exposure.	1997 KCA5.4.2/ 01
Rat hepatocyte unscheduled DNA synthesis test OECD TG 482, 23 Oct. 1986 and September	Foramsul-furon purity 98.4% (w/w)	Groups of 8 males were given a single gavage dose of 0, 600 or 2000 mg/kg bw in aqueous 1% w/v methyl cellulose. 2 male rats per dose, were given a single gavage dose of either 4 mg dimethylnitrosamine/kg bw (2-h sampling time) or	Negative, there were no significant increases in the gross or net nuclear grain count at either dose level of foramsulfuron at either the 2- or 14-hour sampling times.	1996 KCA5.4.2/ 02

Method, guideline, deviations if any	Test substance,	Relevant information about the study (as applicable)	Observations	Reference
1995, draft of OECD TG 486 (adopted 21 July 1997) Acceptable		50 mg 2-acetylaminofluorene/kg bw (14-h sampling time). Groups of 4 rats from each of the groups were sacrificed 2 and 14 hours post dosing together with the relevant positive control group. After perfusion and excision of the liver, isolated hepatocytes were prepared and suspended in Williams' medium E, complete (WEC). A viable cell count was performed after diluting an aliquot of the cells with an equal volume of trypan blue. The cell yield was also calculated.		

Bacterial tests (Ames test, OECD TG 471 and OECD TG 472)

Material and Methods:

Two independent mutation tests were conducted in both the presence and absence of metabolic activation.

Histidine dependent auxotrophic mutant strains TA1535, TA1537, TA98 and TA100 of *Salmonella typhimurium* and a tryptophan dependent auxotrophic mutant strain of *Escherichia coli*, WP2uvrA, were exposed to foramsulfuron dissolved in ethanol. For each bacterial strain and dose level, triplicate plates were used in both the presence and absence of an Aroclor 1254-induced rat liver metabolic activation system (S-9 mix). After 48 hours of incubation at 37°C, the numbers of revertant plates were scored using an automated colony counter.

For both experiments negative (untreated) controls and vehicle controls were used, along with positive controls. Positive control compounds used in the absence of metabolic activation were sodium azide (for TA100 and TA1535), 9-aminoacridine (TA1537), 2-nitrofluorene (TA98) and 1-methyl-3-nitro-1-nitrosoguanidine (WP2uvrA). In the presence of the S9 mix, 2-aminoanthracene was used for all strains.

Dose levels of technical foramsulfuron used in the first test for all bacterial strains were 0, 4, 20, 100, 500, 2500 and 5000 µg/plate. In the second test, concentrations for all the *Salmonella typhimurium* strains were 0, 0.032, 0.16, 0.8, 4, 20 and 100 µg/plate to account for the differences in the sensitivities of these strains. For *Escherichia coli* WP2uvrA, the concentrations were the same as those in the first test i.e. 0, 4, 20, 100, 500, 2500 and 5000 µg/plate.

A toxicity test with *Salmonella* strain TA100 was conducted in parallel with the second mutation test both with and without S-9 mix. It used triplicate plates of 0.1 ml of a 10^6 dilution of an overnight culture of TA100 (designated TA100 D) and the solvent plated on to histidine and biotin rich top agar. The dose levels of foramsulfuron evaluated were 0, 0.032, 0.16, 0.8, 4, 20 and 100 µg/plate.

Prior to the start of the study the stability of a 5 and 20% concentration of the test compound in ethanol was confirmed over 4 hours. For the 5% concentration the mean percentage of nominal was 115% after 4 hours compared with 108% at time '0', and 114% after 4 hours compared with 113% at time '0' for the 20% concentration. Thus foramsulfuron was stable at these concentrations in ethanol over 4 hours.

Findings:

Foramsulfuron was toxic in both mutation tests to all *Salmonella typhimurium* strains at concentrations of 20 µg/plate and above both with and without metabolic activation. In the toxicity test with a dilution of the 10^6 overnight culture of strain TA100 (designated TA100 D), toxicity was observed at concentrations of 4 µg/plate and above in the absence of metabolic activation. However, there was no toxicity in the presence of metabolic activation at dose levels up to 100 µg/plate, the highest evaluated. The test compound was not toxic to *Escherichia coli* WP2uvrA at any concentration tested.

Foramsulfuron did not cause any significant increases in the number of revertant colonies in either the presence or absence of metabolic activation. All the positive control compounds produced expected increases in the number of revertant colonies, thereby demonstrating the sensitivity of the assay and the efficacy of the S-9 mix.

Mammalian cell tests

Chromosome aberrations in human lymphocytes (OECD TG 473)

Material and Methods:

Human blood collected from healthy male donors was pooled and diluted with RPMI tissue culture medium containing 16.7% foetal calf serum (PAA). These cultures were incubated at 37 °C for 48 h in the presence of phytohaemagglutinin (0.4 ml blood: 4.5 ml media: 0.1ml phytohaemagglutinin) to stimulate cell division. The cycle time for human lymphocytes in the testing facility was approx. 15 h.

Three separate tests were carried out both with and without an exogenous metabolic activation system, S-9 mix, derived from the livers of rats induced with Aroclor 1254. A fourth test was conducted using 21 h exposure and no S9-mix. The exposure scheme and test concentrations applied are summarised in Table 42: Exposure scheme and test concentrations applied :

Table 42: Exposure scheme and test concentrations applied

Incubation period:	With S9-mix		Without S9-mix	
	With foramsulfuron	Total	With foramsulfuron	Total
Test I	3 h	21 h	21 h	21 h
Test IIa	3 h	21 h	21 h	21 h
Test IIb	3 h	45 h	45 h	45 h
Test III	–	–	21 h	21 h
Test concentrations:				
Test I	0 (ethanol solvent)–18.8–37.5–75–150–300–600–1200–2400 µg/ml			
Test IIa+b	0 (ethanol solvent)–600–1200–2400 µg/ml			
Test III	0 (ethanol solvent)–2400 µg/ml			

Duplicate cultures were used for each treatment with the test substance. Four other cultures were treated with ethanol as the solvent control, while Mitomycin C, the positive control used in the absence of S-9 mix, was added to duplicate cultures at final concentrations of 0.2, 0.4 and 0.8 µg/ml. In the presence of metabolic activation, the positive control cyclophosphamid was added to duplicate cultures at final concentrations of 20, 25 and 30 µg/ml. Two hours before the cells were harvested, mitotic activity was

arrested by addition of colchicine (colcemid) to each culture at a final concentration of 0.1 µg/ml. Cells were susbsequently harvested and processed for scoring.

Slides were initially examined to record the proportion of mitotic cells per 1000 cells in each culture (except for the positive control cultures). This was used to establish the highest dose level for metaphase analysis. The intermediate and low dose levels for analysis were also chosen. Following coding, 100 metaphase figures in each culture were evaluated for aberrations. Only cells with 44 to 46 chromosomes were analysed. The number of aberrant metaphase figures in each treated group was compared statistically with the solvent control group using a Fisher's Exact test.

Findings:

In the presence of S-9 mix, for the 21-h harvest time, dose levels selected for metaphase analysis were 600, 1200 and 2400 µg/ml both the first and second tests. For the 45-h harvest of the second test conducted both with and without S-9 mix, and for the third test conducted only in the absence of S-9 mix, the highest test concentration of 2400 µg/ml was evaluated.

First assay (I): Foramsulfuron was non-toxic in both the absence and presence of S-9 mix. The relative mitotic index at 2400 µg/ml was 121% in the absence of S-9 mix and 85% in its presence. Therefore, dose levels of 600, 1200 and 2400 µg/ml were selected for metaphase analysis.

No statistically significant increases in the proportion of aberrant cells, when compared to the solvent controls, were seen in cultures treated with foramsulfuron in either the presence or absence of S-9 mix. Both the positive control compounds caused statistically significant ($p<0.001$) increases in the proportion of aberrant cells, demonstrating the efficacy of the S-9 mix and the sensitivity of the test system.

Table 43 Foramsulfuron metaphase analysis data – tests with S-9 mix

Compound / Concentration			No. of aberrant cells[1]		Rel. Mitotic index %
Test-No.	Incubation period (h)	Concentration	Excl. gaps Mean %	Incl. gaps Mean %	
Solvent control[2] [µl/ml]					
I	21-h	10	1.5	1.5	100
IIa	21-h	10	0.75	0.75	100
IIb	45-h	10	2.5	2.75	100
III	21-h	10	0.5	0.5	100
Foramsulfuron [µg/ml]					
I	21-h	600	1.0	1.0	85
		1200	1.0	1.5	109
		2400	0.0	0.5	85
IIa	21-h	600	0.0	0.0	95
		1200	0.0	1.0	89
		2400	0.5	0.5	82
IIb	45-h	2400	0.0	0.0	119
Cyclophopamide [µg/ml]					
I	21-h	30	11.0*	11.0*	–
IIa	21-h	30	9.5*	10.5*	–

[1] 100 cells were examined for aberrations per culture. Four cultures incubated with solvent control only were evaluated per assay, while duplicate cultures were assayed in the case of foramsulfuron and for positve control cyclophopamide incubations.

[2] Only negative control assay results of cultures are presented which harboured aberrations.

***** $p<0.001$, otherwise $p>0.01$

Table 44: Foramsulfuron metaphase analysis data - tests without S-9

Compound / Concentration			No. of aberrant cells[1]		Rel. Mitotic index %
Test-No.	Incubation period (h)	Concentration	Excl. gaps Mean %	Incl. gaps Mean %	
Solvent control[2] [µl/ml]					
I	21-h	10	0.75	0.75	100
IIa	21-h	10	0.5	0.5	100
IIb	45-h	10	0.75	0.75	100
III	21-h	10	0.5	0.5	100
Foramsulfuron [µg/ml]					
I	21-h	600	0.0	0.0	141
		1200	0.0	0.0	127
		2400	0.5	0.5	121
IIa	21-h	600	0.0	1.0	115
		1200	0.5	1.0	74
		2400	5.5*	6.0*	79
IIb	45-h	2400	6.5*	8.5*	55
III	21-h	2400	7.0*	7.0*	74
Mitomycin C[µg/ml]					
I	21-h	0.4	13.0*	13.0*	–
IIa	21-h	0.8	11.0*	11.0*	–

[1] 100 cells were examined for aberrations per culture. Four cultures incubated with solvent control only were evaluated per assay, while duplicate cultures were assayed in the case of foramsulfuron and for positve control Mitomycin C incubations.
[2] Only negative control assay results of cultures are presented which harboured aberrations.
***** $p<0.001$, otherwise $p>0.01$

Second test, 21-h harvest (IIa): 2400 µg/ml foramsulfuron reduced the mitotic index to 79% and 82% of the solvent control value in the absence and presence of S-9 mix, respectively.

In the absence of S-9 mix, foramsulfuron caused a slight increase in the number of aberrant cells at 2400 µg/ml. In the presence of S-9 mix, there were no statistically significant increases in the proportion of aberrant cells when compared to the solvent control, at any dose level. Both positive control compounds caused statistically significant increases in aberrant cells.

Second test, 21-h harvest (IIa): In the absence of S-9 mix at 2400 µg/ml reduced the mitotic index to 55% of the control. However, in the presence of S-9 mix the mitotic index showed no toxicity. In the absence of S-9 mix, 2400 µg/ml caused a statistically significant increase in the number of aberrant cells (6.5%) at the 45-hour harvest time. In the presence of S-9 mix, foramsulfuron showed no statistically significant increases in the number of aberrant cells compared to the control.

Third test, 21-h harvest (III): At the 21-hour harvest time in the absence of S-9 mix, 2400 µg/ml was not toxic since the relative mitotic index was 74%. An increase in the number of aberrant cells (7%) was observed.

Measurement of osmolality indicated no difference in the treated and solvent control cultures.

Note:

According to the authors of the study report, the increased mean percentage of cells with chromosomal abberations in cultures exposed to 2400 µg/ml foramsulfuron lie just outside the upper range of historical

control data. However, only a brief summary of historical control data was presented in the study report, which did not include any information (1) whether or which underlying studies were compliant with GLP or OECD Test Guideline requirements, (2) whether or which of the studies used ethanol as control solvent, or (3) the duration of incubation with solvent performed in each study. Therefore, the reported historical control data was regarded to be unreliable by the Dossier Submitter and could not be considered for the overall assessment of the study results.

Conclusion:

Foramsulfuron, dissolved in ethanol, showed evidence of clastogenic activity in the absence of S-9 mix at the highest test concentration of 2400 µg/ml only, while a negative test result was obtained in the presence of a metabolic activation system in this *in vitro* cytogenetic test.

Gene mutation tests

Chinese hamster lung cells (V79), OECD TG 476

Material and Methods:

In preliminary assessment of cytotoxicity (determination of cell survival via crystal violet extinction) for selection of appropriate dose levels for the mutation assay, evaluation of the solubility of foramsulfuron showed that 2000 µg/ml produced a slight precipitate and was therefore the highest practicable test concentration. Accordingly, the preliminary toxicity study was carried out using a dose range from 1–2000 µg/ml. The cell cultures were subjected to the same treatment conditions as in the subsequent mutation assays. Both in the presence or absence of exogenous metabolic activation system (S9-mix) derived from rat livers induced with Aroclor 1254, there was no indication of toxicity up to the limit of solubility.

Ethanol was used as solvent control. The stability of 5% and 20% concentrations of formasulfuron in ethanol were established. At the 5% concentration, the mean percentage of nominal was 115% at 4 hours compared with 108% at time ‘0’, and 114% of nominal at 4 h compared with 113% at time ‘0’ for the 20% concentration. Thus both concentrations of foramsulfuron were stable over 4 h.

Based on these results, two independent assays for mutation to 6-thioguanine resistance were performed in the presence and absence of S9 metabolic activation using dose levels of 250, 500, 1000 and 2000 µg/ml. Before treatment, the pH values and osmolality of the treatment media were determined. The addition of test compound solutuions did not have any effect on these parameters. Negative and solvent controls were used for each test. Ethyl methane sulphonate and 9,10-dimethyl-1,2-benzanthracene were used as positive controls in the absence and presence of metabolic activation, respectively.

The mutation tests were conducted as follows:

Day 1: A) Exponentially growing cultures of Chinese hamster lung V97 cells were subcultured to establish cultures of about 4500 cells per well of the microtitre plate for plating efficiency.

B) For the mutation test, a single 175 cm^2 flask with 30 ml medium containing 6 x 10^5 to 1 x 10^6 cells were established for each concentration and time point. Two sets of cultures were prepared, one for treatment in the absence of S9-mix and one for treatment in its presence.

Day 2: Cell cultures A) and B) were treated with foramsulfuron, the solvent or positive control in both the presence and absence of S9-mix for 4 hours.

Day 3: Fixation and staining of the cells from the plating efficiency culture a) to determine plating efficiency.

Day 5: Subculturing of the main mutation test cultures b).

Day 9: Subculturing of B) in five 75 cm^2 flasks with culture medium containing 6-thioguanine (about 11 µg/ml) for mutant selection (approx. 300000 cells/flask) and of two 25 cm^2 flasks for plating efficiency (about 400 cells per flask).

Day 16: Cell colonies from the Day 9 plating efficiency cultures were fixed and stained with methylene blue stain in 0.01% w/v KOH solution.

All incubations were at approximately 37 °C and in a 4% CO_2 atmosphere. Only colonies with more than 50 cells were counted.

Findings:

No relevant reproducible dose-related increases in the mutant colonies or mutant frequency were seen at any of the concentrations of foramsulfuron tested, in either the presence or absence of metabolic activation. The sensitivity of the test system was demonstrated by statistically significant increases in mutation frequency in the cell cultures treated with the positive control compounds.

Table 45 Mutagenicity data (Main experiment)

	Dose µg/ml	S9-mix	Number of mutant colonies					mean	Stand. dev.	Mut. freq.	Stat. sig.		
			I	II	III	IV	V						
Negative control	0.0	-	8	10	6	7	5	7.2	1.92	25.7			
Solvent control (ethanol)	0.0	-	15	14	5	8	7	9.8	4.44	38.8			
Positive control (EMS)	1000.0	-	102	115	131	127	125	120.0	11.66	659.3			*
Foramsulfuron	250.0	-	4	6	4	3	3	4.0	1.22	16.2			
	500.0	-	2	0	0	1	0	0.6	0.89	2.3			
	1000.0	-	1	2	4	0	4	2.2	1.79	8.5			
	2000.0	-	1	0	2	2	2	1.4	0.89	6.7			
Negative control	0.0	+	3	3	3	4	4	3.4	0.55	12.6			
Solvent control (ethanol)	0.0	+	4	3	2	2	4	3.0	1.00	13.3			
Positive control (DMBA)	7.7	+	21	12	18	20	17	17.6	3.51	70.5			*
Foramsulfuron	250.0	+	4	3	6	5	1	3.8	1.92	18.0			
	500.0	+	1	6	5	6	7	5.0	2.35	21.4			

	1000.0	+	1	2	0	1	1	1.0	0.71	4.1			
	2000.0	+	3	3	3	8	3	4.0	2.24	19.1			

Mutation frequency (mutant colonies per 1 million cells): mean value / cells surviving

* Statistical significant ($p \leq 0.05$) Mann-Whitney-U-Test

Table 46: Toxicity data (Main mutation experiment)

	Dose	S9 mix	Relative survival
Negative ctrl	0	-	100.2
Solvent ctrl	0	-	100.0
Positive ctrl	1000	-	92.5
Foramsulfuron	250	-	96.0
	500	-	103.4
	1000	-	102.1
	2000	-	98.4

Table 47: Toxicity data (Main mutation experiment)

	Dose	S9 mix	Relative survival
Negative ctrl	0	+	100.9
Solvent ctrl	0	+	100.0
Positive ctrl	1000	+	98.1
Foramsulfuron	250	+	96.4
	500	+	101.0
	1000	+	102.1
	2000	+	101.8

Table 48: Toxicity data (Repeat mutation experiment)

	Dose	S9 mix	Relative survival
Negative ctrl	0	-	99.2
Solvent ctrl	0	-	100.0
Positive ctrl	1000	-	92.7
Foramsulfuron	250	-	101.9
	500	-	107.1
	1000	-	105.5

	2000	-	100.1

Table 49: Toxicity data (Repeat mutation experiment)

	Dose	S9 mix	Relative survival
Negative ctrl	0	+	103.4
Solvent ctrl	0	+	100.0
Positive ctrl	1000	+	103.4
Foramsulfuron	250	+	103.2
	500	+	103.2
	1000	+	109.5
	2000	+	105.7

Table 50 Mutagenicity data (Repeat)

	Dose µg/ml	S9-mix	Number of mutant colonies					mean	Stand. dev.	Mut. freq.	Stat. sig.
			I	II	III	IV	V				
Negative control	0.0	-	1	2	1	4	2	2.0	1.22	8.2	
Solvent control (ethanol)	0.0	-	9	4	6	5	6	6.0	1.87	22.9	
Positive control (EMS)	1000.0	-	157	164	149	136	164	154.0	11.81	775.1	*
Foramsulfuron	250.0	-	2	2	1	0	1	1.2	0.84	5.8	
	500.0	-	0	1	4	2	2	1.8	1.48	9.1	
	1000.0	-	1	2	2	2	0	1.4	0.89	8.4	
	2000.0	-	3	2	3	2	1	2.2	0.84	11.3	
Negative control	0.0	+	7	2	7	5	4	5.0	2.12	26.9	
Solvent control (ethanol)	0.0	+	1	0	3	3	2	1.8	1.30	8.9	
Positive control (DMBA)	7.7	+	24	26	23	22	17	22.4	3.36	93.3	*
Foramsulfuron	250.0	+	0	0	0	1	0	0.2	0.45	0.8	
	500.0	+	1	2	1	2	0	1.2	0.84	4.9	
	1000.0	+	1	3	1	2	2	1.8	0.84	7.6	
	2000.0	+	3	3	0	1	2	1.8	1.30	8.7	

Mutation frequency (mutant colonies per 1 million cells): mean value / cells surviving

* Statistical significant ($p \leq 0.05$) Mann-Whitney-U-Test

Conclusion:

Foramsulfuron was not mutagenic in Chinese hamster lung V79 cells either in the presence or absence of an exogenous metabolic activation system in this *in vitro* test.

In vivo studies in somatic cells

Mouse micronucleus study (OECD TG 474)

Material and Methods:

Groups of 5 male and 5 female NMRI mice were given a single oral dose by gavage of either 200, 1000 or 2000 mg/kg body weight of foramsulfuron suspended in 1% w/v aqueous methylcellulose. A similar sized negative control group received a single oral dose of the vehicle alone. Another group of 5 males and 5 females was given a single gavage dose of 50 mg/kg body weight of Endoxan (cyclophosphamide) as the positive control. In all cases the dose volume was 10 ml/kg body weight.

All positive control animals were sacrificed 24 hours post-dosing whilst 5 males and 5 females from each of the test and negative control groups were sacrificed 12, 24 and 48 hours after dosing. A bone marrow smear was prepared from the femur of each animal. Following fixation and staining with Giemsa, the slides were air-dried then examined for the number of micronuclei in 1000 polychromatic erythrocytes and, as a control measure, the incidence in 1000 normochromatic erythrocytes from each mouse. In addition, the ratio of polychromatic to 1000 normochromatic erythrocytes was determined. The incidences of micronucleated polychromatic erythrocytes and of normochromatic erythrocytes were statistically evaluated using Wilcoxon tests.

The highest dose level of foramsulfuron, 2000 mg/kg bw, was based on the results of a range finding study in which no mortality and no clinical signs of toxicity were observed at this dose level. Therefore, since this level was defined as the international limit dose according to guidelines, it was chosen as the highest dose for the micronucleus test.

This dose level was prepared as a 20% suspension concentration in the vehicle, 1% w/v aqueous methylcellulose. This was tested for stability of the test substance over 3 hours prior to the start of the study. After 3 hours the mean percent of nominal was 103% compared with 108% at time ‘0’. Thus a 20% concentration of AE F1309360 in 1% aqueous methylcellulose was stable over this 3-hour time period.

Findings:

There was no mortality in any of the dose groups treated with foramsulfuron. Moreover, no clinical signs of toxicity were observed and there were no macroscopic findings at necropsy.

There were no statistically significant increases in micronucleated polychromatic and normochromatic erythrocytes in animals treated with foramsulfuron. All values were within the normal range of the negative control groups. No treatment-related change of the ratio of polychromatic to normochromatic erythrocytes was observed. The positive control cyclophosphamide induced a marked and statistically significant increase in the number of polychromatic erythrocytes with micronuclei, confirming the sensitivity of the test system.

Table 51 Summary of findings in bone marrow erythrocytes

Sex	Dose mg/kg	Sample time	No. of animals	Erythrocytes P/N		Erythrocytes with micronuclei							
				Mean	SD	Polychromatic (mean)			Mut.I.	Normochromatic (mean)			Mut.I.
						No.	%	SD		No.	%	SD	

Pooled	0	12 h	10	0.7	0.16	1.50	0.2	0.12	1.0	1.10	0.1	0.09	1.0
	200	12 h	10	0.9	0.13	1.60	0.2	0.12	1.1	0.70	0.1	0.08	0.6
	1000	12 h	10	0.7	0.08	0.90	0.1	0.06	0.6	1.50	0.2	0.11	1.4
	2000	12 h	10	0.9	0.07*	1.60	0.2	0.10	1.1	1.10	0.1	0.09	1.0
Pooled	0	24 h	10	0.7	0.20	1.70	0.2	0.09	1.0	1.10	0.1	0.10	1.0
	200	24 h	10	1.0	0.15	1.10	0.1	0.10	0.6	1.70	0.2	0.14	1.5
	1000	24 h	10	0.9	0.21	0.70	0.1	0.08	0.4	1.20	0.1	0.11	1.1
	2000	24 h	10	0.8	0.18	0.70	0.1	0.07	0.4	1.40	0.1	0.10	1.3
	P.contr.	24 h	10	0.9	0.09	34.0	3.4	0.90*	20.0	1.80	0.2	0.06	1.6
Pooled	0	48 h	10	0.9	0.16	1.20	0.1	0.14	1.0	1.20	0.1	0.04	1.0
	200	48 h	10	0.8	0.17	0.80	0.1	0.08	0.7	1.00	0.1	0.12	0.8
	1000	48 h	10	0.9	0.15	1.00	0.1	0.13	0.8	1.10	0.1	0.09	0.9
	2000	48 h	10	0.9	0.11	1.00	0.1	0.11	0.8	1.10	0.1	0.09	0.9

Mut.I. = Mutagenic index = erythrocytes with micronuclei in dose group / erythrocytes with micronuclei in control

Control = Vehicle

P.contr = Positive control = endoxan (used only in 24 h exposure group) * = Significantly different from control ($P < 0.05$)

Table 52 Summary of findings in bone marrow erythrocytes

Sex	Dose mg/kg	Sample time	No. of animals	Erythrocytes P/N		Erythrocytes with micronuclei							
				Mean	SD	Polychromatic (mean)			Mut.I.	Normochromatic (mean)			Mut.I.
						No.	%	SD		No.	%	SD	
Male	0	12 h	5	0.8	0.15	1.40	0.1	0.15	1.0	1.20	0.1	0.11	1.0
	200	12 h	5	1.0	0.09	1.60	0.2	0.09	1.1	0.80	0.1	0.11	0.7
	1000	12 h	5	0.7	0.07	0.60	0.1	0.05	0.4	1.40	0.1	0.13	1.2
	2000	12 h	5	0.9	0.08	1.60	0.2	0.11	1.1	1.00	0.1	0.10	0.8
Female	0	12 h	5	0.7	0.18	1.60	0.2	0.09	1.0	1.00	0.1	0.07	1.0
	200	12 h	5	0.9	0.15	1.60	0.2	0.15	1.0	0.60	0.1	0.05	0.6
	1000	12 h	5	0.7	0.09	1.20	0.1	0.04	0.8	1.60	0.2	0.09	1.6
	2000	12 h	5	0.9	0.08	1.60	0.2	0.09	1.0	1.20	0.1	0.08	1.2
Male	0	24 h	5	0.6	0.19	1.40	0.1	0.11	1.0	1.20	0.1	0.08	1.0
	200	24 h	5	1.0	0.08	1.20	0.1	0.13	0.9	1.80	0.2	0.18	1.5
	1000	24 h	5	1.0	0.21	0.80	0.1	0.08	0.6	1.40	0.1	0.15	1.2
	2000	24 h	5	0.8	0.25	0.40	0.0	0.09	0.3	1.20	0.1	0.11	1.0
	P.contr.	24 h	5	0.9	0.09	37.2	3.7	0.61	26.6	2.00	0.2	0.07	1.7

Female	0	24 h	5	0.9	0.06	2.00	0.2	0.07	1.0	1.00	0.1	0.12	1.0
	200	24 h	5	1.0	0.20	1.00	0.1	0.07	0.5	1.60	0.2	0.11	1.6
	1000	24 h	5	0.9	0.23	0.60	0.1	0.09	0.3	1.00	0.1	0.07	1.0
	2000	24 h	5	0.8	0.09	1.00	0.1	0.00	0.5	1.60	0.2	0.09	1.6
	P.contr.	24 h	5	0.8	0.05	30.8	3.1	1.09	15.4	1.60	0.2	0.05	1.6
Male	0	48 h	5	0.8	0.16	1.40	0.1	0.11	1.0	1.20	0.1	0.04	1.0
	200	48 h	5	0.8	0.10	1.00	0.1	0.10	0.7	1.80	0.2	0.13	1.5
	1000	48 h	5	0.8	0.03	1.60	0.2	0.15	1.1	1.20	0.1	0.08	1.0
	2000	48 h	5	0.9	0.13	0.60	0.1	0.09	0.4	0.80	0.1	0.08	0.7
Female	0	48 h	5	1.0	0.06	1.00	0.1	0.17	1.0	1.20	0.1	0.04	1.0
	200	48 h	5	0.7	0.22	0.60	0.1	0.05	0.6	0.20	0.0	0.04	0.2
	1000	48 h	5	0.9	0.23	0.40	0.0	0.09	0.4	1.00	0.1	0.10	0.8
	2000	48 h	5	0.8	0.08	1.40	0.1	0.11	1.4	1.40	0.1	0.09	1.2

Mut.I. = Mutagenic index = erythrocytes with micronuclei in dose group / erythrocytes with micronuclei in control

Control = Vehicle

P.contr = Positive control = endoxan

Conclusion:

Foramsulfuron did not induce micronuclei, i.e., was not clastogenic or aneugenic, in this mouse bone marrow erythrocyte micronucleus test.

***In vivo* rat hepatocyte unscheduled DNA synthesis (OECD TG 482)**

Material and Methods:

In the preliminary USD test four males were given a single oral gavage dose of 2000 mg/kg bw by gavage and observed for 4 days for mortality or clinical signs of toxicity. The vehicle used for the test substance was 1% w/v aqueous methyl cellulose. For the main test, groups of 8 males were given a single gavage dose of either 600 or 2000 mg/kg bw in aqueous 1% w/v methyl cellulose. The negative control group was given the vehicle only. The two positive control groups, each consisting of 2 male rats, were given a single gavage dose of either 4 mg dimethylnitrosamine/kg bw (2-h sampling time) or 50 mg 2-acetylaminofluorene/kg bw (14-h sampling time). In all cases the dose volume was 10 ml/kg bw. The highest dose level, 2000 mg/kg, was selected in the absence of clinical signs and mortality in the preliminary test. It is also the limit dose recommended in the OECD and EEC testing guidelines for acute oral toxicity testing.

Groups of 4 rats from each of the negative control and foramsulfuron-treated groups were sacrificed 2 and 14 hours post dosing together with all animals from the relevant positive control group. Following perfusion and subsequent excision of the liver, isolated hepatocytes were prepared and suspended in Williams' medium E, complete (WEC). A viable cell count was performed after diluting an aliquot of the cells with an equal volume of trypan blue. The cell yield was also calculated.

Twelve replicate cultures of the isolated hepatocytes from each animal were established in multi-well plates, each well containing a glass coverslip and Williams' medium E supplemented with 10% foetal calf serum (WEC). They were incubated for 90 minutes at 37 °C and in a humid atmosphere of 5% CO_2 to allow the cells to attach to the coverslip. The medium was then replaced with Williams' medium C

without foetal calf serum (WEI) containing high specific activity (methyl-^{3}H) thymidine at a final activity of 10 μCi/ml. Following 4 hours of incubation, the medium was replaced with 'cold' thymidine in WEI for a 24-hour 'chase' period. The coverslips were then removed from the culture medium, given three 5-minute washes in Hanks' balanced salts solution then fixed in 2.5% v/v acetic acid in ethanol and allowed to dry. They were then mounted on glass microscope slides. Autoradiographs were prepared from six cultures per animal per dose level and sampling point. These slides were then randomised and grain count analysis conducted on three slides per animal using image analysis. A total of 150 (50 from each of 3 cultures per animal) hepatocytes were scored for the foramsulfuron-treated animals. Only 75 cells for the positive controls were examined because of evident cell toxicity. Only results from hepatocytes not in S-phase with normal morphology (i.e., not pyknotic or lysed) without staining artifacts or debris were recorded. For each cell the number of silver grains overlying the nucleus was estimated then the number of grains in an equivalent sized, most heavily grained adjacent area of cytoplasm was scored. The net nuclear grain count was derived by subtracting the cytoplasmic grain count from the gross nuclear grain count. For slides with a strong response, i.e., the mean net grain count was above 10, only 25 cells were examined. The number of cells with a net grain count greater than or equal to 5 was recorded in the raw data. Both gross and net nuclear grain counts for treated animals were compared with the vehicle control counts statistically (one-way analysis of variance followed by a Student's t test with appropriate transformation if necessary).

Findings:

Preliminary toxicity test:

No mortality and no clinical signs of toxicity were observed in animals treated with 2000 mg/kg body weight.

Main UDS test:

No mortality and no clinical signs of toxicity were observed in either the preliminary or the main toxicity test in animals treated with foramsulfuron.

There were no significant increases in the gross or net nuclear grain count at either dose level of foramsulfuron at either the 2- or 14-hour sampling times. Grain counts were similar to the vehicle control values and were within the historical control values.

Animals treated with the positive controls dimethylnitrosamine and 2-acetylaminofluorene showed a significant increase ($P<0.001$) in the net nuclear grain count and accompanying substantial increases in the gross nuclear grain count. Values were comparable with those from previous studies. Therefore the sensitivity of the test was confirmed.

Table 53 Results for the 2-hour expression time

Test substance	Dosage (mg/kg)	Gross nuclear grain count					Cytoplasmic grain count			Net nuclear grain count				
		x^1	x^2	x^3	Mean/animal	Mean/group	x^1	x^2	x^3	x^1	x^2	x^3	Mean/animal	Mean/group
Vehicle	-	16.6	16.6	16.3	16.5	**16.5**	19.0	18.4	18.6	-2.4	-1.8	-2.3	-2.2	**-1.7**
		14.5	15.7	14.4	14.9		14.7	17.8	16.3	-0.2	-2.1	-1.9	-1.4	
		17.1	14.0	16.1	15.7		20.3	14.6	16.6	-3.2	-0.6	-0.5	-1.4	
		19.4	18.5	19.1	19.0		20.5	20.3	21.4	-1.1	-1.8	-2.2	-1.7	
HOE 130360	600	14.7	14.1	12.9	13.9	**15.3ns**	16.7	15.7	15.0	-2.0	-1.5	-2.1	-1.9	**-1.7ns**
		17.2	18.0	16.6	17.3		18.6	20.2	19.0	-1.4	-2.2	-2.4	-2.0	
		16.2	16.4	14.5	15.7		16.9	17.6	16.7	-0.8	-1.3	-2.2	-1.4	
		13.0	14.4	15.0	14.1		15.3	15.7	16.2	-2.3	-1.3	-1.2	-1.6	
	2000	15.9	14.3	15.2	15.1	**15.9ns**	17.0	15.4	16.9	-1.0	-1.0	-1.7	-1.2	**-1.7ns**
		15.6	15.7	18.1	16.5		18.5	16.9	19.0	-2.8	-1.2	-0.9	-1.6	
		14.5	17.8	18.6	17.0		18.7	17.5	20.0	-4.2	0.3	-1.4	-1.8	
		14.7	14.2	15.7	14.9		17.7	16.2	17.5	-3.0	-2.0	-1.8	-2.3	
Dimethyl-nitrosamine	4	51.0	52.1	47.8	50.3	**50.4****	19.9	19.8	20.3	31.1	32.3	27.5	30.3	**31.2****
		48.8	52.8	49.5	50.4		18.6	18.9	17.6	30.2	33.9	31.9	32.0	

x^1, x^2, x^3 Mean results for each replicate culture

Results of statistical analysis (one-way analysis of variance followed by a Student's *t* test with critical one-sided probability levels):

** P < 0.001 (highly significant)

* P < 0.01 (significant)

ns P > 0.01 (not significant)

For each cell examined, Net nuclear grain count = Gross nuclear grain count - Cytoplasmic grain count. An occasional apparent discrepancy of 0.1 net grains may occur due to rounding of mean values for presentation in the table.

Table 54 Results for the 14-hour expression time

Test substance	Dosage (mg/kg)	Gross nuclear grain count					Cytoplasmic grain count			Net nuclear grain count				
		x^1	x^2	x^3	Mean/animal	Mean/group	x^1	x^2	x^3	x^1	x^2	x^3	Mean/animal	Mean/group
Vehicle	-	15.7	14.6	16.4	15.6	**16.4**	18.0	18.7	18.2	-2.4	-4.1	-1.8	-2.8	**-3.2**
		15.8	15.6	14.6	15.3		18.3	18.9	17.8	-2.5	-3.3	-3.2	-3.0	
		15.9	21.7	19.0	18.9		18.1	24.2	21.9	-2.1	-2.6	-2.9	-2.5	
		15.2	15.3	16.2	15.6		19.1	20.5	20.6	-3.9	-5.3	-4.4	-4.5	
HOE 130360	600	12.7	16.9	15.8	15.1	**16.7ns**	15.5	19.5	17.0	-2.8	-2.5	-1.2	-2.2	**-2.8ns**
		20.0	19.9	18.7	19.5		22.8	22.5	21.7	-2.8	-2.6	-3.0	-2.8	
		14.5	16.5	16.3	15.8		18.9	19.8	19.3	-4.4	-3.3	-3.0	-3.6	
		15.8	16.3	17.1	16.4		18.7	18.2	19.8	-2.9	-1.8	-2.7	-2.5	
	2000	14.2	12.9	15.7	14.3	**14.8ns**	17.7	15.1	17.9	-3.5	-2.3	-2.3	-2.7	**-3.6ns**
		15.8	17.4	14.2	15.8		19.4	20.3	18.2	-3.6	-2.9	-4.0	-3.5	
		16.7	14.8	13.9	15.1		21.1	20.0	18.3	-4.5	-5.2	-4.4	-4.7	
		12.6	14.2	15.0	13.9		15.3	18.2	18.4	-2.7	-4.1	-3.5	-3.4	
	50	55.0	48.4	45.0	49.5	**45.5****	25.2	24.6	22.5	29.8	23.8	22.5	25.4	**22.9****

2-Acetyl-aminofluorene		42.4	43.7	38.4	41.5		22.6	22.8	18.2	19.8	21.0	20.1	20.3	

x^1, x^2, x^3 Mean results for each replicate culture

Results of statistical analysis (one-way analysis of variance followed by a Student's *t* test with critical one-sided probability levels):

** $P < 0.001$ (highly significant)

* $P < 0.01$ (significant)

ns $P > 0.01$ (not significant)

For each cell examined, net nuclear grain count = gross nuclear grain count - cytoplasmic grain count. An occasional apparent discrepancy of 0.1 net grains may occur due to rounding of mean values for presentation in the table.

Conclusion:

Foramsulfuron did not cause unscheduled DNA synthesis (indicative of DNA repair) in rat hepatocytes following *in vivo* oral treatment with up to 2000 mg/kg, the internationally accepted dose limit for such studies.

10.8.1 Short summary and overall relevance of the provided information on germ cell mutagenicity

The genotoxic potential of foramsulfuron was evaluated in tests which examined gene mutation in bacteria and mammalian cells, chromosome damage *in vitro* and *in vivo* and DNA damage in mammalian cells *in vivo.* There were no significant deviations from the followed guidelines so that all studies were acceptable. Although the Ames test is from 1996, five bacterial strains, including *Escherichia coli* strain WP2 uvrA were used, which is currently required by the OECD guideline. All studies were negative, with the only exception of a slightly increased incidence of chromosomal aberrations observed in an *in vitro* assay with human lymphocytes. However, the increased incidences occurred only at the highest dose level tested, 2400 µg/mL which showed precipitation and some degree of cytotoxicity, and only in the absence of exogenous metabolic activation. Furthermore, the number of aberrant cells at the high dose level of 2400 µg/mL, was only just outside the historical control range. Since this slight increase occurred at a precipitating and apparently cytotoxic dose and only in the absence of exogenous metabolic activation, this result has no relevance for in vivo conditions. Therefore, and since there was no evidence of chromosomal damage in vivo, and in view of the negative test result obtained in the in vivo assay for unscheduled DNA synthesis, this isolated positive test result is considered to be a spurious in vitro effect which has no relevance for in vivo conditions. Overall therefore, the weight of evidence suggests that foramsulfuron is of no genotoxic concern.

10.8.2 Comparison with the CLP criteria

The results of the available *in vivo* tests are both negative. No in vivo gene mutation tests are available, but both in vitro studies for gene mutation were negative. Thus the criteria for Category 1A or B classification is not fulfilled. Also classification in Category 2 is not justified based on the available *in vitro* tests or *in vivo* mammalian somatic cell chromosomal aberration or genotoxicity tests. According to CLP, a classification for germ cell mutagenicity category 2 is based on positive somatic cell mutagenicity tests i*n vivo*, in mammals, or other positive *in vivo* somatic cell genotoxicity tests which are supported by positive results from *in vitro* mutagenicity assays, or positive *in vitro* mammalian mutagenicity assays for substances which also show chemical structure activity relationship to known germ cell mutagens.

Based on the genotoxicity results with foramsulfuron, the aforementioned classification criteria are not met. Classification criterion for substances which show chemical structure activity relationship to known germ cell mutagens is also not met since foramsulfuron does not have a chemical structure which would suggest an activity relationship to known germ cell mutagens.

10.8.3 Conclusion on classification and labelling for germ cell mutagenicity

No classification is proposed concerning mutagenicity.

RAC evaluation of germ cell mutagenicity

Summary of the Dossier Submitter's proposal

In vitro, foramsulfuron did not induce gene mutation in bacteria or in mammalian cells (Chinese hamster lung V79 cells). However, it was clastogenic *in vitro* in the absence of S9 mix following 21 h or 45h harvest but not in presence of S9 mix. The DS considered that the positive *in vitro* findings had no relevance *in vivo* as they were only observed at the top dose of 2400 µg/ml, in presence of precipitation and in presence of some degree of cytotoxicity. Moreover, *in vivo*, foramsulfuron did not induce micronuclei in the mouse bone marrow erythrocyte micronucleus test at doses up to 2000 mg/kg bw. Foramsulfuron did not cause unscheduled DNA synthesis in rat hepatocytes following *in vivo* oral treatment with doses up to 2000 mg/kg bw.

All the studies were carried out in accordance with OECD test guidelines. No major shortcomings were noted in the studies.

Overall, the DS considered that **no classification for germ cell mutagenicity is warranted for foramsulfuron.**

Comments received during consultation

One industry representative communicated support for the DS's proposal.

Assessment and comparison with the classification criteria

In vitro data

The outcome of two independent bacterial gene mutation assays were negative. The tests were equivalent to OECD TG 471 and they were performed according to GLP (1996 KCA5.4.1/01). Foramsulfuron was cytotoxic in all tested *S. typhimurium* strains with and without metabolic activation. One limitation was noted by RAC as only 2-aminoanthracene was used as positive control with metabolic activation whereas at least a second positive control is recommended in the test guideline. RAC considered this negative study reliable with limitations.
Foramsulfuron was negative in an *in vitro* gene mutation assay in mammalian cells, conducted according to OECD TG 476.

With regard to the *in vitro* chromosomal aberration study in human lymphocytes, the study was similar to OECD TG 473 but no short-term exposure was performed without S9 mix. As noted by the DS, this is not considered to be a major limitation as a long-term treatment was performed. At the top dose of 2400 µg/l, some precipitation was noted at 21-h harvest. At this dose, an increase in aberrant cells excluding gaps was noted and repeated in three out of four assays (21h or 45h harvest times). RAC considers that cytotoxicity was not high

at this dose; a reduction of about 50 percent of cell growth was not exceeded. The increase was slightly above the historical control data. Nevertheless, according to the DS, the historical control data may not be reliable due to missing information on the underlying studies. Overall, RAC considers the assay positive in the absence of S9 mix and negative in the presence of metabolic activation.

In vivo data

In vivo, negative results were obtained in a micronucleus test performed in mice. The study was performed according to OECD TG 474 (GLP-compliant) by oral gavage at the limit dose of 2000 mg/kg bw. The study was acceptable with a minor limitation as a low number of polychromatic erythrocytes were scored (1000 instead of 2000 recommended in the current OECD TG 474).

With regards to bone marrow exposure, there was no direct evidence of bone marrow exposure in the study:

- No alteration of PCE:NCE ratio was observed;
- No clinical signs or macroscopic findings were noted in the study.

There was also limited evidence of systemic toxicity:

- In the 28-day and 90-day toxicity studies in mice, no toxicity was observed up to doses around 1000 mg/kg bw/day,
- In the ADME studies, low levels of radioactivity detected in plasma and bone marrow suggest bone marrow exposure. Nevertheless, RAC notes that ADME studies were only available in rats.

Overall, RAC considers that there is limited evidence of bone marrow exposure.

A negative outcome was also obtained in an *in vivo* rat hepatocyte unscheduled DNA synthesis. Four male rats were given a single gavage dose of 2000 mg/kg bw foramsulfuron. There was no proof of liver exposure reported in the study. In the ADME studies, low level of radioactivity was detected in plasma and liver suggestive of liver exposure in rats.

RAC notes that the *in vivo* studies had only limited evidence of target organ exposure. RAC agrees with the DS that based on the negative results observed in the *in vivo* studies, **no classification fpr germ cell mutagenicity is warranted** according to the CLP criteria.

10.9 Carcinogenicity

Table 55: Summary table of animal studies on carcinogenicity

Method, guideline, deviations if any, species, strain, sex, no/group	**Test substance, dose levels duration of exposure**	**Results**	**Reference**
2-year chronic toxicity/ oncogenicity OECD TG 453, 1981 EU: 88/302/EEC, USEPA: 83-5, JMAFF: 422 Rat: Sprague Dawley CRL:CD (IGS) BR 70/sex/group	Foramsulfuron purity: 94.6% (w/w) 0, 100, 600, 6000 and 20000 ppm corresponding to 0, 5, 25, 246 and 849 mg/kg bw/d in males 0, 6, 34, 339, and 1135 mg/kg bw/d in females	**<u>Non-neoplastic findings</u>** **At 52 weeks:** <u>20000ppm</u> **Thyroid hypertrophy of the follicular epithelium**, males, 7/20 (35%); 5/20 (25%) in controls; HCD 0-25% **Pituitary focal hyperplasias-pars distalis,** females, 7/20 (35%); 5/20 (25%) in controls; HCD 0-30% **At the end of study:** <u>20000 ppm</u> **Reduced or absent spermatozoa (severe) in epididymides** 9/50 (18%); 6/50 (12%) in controls, HCD 2-12% **Endometrial stromal polyps** 10/50 (20%); 6/50 (12%) in controls, 5/20 (25%), HCD 0-12% **Pituitary cysts**, males 7/50 (14%), control 3/50 (6%), HCD 0-6% <u>6000 ppm</u> **Reduced or absent spermatozoa (severe) in epididymides** 8/50 (16%) **<u>Neoplastic findings</u>** All neoplastic findings were statistically insignificant <u>Tumour incidences at 0, 100, 600, 6000 and 20000 ppm</u> Males (n=50) **Astrocytoma (brain and spinal cord)** 2%, 2%, 4%, 6%, 2% (HCD: 0-2%) **Malignant lymphoma** 0%, 0%, 2%, 2%, 4% (HCD 0-2%)	dRAR B.6.5.1; year 2000

Method, guideline, deviations if any, species, strain, sex, no/group	**Test substance, dose levels duration of exposure**	**Results**	**Reference**
		Thyroid follicular cell adenoma 4%, 2%, 0%, 0%, 8% (HCD 2-4%) **Thyroid follicular cell carcinoma** 2%, 2%, 0%, 0%, 0% (HCD 0-4%) **Thyroid c cell adenoma** 22%, 32%, 10%, 28%, 22% (HCD 10-22%) **Thyroid c cell carcinoma** 0%,0%,4%,0%,4% (HCD 0-2%) Females (n=50) **Astrocytoma (brain and spinal cord):** 2%, 0%, 2%, 0%, 6% (HCD 0-2%) **Malignant lymphoma** 0%, 0%, 4%, 0%, 2% (HCD 0-5%) **Thyroid follicular cell adenoma** 0%, 0%, 2%, 2%, 2% (HCD 0-2%) **Thyroid follicular cell carcinoma** 0%,0%,2%,4%,2%, (HCD 0%) **Thyroid c cell adenoma** 12%,12%,20%,12%,22% (HCD 4-22%) **Thyroid c cell carcinoma** 0%,2%,2%,0%,0% (0-2%)	
Mouse dietary oncogenicity study OECD TG 451, 1981, US EPA FIFRA 83-2, 1985 JMAFF 59, 1985 Mice:Crl:CD-1(OCR)BR 51 sex/group	Foramsulfuron, purity: 96.4 (w/w) 0,40,800 and 8000 ppm corresponding to 0, 5, 109 and 1115 mg/kg bw/d in males 0, 7, 134 and 1358 mg/kg bw/d in females	No clinical signs of toxicity and no treatment-related effects on survival, body weight, food consumption, haematology, organ weights or macroscopic findings. No microscopic non-neoplastic findings indicative of toxicity. No evidence of an increased incidence of any tumour or hyperplasia indicative of oncogenicity.	dRAR 6.5.2; year 1999

Method, guideline, deviations if any, species, strain, sex, no/group	**Test substance, dose levels duration of exposure**	**Results**	**Reference**
80 weeks			

Table 56: Summary table of human data on carcinogenicity

Type of data/report	**Test substance,**	**Relevant information about the study (as applicable)**	**Observations**	**Reference**
No evidence on carcinogenicity in humans				

Combined chronic toxicity and oncogenicity study in rats

2-year carcinogenicity study in rats (dRAR 6.5.1) was performed according to OECD TG 453 without deviations. Groups of rats were subjected to continuous dietary treatment of foramsulfuron with dose levels of 0, 5, 25, 246 and 849 mg/kg bw/d in males 0, 6, 34, 339 and 1135 mg/kg bw/d in females.

Animals were observed daily for mortality and clinical signs. They were given a detailed physical examination, which included palpation for masses, at weekly intervals immediately prior to weighing. Individual body weights were recorded immediately prior to the start of treatment, at weekly intervals to week 14, every second week thereafter and at necropsy. Food consumption was measured weekly for the first 13 weeks of treatment and approximately every four weeks thereafter.

Ophthalmoscopy was conducted on all animals prior to the start of treatment, on all animals in the control and highest dose group in week 52 and on all surviving animals prior to termination (month 24).

Blood samples for biochemistry and haematology and samples of urine for analysis were obtained from numerically the first ten surviving rats of each sex in each group at 3, 6, 12, 18 and 24 months.

After 52 weeks of treatment, the first 20 surviving animals of each sex and dose level were sacrificed for assessment of chronic toxicity; survivors remaining after 104 weeks were assessed for oncogenic potential.

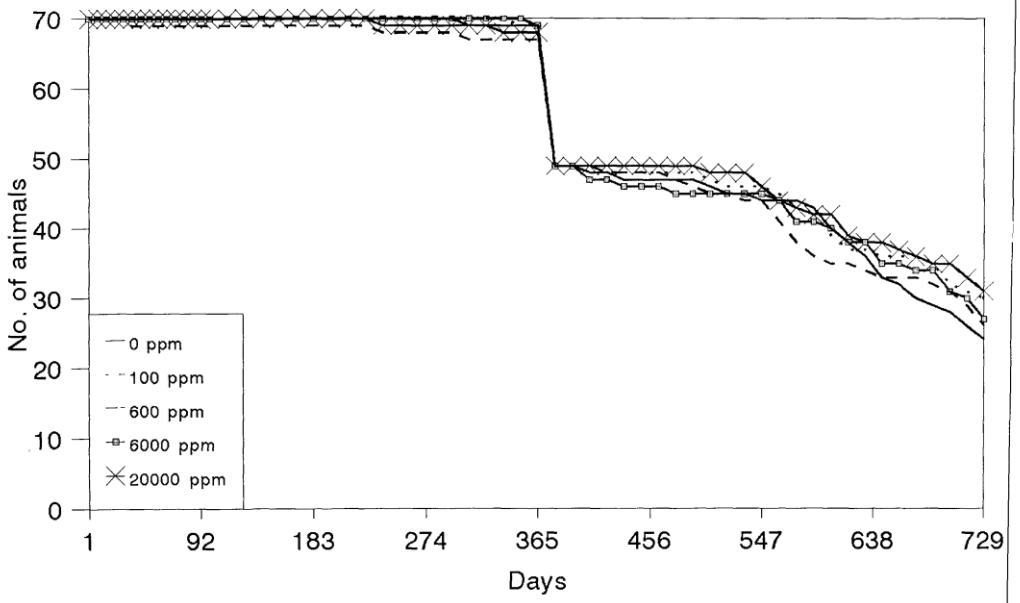
All animals, including decedents, were necropsied. Each animal was examined thoroughly for macroscopic abnormalities, the weights of discrete organs recorded and an extensive range of tissues preserved. A bone marrow smear was also prepared from all animals except decedents. Subsequently all tissues from all decedents and animals surviving to the scheduled necropsy were examined histopathologically.

Results

Incidence of mortality at 24 months was 26/50, 20/50, 24/50, 27/50 and 20/50 for males and 31/50, 19/50, 34/50, 30/50 and 23/50 for females at 0, 100, 600, 6000 and 20000 ppm, respectively. There were no treatment-related effects on survival (Figures 1.2 and 1.3), clinical signs of toxicity, effects on palpable masses body weight, food consumption, biochemistry, haematology, urinalysis, organ weights or macroscopic findings.

Figure 1.2

GROUP SURVIVAL - MALES



TOX 96119

Interim kill after 1 year

AgrEvo

A company of Hoechst and Schering

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Report No. TOX/99/262-42

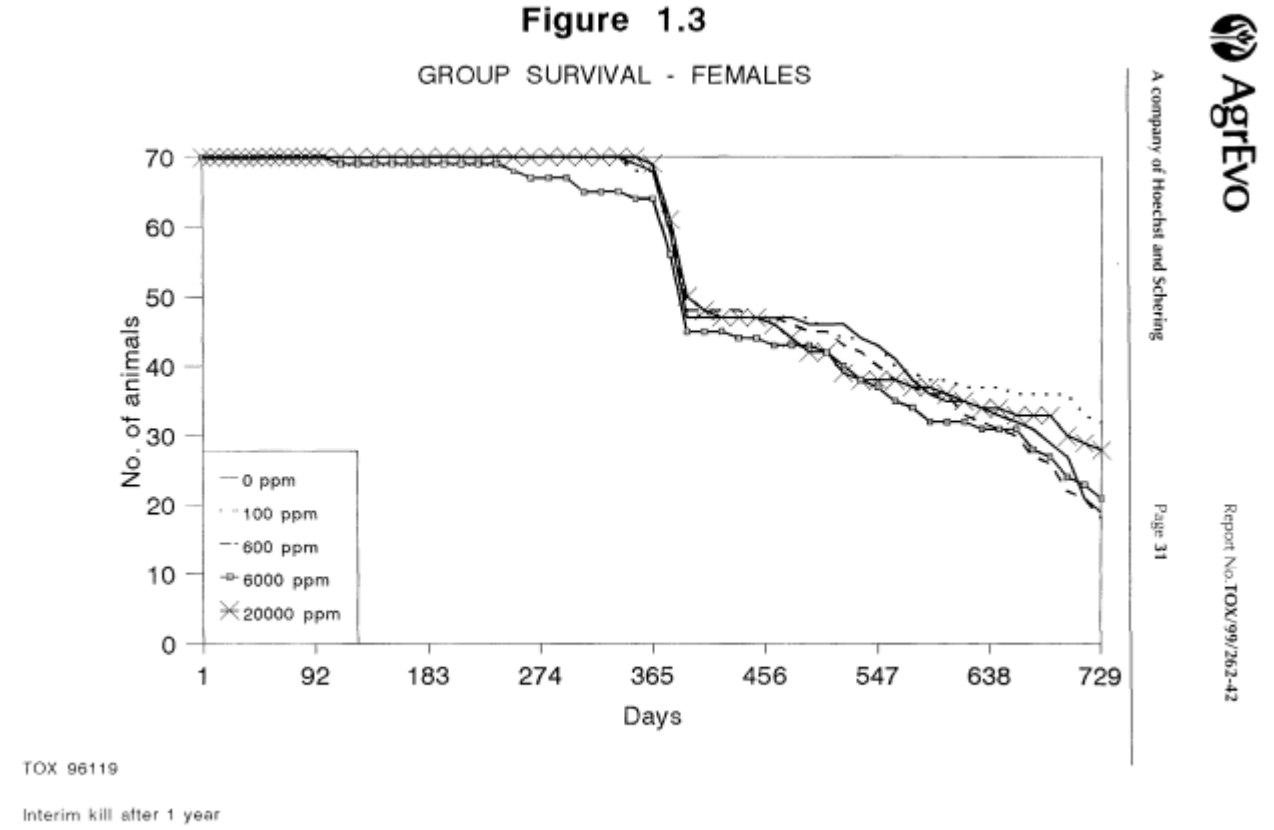


Table 57 Non-neoplastic microscopic findings at interim kill (after 1 year)

Findings/dose	0 ppm	100 ppm	600 ppm	6000 ppm	20000 ppm	HCD
Males						
Pituitary focal hyperplasia-pars distalis	2/20 10%	6/20 30%	1/20 5%	4/20 20%	2/20 10%	0-35%
Thyroid hyperthrophy of the follicular epithelium, total	5/20 25%	6/20 30%	7/20 35%	10/20 50%	7/20 35%	0-25%
Females						
Pituitary focal hyperplasia-pars distalis	5/20 25%	7/20 35%	5/20 25%	7/20 35%	7/20 35%	0-30%
Thyroid hyperthrophy of the follicular epithelium, total	0/20 0%	0/20 0%	0/20 0%	0/20 0%	0/20 0%	0%

An increased number of thyroid hypertrophy of follicular epithelium was observed in all males after 1 year of treatment as compared to control group.

A slight increase in the number of pituitary focal hyperplasia was detected in females in the groups of 100 ppm, 6000 ppm and 20000 ppm. The frequencies exceeded the HCD.

Table 58 Non-neoplastic microscopic findings at terminal kill

Findings/dose	**0 ppm**	**100 ppm**	**600 ppm**	**6000 ppm**	**20000 ppm**	**HCD**
Males						
Epididymides, reduced or absent	10/50 20%	9/50 18%	5/50 10%	9/50 18%	13/50 26%	6-20%
Epididymides, reduced or absent, severe	6/50 12%	5/50 10%	4/50 8%	8/50 16%	9/50 18%	2-12%
Pituitary cyst	3/50 6%	3/50 6%	3/50 6%	3/50 6%	7/50 14%	0-6%
Pituitary focal hyperplasia-pars distalis	11/50 22%	15/50 30%	11/50 22%	13/50 26%	10/50 20%	10-32%
Females						
Pituitary cyst	2/50 4%	3/50 6%	5/50 10%	1/50 2%	1/50 2%	0-2%
Pituitary focal hyperplasia-pars distalis	4/50 8%	6/50 12%	6/50 12%	8/50 16%	7/50 14%	6-22%
Uterus, stromal polyp	6/50 12%	7/50 14%	6/50 12%	5/50 10%	10/50 20%	0-12%

An elevated incidence of pituitary cysts in males at the top dose is outside the HCD and is considered treatment related.

Regarding pituitary hyperplasia, both sexes exhibited increased incidences, but within the range of HCD.

Effects on epididymides in males were seen at the highest dose level. The elevations are above the range of HCD.

Increased incidences of endometrial stromal polyps were observed at the top dose group of females. The elevation exceeds the upper limit of HCD.

Neoplastic findings and historical control data

Increased incidences of astrocytomas (brain+spinal cord), lymphomas, thyroid follicular and c cell tumours were seen in treated animals as compared to concurrent controls. The incidences were statistically non-significant.

The rat carcinogenicity study was performed during period of 12/96-12/98. Historical control data (HCD) from studies performed in the testing laboratory and covering a 5-year period before the study was available from four studies on 200 animals of the same breed. The studies are considered valid for use as of HCD in the study of foramsulfuron.

1. Astrocytomas, brain and spinal cord

Table 59 Incidences of astrocytomas, brain + spinal cord at terminal kill

Group/dose ppm	0	100	600	6000	20000	HCD
Males	1/50 2%	1/50 2%	2/50 4%	3/50 6%	1/50 2%	0-2%*
Females	1/50 2%	0/50 0%	1/50 2%	0/50 0%	3/50 6%	0-2%*

*HCD is for astrocytoma of brain. Range of incidence of astrocytoma of spinal cord (0-1.3%) according to Nagatani et al. 2013.

One case of astrocytoma was diagnosed in both male and female controls. Males at dose level of 600 ppm showed two and at 6000 pm three astrocytomas. In the high-dose group one case was diagnosed. Females of the high dose group exhibited three cases. No dose-relationship can be seen in male and female groups.

Table 60 Incidences of astrocytomas, brain + spinal cord at interim kill

Group/dose ppm	0	100	600	6000	20000
Males	0/20	0/20	0/20	1/20	0/20
Females	0/20	1/20	0/20	0/20	0/20

One male at the top dose and one female at the lowest dose were diagnosed with spinal cord astrocytoma.

In the combined group of both sexes from interim and terminal kill a dose-response relationship can be seen: Control: 2/140, 100 ppm: 2/140, 600 ppm: 3/140, 6000 ppm: 4/140, 20000 ppm: 4/140 reflecting a possible treatment-related effect.

Table 61 Age (days) at detection of astrocytomas (brain and spinal cord).

Group/dose	Males	Females
Control	752	702
100 ppm	498	380
600 ppm	599, 720	508
6000 ppm	375, 567,696,752	-
20000ppm	604	407,714,750

Mean of treatment groups	601	552

Among treatment groups a reduced latency period compared to controls was observed (Table 61). The mean age of both sexes were lower than that of controls. The latency periods for astrocytomas diagnosed in control SD rats in the publication of Nagatani et al. 2013 were as follows: males (n=34), range 371-773, females (n=20) 350-771. It can be concluded that the involvement of foramsulfuron treatment to the age of astrocytoma incidence is unclear.

2. Malignant lymphoma

Table 62 Incidences of malignant lymphomas at terminal kill

Group/dose ppm	0	100	600	6000	20000	HCD
Males	0/50 0%	0/50 0%	1/50 2%	1/50 2%	2/50 4%	0-2%
Females	0/50 0%	0/50 0%	2/50 4%	0/50 0%	1/50 2%	0-5%

In males at the top dose level the incidence of lymphomas was elevated when compared to concurrent control and HCD. In females the incidences were within the HCD range.

Table 63 Incidences of malignant lymphomas at interim kill

Group/dose ppm	0	100	600	6000	20000
Males	0/20	0/20	1/20	0/20	0/20
Females	0/20	0/20	0/20	1/20	0/20

One male at 600 ppm and one female at 6000 ppm was diagnosed with lymphoma at interim kill.

3. Thyroid follicular cell tumours

3.1. Thyroid follicular cell adenomas

Table 64 Incidences of thyroid follicular cell adenomas at terminal kill

Group/dose ppm	0	100	600	6000	20000	HCD
Males	2/50	1/50	0/50	0/50	4/50	2-4%

	4%	2%	0%	0%	8%	
Females	0/50 0%	0/50 0%	1/50 2%	1/50 2%	1/50 2%	0-2%

The incidence of thyroid follicular cell adenomas at high dose group of males exceeds the level of laboratory 5-year HCD without a dose-response relationship.

Table 65 Incidences of thyroid follicular cell adenomas at interim kill

Group/dose ppm	**0**	**100**	**600**	**6000**	**20000**
Males	0/20	1/20	0/20	0/20	0/20
Females	0/20	0/20	0/20	0/20	0/20

The finding was observed in one male of the lowest dose group.

3.2. Thyroid follicular cell carcinomas

Table 66 Incidences of follicular cell carcinomas at terminal kill

Group/dose ppm	**0**	**100**	**600**	**6000**	**20000**	**HCD**
Males	1/50 2%	1/50 2%	0/50 0%	0/50 0%	0/50 0%	0-4%
Females	0/50 0%	0/50 0%	1/50 2%	2/50 4%	1/50 2%	0%

In female controls (concurrent and historical) did not show tumours. Among animals at dose levels 600 ppm, 6000 ppm and 20000 ppm showed 1-2 cases of follicular cell carcinomas without trend of dose-response.

Table 67: Incidences of thyroid follicular cell adenomas and carcinomas at terminal kill (combined)

Group/dose ppm	**0**	**100**	**600**	**6000**	**20000**	**HCD**
Males	3/50 6%	2/50 4%	0/50 0%	0/50 0%	4/50 8%	2-8%
Females	0/50 0%	0/50 0%	2/50 4%	3/50 6%	2/50 4%	0-2%

The combination of thyroid follicular adenomas and carcinomas in females showed elevations in incidences, which exceed HCD.

4. Thyroid c cell tumours

Table 68 Incidences of thyroid c cell adenomas at terminal kill

Group/dose ppm	0	100	600	6000	20000	HCD
Males	11/50 22%	16/50 32%	5/50 10%	14/50 28%	11/50 22%	10-22%
Females	6/50 12%	6/50 12%	10/50 20%	6/50 12%	11/50 22%	4-22%

Table 69 Incidences of thyroid c cell carcinomas at terminal kill

Group/dose ppm	0	100	600	6000	20000	HCD
Males	0/50 0%	0/50 0%	2/50 4%	0/50 0%	2/50 4%	0-2%
Females	0/50 0%	1/50 2%	1/50 2%	0/50 0%	0/50 0%	0-2%

In males a slight increase in the incidence of thyroid c cell adenomas at doses of 100 ppm and 6000 ppm and carcinomas at 600 ppm and 20000 ppm is observed. No dose-response trend can be seen but incidencies are above the HCD range.

Carcinogenicity study in mice

Carcinogenicity study in mice (dRAR 6.5.2) had been conducted according to OECD TG 451 without deviations. Groups of 51 male and 51 female CD-mice were given dietary concentrations of 0, 40, 800 or 8000 ppm of foramsulfuron for 80 consecutive weeks.

Animals were observed twice daily for morbidity and mortality. They were observed daily for clinical signs of toxicity and were given a detailed physical examination at weekly intervals, including palpation for masses. Individual body weights were recorded immediately prior to the start of treatment, at weekly intervals for the first 16 weeks, once every four weeks thereafter, and at necropsy. Cage group food consumption was measured weekly for the first 16 weeks of treatment, then once in every four weeks thereafter. A blood smear was prepared from all animals at weeks 52 and 53. Blood samples were obtained from numerically the first ten mice of each sex in each group at necropsy and the white blood cell count determined. However, practical difficulties meant that the count was actually scored in 8 to 10 per sex per group, apart from in females from the intermediate dose group where only 5 were evaluated. Blood smears were also taken from all animals at the scheduled terminal necropsy but were not examined. All animals, including decedents were necropsied. Each animal was examined thoroughly for macroscopic abnormalities, the weights of adrenals, brain, heart, kidney, liver, spleen and testes (incl. epididymides) were recorded and an extensive range of tissues preserved. Subsequently tissues from all animals, including decedents, were examined histopathologically. Bone marrow smears were also examined from all of the terminal sacrifice animals.

There were no clinical signs of toxicity and no treatment-related effects on survival, body weight, food consumption, haematology, organ weights or macroscopic findings.

Table 70: Neoplastic findings

Findings/dose (ppm)	0	40	800	8000

Males				
Harderian gland adenoma	3/51	4/51	5/50	5/50
Lung alveolar adenoma	5/51	10/51	13/51	7/51
Lung alveolar carcinoma	2/51	0/51	3/51	0/51
Findings/dose (ppm)	**0**	**40**	**800**	**8000**
Females				
Uterus haemangioma	1/51	1/51	2/51	0/50
Uterus leiomyoma	1/51	0/51	3/51	1/50
Uterus histiocytic sarcoma	0/51	1/51	2/51	2/51
Lung carcinoma	1/51	1/51	1/51	2/51

Table 71: Non-neoplastic microscopic findings

Findings/dose (ppm)	**0**	**40**	**800**	**8000**
Males				
Spleen lymphoid hyperplasia	2/50	7/51	9/51	5/50
Pancreas lobular atrophy	0/49	1/51	1/50	3/50
Pancreas islet cell hyperplasia	3/49	2/51	8/50	1/50
Thyroid, cystic follicles	22/51	22/51	25/51	29/51
Pituitary focal hyperplasia	0/50	4/50	0/51	2/51
Lacrimal gland atrophy	3/51	4/50	3/51	8/51
Findings/dose (ppm)	**0**	**40**	**800**	**8000**
Females				
Mammary gland acinar hyperplasia	1/51	3/48	5/50	4/51
Spleen lymphoid hyperplasia	8/49	17/50	9/51	8/50
Pancreas lobular atrophy	1/50	2/50	0/51	0/50
Pancreas islet cell hyperplasia	1/50	0/50	0/51	3/50

Pancreas inflammatory cell foci	1/50	6/50	4/51	3/50
Ovary, hemorrhage	2/51	5/51	7/51	9/51
Thyroid, cystic follicles	15/51	15/50	19/51	30/51
Pituitary focal hyperplasia	1/51	1/51	0/51	2/49
Lacrimal gland atrophy	2/50	3/51	6/48	1/51

The selected non-neoplastic and neoplastic findings in the mouse carcinogenicity study are shown in Table 70 and Table 71.

There were sporadic increases in the frequencies of few non-neoplastic effects and neoplasms in treated animals. However, it is considered that the changes in the tumor incidences are due to variability within the normal background ranges. No evidence of an increased incidence of any tumour or hyperplasia indicative of carcinogenicity was observed

5. **Information on mode of action and its relevance for humans**

Mutagenicity studies of foramsulfuron do not provide evidence of genotoxity.

No studies investigating cytotoxicity with growth stimulation, mitogenesis or immunosuppression is available for foramsulfuron.

The carcinogenesis process of thyroid follicular cells proceeds through stages which include thyroid cell hypertrophy, hyperplasia, and benign and sometimes malignant neoplasms. Conditions that result in stimulation of the thyroid can also result in stimulation of pituitary, with the development of hyperplastic and neoplastic changes (Hill et al. 1989). Indication of stimulation of thyroid follicular cells can be observed in the findings of the satellite group (interim kill at 1 year) with increased number of hyperthrophy of the follicular epithelium in all treated males. In clinical chemistry analyses or repeated dose toxicity studies elevated thyroid hormones, TSH, increased organ weight are not reported. A slight increase of pituitary hyperplasia is seen among treated females in the interim kill. However, at the end of the study, the frequencies of hyperplasia of pituitary gland in the treated animals in the carcinogenicity study were similar as in the control animals No increase in thyroid weight was observed in repeated-dose toxicity or in the carcinogenicity studies. Clear evidence on the involvement of hypothalamus-pituitary-thyroid axis MoA is lacking. In coclusion, there is no mechanistic data that raises doubt about human relevance of the observed tumours being not relevant to humans.

10.9.1 Short summary and overall relevance of the provided information on carcinogenicity

In the 2-year carcinogenicity study in rats, incidences of astrocytomas, thyroid tumours and malignant lymphomas were slightly increased when compared to concurrent and historical control levels. The findings were statistically insignificant. A slight dose-response relationship in astrocytomas can be identified when the

incidencies from bothe sexes and interim and terminal kills are combined.In astrocytomas a reduced latency as compared to concurrent controls was observed.

In the corresponding study in mice, no evidence of carcinogenicity was found.

Based on ADME foramsulfuron is rapidly eliminated from the body following absorption. After repeated administration at low dose the increases of foramsulfuron were elevated in male tissues as compared to the first dosing of the substance: brain (20 x increase), testes (15x), thyroid (10x) and heart (6.5x). Although the total amounts of radioactive residues of formasulfuron detected were low and accumulation in brain was found only in males (increased incidences of astrocytomas were seen in both sexes) it can be concluded that foramsulfuron can reach brain and thyroid tissue. Unfortunately data on repeated administration at high dose is lacking making it difficult to evaluate the magnitude of exposure of these tissues.

Table 72: Compilation of factors to be taken into consideration in the hazard assessment

Species and strain	Tumour type and background incidence	Multi-site responses	Progression of lesions to malignancy	Reduced tumour latency	Responses in single or both sexes	Confounding effect by excessive toxicity?	MoA and relevance to humans
Rat, Sprague-Dawley	Astrocytoma, brain and spinal cord 4% and 6% in males 600 and 6000 ppm, respectively 6% in females at 20000 ppm HCD: 0-2% (males) 0-2% (females)	Yes		A mean period of latency was lower than in concurrent control animals but within the reported range of control SD rats in the publication	Both sexes	No	MoA cannot be identified Tumour type is relevant to humans
Rat, Sprague-Dawley	Lymphoma 4% in males HCD: 0-2%	Yes			Males only	No	MoA cannot be identified Tumour type is relevant to humans
Rat, Sprague-Dawley	Thyroid follicular cell adenoma 8% in males at 20000 ppm HCD: 2-4%	Yes	No thyroid hyperplasias detected in the study		Adenomas in males only. However, increased incidence of carcinomas were observed in females	No	MoA cannot be identified Tumour type is relevant to humans

Species and strain	Tumour type and background incidence	Multi-site responses	Progression of lesions to malignancy	Reduced tumour latency	Responses in single or both sexes	Confounding effect by excessive toxicity?	MoA and relevance to humans
Rat, Sprague-Dawley	Thyroid follicular cell carcinoma 4% in females at 6000 and 20 000 ppm 2% in females at 600 ppm HCD: 0%	Yes			Carcinomas in females only. In males increased incidence of adenomas were observed.	No	MoA cannot be identified Tumour type is relevant to humans
Rat, Sprague-Dawley	Thyroid c cell carcinoma 4% in males at 600 ppm and 20000 ppm HCD: 0-2%	Yes	Yes		Males only	No	MoA cannot be identified Tumour type is relevant to humans

10.9.2 Comparison with the CLP criteria

According to CLP criteria, a substance is classified in Category 1A, if known to have carcinogenic potential for humans largely based on human evidence. Category 1A is not applicable for foramsulfuron, which lacks such evidence.

Classification in Category 1B, presumed to have carcinogenic potential for humans, may be derived from animal experiments for which there is sufficient evidence to demonstrate animal carcinogenicity. The sufficient evidence according to CLP guidance:

“a causal relationship has been established between the agent and an increased incidence of malignant neoplasms or of an appropriate combination of benign and malignant neoplasms in (a) two or more species of animals or (b) two or more independent studies in one species carried out at different times or in different laboratories or under different protocols. An increased incidence of tumours in both sexes of a single species in a well-conducted study, ideally conducted under Good Laboratory Practices, can also provide sufficient evidence. A single study in one species and sex might be considered to provide sufficient evidence of carcinogenicity when malignant neoplasms occur to an unusual degree with regard to incidence, site, type of tumour or age at onset, or when there are strong findings of tumours at multiple sites.” Category 1B is not applicable since malignant neoplasms occurred only in one species (rat) and one study. The substance is not genotoxic and no other relevant MoA could be shown. The elevations in incidences were low and statistically insignificant.

Classification in Category 2, suspected human carcinogen, is done on the basis of evidence obtained from human and/or animal studies, but which is not sufficiently convincing to place the substance in Category 1A

or 1B, based on strength of evidence. Such evidence may be derived either from limited evidence of carcinogenicity in human studies or from limited evidence of carcinogenicity in animal studies. Limitations for making a definitive evaluation because, e.g (a) the evidence of carcinogenicity is restricted to a single experiment; (b) there are unresolved questions regarding the adequacy of the design, conduct or interpretation of the studies; (c) the agent increases the incidence only of benign neoplasms or lesions of uncertain neoplastic potential; or (d) the evidence of carcinogenicity is restricted to studies that demonstrate only promoting activity in a narrow range of tissues or organs.Strength of evidence in classification a substance as carcinogen involves the enumeration of tumours in human and animal studies and determination of their level of statistical significance.

Classification with Carc. 2; H351 is appropriate due to slight increase in the incidences of malignant astrocytomas in both sexes, lymphomas in males, thyroid follicular cell adenomas in males, thyroid follicular cell carcinomas in females and thyroid c cell adenomas and carcinomas in males in the rat carcinogenicity study. Although the possibility of a chance cannot be fully ruled out, positive association is interpreted to be in line with the CLP regulation: "A positive association has been observed between exposure to the substance and neoplasms for which a causal interpretation is considered to be credible, but chance, bias or confounding could not be ruled out with reasonable confidence. "

10.9.3 Conclusion on classification and labelling for carcinogenicity

Due to the slight increase in the incidences in malignant astrocytomas in both sexes, lymphomas and thyroid follicular cell adenomas, thyroid c cell adenomas and carcinomas in males and thyroid follicular cell carcinomas in females in the rat carcinogenicity study classification Carc. 2; H351 is proposed for foramsulfuron.

RAC evaluation of carcinogenicity

Summary of the Dossier Submitter's proposal

The assessment of carcinogenicity was based on two carcinogenicity studies performed in mice and rats.

The DS proposed to classify foramsulfuron as Carc. 2, H351. This was based on a weight of evidence analysis of the neoplastic findings observed in the rat carcinogenicity study:

- Increased incidence of malignant astrocytoma in both sexes,
- Increased incidence of malignant lymphoma in males,
- Increased incidence in thyroid follicular cell adenoma in males and thyroid follicular cell adenoma and/or carcinoma in females,
- Increased incidence in thyroid c cell carcinoma in males.

The DS noted that there was no mechanistic data providing evidence that these tumours would not be relevant to human. The DS considered that although the increases in tumour incidences were slight, a causal relationship between foramsulfuron and the observed tumours was plausible. As chance could not be fully ruled out, the DS proposed a category 2 as the most appropriate classification.

Comments received during consultation

One MSCA agreed with the DS's proposal.

One industry representative disagreed with the DS's proposal and considered that none of the tumours were treatment-related. They provided the following justification:

- Astrocytomas were due to normal biological variability within the normal background range. Moreover, preneoplastic findings such as gliosis or effects at other sites in the nervous system (e.g. spinal cord) should have been seen in the chronic study in case of a treatment-related effect. Industry also questioned the relevance of this tumour type in human.
- Malignant lymphomas were considered to lie within the historical control data range. Moreover, industry pointed out that reduced tumour latency was not seen and that the number of organs with malignant lymphoma metastasis were not increased with dose levels.
- Thyroid tumours were considered not treatment-related in the absence of dose-response and as no other findings on the hypothalamo-pituitary system were noted.
- Industry highlighted that no treatment-related effects were noted in total incidences of tumours.

In addition, industry representative provided an analysis of carcinogenicity of other compounds from the sulfonylurea class, QSARs analysis, ToxCast/Tox21 data and additional historical control data with the same strain of rats performed by other laboratories.

Assessment and comparison with the classification criteria

Two carcinogenicity assays were included in the CLH report, one in CD-1 mice (dRAR 6.5.2, 1999) and one in Sprague-Dawley CRL:CD(IGS)BR rats (dRAR B.6.5.1, 2000).

No evidence of an increased incidence of neoplastic lesions were found in mice.

In rats, 70 rats/group per sex received dietary foramsulfuron at 100, 600, 6000 or 20000 ppm (equivalent to 0, 4.5, 25, 246 and 849 mg/kg bw/day for males and 0, 5.6, 34, 339 and 1335 mg/kg bw/day for females). After week 52, 20 males and 20 females were necropsied for assessment of chronic toxicity. The remaining animals were sacrificed at termination after an exposure period of 104 weeks. The study was performed according to OECD TG 451 and was GLP-compliant.

In this study, there were no treatment-related effects on survival, clinical signs of toxicity, body weight, food consumption or organ weight.

Astrocytoma

An increased incidence of malignant astrocytoma (brain + spinal cord) was observed in both male and female rats. Brain and spinal cord astrocytomas at interim and terminal kills are reported in the tables below. No other findings in brain were seen in the chronic study. RAC notes that pre-neoplastic findings for this type of tumours may not be seen.

***Table**: Brain and spinal cord astrocytomas at interim kill*

Astrocytoma, brain + spinal cord at interim kill (Incidence, n=20/group)					
Dose (ppm)	**0**	**100**	**600**	**6000**	**20000**
Males					
Brain	0	0	0	1	0
Spinal cord	0	0	0	0	0
Females					
Brain	0	0	0	0	0
Spinal cord	0	1	0	0	0

***Table**: Brain and spinal cord astrocytomas at terminal kill*

Astrocytoma, brain + spinal cord at terminal kill (Incidence, %)					
Dose (ppm)	**0**	**100**	**600**	**6000**	**20000**
Males (n=50)					
Brain	1 2%	0	2 4%	3 6%	1 2%
Spinal cord	0	1 2%	0	0	0
Brain+spinal cord	1 2%	1 2%	2 4%	3 6%	1 2%
Females (n=50)					
Brain	1 2%	0	1 2%	0	3 6%
Spinal cord	0	0	0	0	0

Statistical significance and dose-response relationship

The increase was not statistically significant either in males or in females. RAC notes that as these tumours are rarely seen in controls, the absence of dose-response is not sufficient to exclude a treatment-related effect.

At terminal kill, a dose-response relationship was not observed in males and the increase in incidence was only noted at the top dose in females in brain.

The DS pointed out that considering the combined group of both sexes from interim and terminal kill, a dose-response relationship was seen: 2/140 in control, 2/140 at 100ppm, 3/140 at 600 ppm, 4/140 at 6000 ppm, 4/140 at 20,000 ppm. RAC agrees with the DS that this suggests a possible treatment-related effect.

Comparison with historical control data (HCD)

In the controls of the current study, one case of brain astrocytoma was observed in both males and females.

The study was performed during the period 12/96 to 12/98. Three sets of HCD were submitted.

HCD from the laboratory compiled the results of nine studies conducted between 1982 and 1998 with the same strain of rat, including the current study (2000, M-193439-01-1). As a 5-year period before the conduct of the study was considered as the most relevant time range, the DS considered the values obtained in four studies conducted before the current study (1995-1998), studies 6 to 9 in the table below, as valid. RAC agrees that studies 6-8 are relevant HCD studies, but excludes the current study from the HCD and considers two

additional studies performed between 1990-1992 as relevant HCD studies because they almost fit within the five-year range before the conduct of the present study. Still, RAC notes that the HCD are limited as only 5 studies are considered relevant. Brain astrocytomas were not seen in these relevant HCD studies, but they were only seen in one study of the laboratory conducted during years 1982-1984 (see the table below). Spinal cord astrocytomas were not reported.

***Table**: Historical control data for brain astrocytomas from the laboratory*

Study	1	2	3	4	5	6	7	8	9 (present study)
Start-end dates	82-84	82-84	85-87	90-92	90-92	95-97	95-97	96-98	96-98
Males	0/50	**1**/50	0/50	0/50	0/50	0/60	0/50	0/50	**1**/50
Females	0/50	**2**/50	0/50	0/50	0/50	0/60	0/50	0/50	**1**/50

Grey: data considered relevant for the present study

HCD published by Nagatani *et al.* (2013), were also provided in the dossier. The following values were given for the same strain of rat (studies performed between 1996 and 2009):

- Spinal cord astrocytoma: 0-1.3%, mean 0.1% (1 case in 29 studies in males and one case in 29 studies in females)
- Brain astrocytoma: 0-6.7% (mean: 2.1%) in males and 0-5% (mean: 1.2%) in females. Maximum of 4/60 or 4/75 cases of malignant astrocytomas per group were detected in two studies out of 29 studies in males and also in two studies in females (3/60 and 3/55 cases).

RAC considers HCD from Nagatani *et al.* (2013) of lower relevance than the laboratory HCD. These data support the HCD range provided in the dossier as the mean incidence for astrocytomas in brain+spinal cord was 1.2% in females and 2.1% in males. RAC notes that the studies in Nagatani *et al.* (2013) were performed with various vehicles and administrations (mostly by gavage) whereas the current study was performed by dietary administration. Nevertheless, the authors did not identify an influence of the vehicle on brain tumour incidence.

Additional historical control data were submitted during the consultation in the ECHA website. These HCD were compiled from studies conducted between 1992 and 1998 by other laboratories with the same strain of rats. The range of brain astrocytomas was between 0.87 and 4.29% in males and between 1.67 and 2.31 % in females. Mean values were not provided. RAC considers these HCD of lower relevance than the historical control data from the same laboratory, but notes that these HCD are in the same range as the HCD published by Nagatani *et al.* (2013).

***Table**: Summary of the available concurrent and historical control data for the same rat strain*

	Males	Females
Current study (controls)	1996-1998: 2%	1996-1998: 2%
Same laboratory	1982-1998: 0-2% 1990-1998: 0	1982-1998: 0-4% 1990-1998 : 0
Nagatani et al. (2013)	1996-2009 : 0-6.7%, mean 2.1%	1996-2009 : 0-5%, mean 1.2%
Compilation of data from other laboratories	1992-1998: 0.87-4.29%	1992-1998: 1.67-2.31%

Overall, historical control data suggest that some variability has been noted for this tumour type but that incidences were generally low. In addition, higher incidences were seen in males compared to females in Nagatani *et al.* (2013) and in the compilation of HCD from other laboratories. HCD also suggest that spinal cord astrocytomas are rarely seen.

In the current study, astrocytomas were seen in 3/50 females (6%) at 20000 ppm. The incidence exceeds the historical control range of all provided historical control data, suggesting that the effect may be treatment-related.

In males, no dose-response was observed, but the incidence (6%) at 6000 ppm was above the most relevant historical control data of the laboratory (maximum 4% over 1982-1998) or at the upper end of all available HCD.

Age at tumour detection and survival

At the interim kill, one case of astrocytoma was noted at 6000 ppm in males and one case at 100 ppm in females. No astrocytoma was noted in controls at interim kill.

The table below summarises the age at detection of astrocytomas (brain + spinal cord) at interim or terminal kill.

***Table**: The age (days) at detection of astrocytomas (brain + spinal cord)*

Group (ppm)	Males	Females
Control	752 (T)	702 (D)
100	498 (D)	380 (I)
600	599 (D); 720 (D)	508 (D)
6000	375 (I); 567 (D); 696 (D); 752 (T)	
20000	604 (D)	407 (D), 714 (D), 750 (T)
Mean of treatment groups	601	552

(D): decedent, astrocytoma was a factor contributory to death; (T): terminal kill, (I): interim kill

This table suggests that a reduced latency period was seen in the treatment groups compared to concurrent controls. Nevertheless, according to Nagatani *et al.* (2013), malignant astrocytomas were spontaneously observed at an age of more than 600 days (range: 371-773 in males and 350-771 in females). Therefore, RAC agrees with the DS that the effect of foramsulfuron on latency period is unclear.

In conclusion, RAC considers that brain + spinal cord astrocytomas occurring in both sexes are of concern. It is plausible that the effects are treatment-related taking into account the rare incidences in the laboratory controls in both sexes.

Thyroid follicular and c cell tumours

Thyroid follicular cell tumours

***Table**: Incidences of thyroid follicular cell tumours*

Thyroid follicular cell tumours (Incidence, %)						
Dose (ppm)	**0**	**100**	**600**	**6000**	**20000**	**HC[1]**
Males						
Adenoma	2/50 4%	1/50 2%	0	0	4/50 8%	2-4%
Carcinoma	1/50 2%	1/50 2%	0	0	0	0-4%
Females						
Adenoma	0	0	1/50 2%	1/50 2%	1/50 2%	0-2%
Carcinoma	0	0	1/50 2%	2/50 4%	1/50 2%	0

[1] Five studies in the testing laboratory and covering a 5-year period before the study (excluding the current study);

In males, an increase in thyroid follicular cell adenomas at the top dose was observed above the historical control data range. The increase was not statistically significant and no dose-response was noted. Although of lower relevance, the incidence was inside the HCD range considering data from 1982 to 1998 from the laboratory (0-8%). The incidence was also inside the HCD range in males (1.67-12%) provided for the same strain of rats in other laboratories (provided during the consultation). An increase in the number of thyroid hypertrophy of follicular epithelium was observed in all males after 1 year of treatment compared to controls, suggesting thyroid exposure. The increase was not observed at terminal kill. An increased incidence of pituitary cysts was also observed at the high dose and exceeded the historical control data range and is considered by RAC as treatment-related. RAC notes that no progression of lesions to carcinoma was noted in males, which decreases the concern.

In females, thyroid follicular cell carcinomas were slightly above the HCD range of the laboratory considering a 5-year range period. The increase was also outside the HCD range considering the time period 1982-1998 (0-2%). The increase was not statistically significant or dose-related. Incidences were limited to one case except at 6000 ppm were 2 cases were found. No preneoplastic findings such as hypertrophy and/or hyperplasia of the follicular cells were noted in females. There was no evidence of reduced latency period for these tumours. Although the slight increase in carcinoma may be of concern, the absence of dose-response, the very low incidences and the absence of concomitant increase in adenoma or other preneoplastic lesions in females raises uncertainties on the toxicological relevance of these lesions.

Overall, RAC considers the incidences of follicular cell adenomas in males and follicular cell carcinomas in females of low weight for classification.

C-cell tumours

As regards c-cell tumours, an increase in adenomas was noted in males above the HCD range at 100, 6000 and 12000 ppm. Nevertheless, no dose-response was noted and the increase was not statistically significant, as shown in the table below. However, the control values of the study were slightly above the historical control data range. In view of the high background

incidence in this strain of rats and the absence of statistical significance, the increase in c-cell adenomas in male rats is considered of uncertain toxicological relevance. As to the increase in carcinoma at 600 and 20000 ppm, the absence of dose-response and preneoplastic finding also raised uncertainties on their toxicological relevance.

***Table**: Incidences of thyroid c-cell tumours*

Thyroid c cell tumours (%)						
Dose (ppm)	**0**	**100**	**600**	**6000**	**20000**	**HC[1]**
Males (n=50)						
Adenoma	22%	32%	10%	28%	22%	10-18%
Carcinoma	0	0	4%	0	4%	0-2%

[1] Five studies in the testing laboratory covering a 5-year period before the study (excluding the current study).

Malignant lymphoma

An increase in malignant lymphoma was noted at the top dose in males. The incidence was slightly above the historical control data range but was not statistically significant. The incidences of malignant lymphomas are reported in the table below.

***Table**: Incidences of malignant lymphomas*

Malignant lymphoma (Incidence, %)						
Dose (ppm)	**0**	**100**	**600**	**6000**	**20000**	**HC[1]**
Males	0	0	1/50 (2%)	1/50 (2%)	2/50 (4%)	0-2%
Females	0	0	2/50 (4%)	0	1/50 (2%)	0-5%

[1] Five studies in the testing laboratory covering a 5-year period before the study (excluding the current study).

It may be noted that the incidences were inside historical control data range considering studies performed during years 1982-1998 (0-4%). Compiled data from the same strain of rats in studies conducted between 1992 and 1998 (by other laboratories) provide range of 0.91-6% for males (mean not provided). Although these data are of lower relevance than the historical control of the laboratory, potential variability in the background incidence of this tumour type is suggested.

The increase in malignant lymphoma in male rats is of concern. Nevertheless, in view of the very low incidence in males at the top dose and the absence of effect in females, the toxicological relevance of this tumour type in males is uncertain and can be considered of low weight for classification.

Mode of action and relevance to human

Foramsulfuron is not genotoxic. There is no data available in the dossier suggesting that the tumours observed in rats would not be relevant to human.

The toxicokinetic data on foramsulfuron indicates that foramsulfuron levels in male and female rat blood, plasma, brains and thyroids are low. Nevertheless, in the study KCA 5.1.1/06 (1999) with a 14-day exposure at a low dose (10 mg/kg bw/day), more than 3-fold increase in residue levels was found in thyroid and brain of males suggesting a potential exposure of these organs. In this study, male rats showed higher brain and thyroid levels of foramsulfuron than females

and may therefore be more sensitive for a tumorigenic effect on astrocytes or thyroid cells. This was not clear in this carcinogenicity study. Nevertheless, as highlighted by the DS, RAC notes that toxicokinetic data were not available following repeated-dose exposure at high dose levels.

Industry pointed out during the standard consultation that differences in reactivity for glial fibrillary acidic protein between rats and other species could question the relevance of this type of tumour to human. RAC considers that although some structural organization differences may exist, there is no data available to support that this type of tumour would not be relevant to human.

Structural similarity

Foramsulfuron is a sulfonylurea. Data on chemicals used in medicine against type-2 diabetes and on other agrochemicals from this class were provided by Industry during the consultation.

RAC considers that the data on these drugs is not relevant for foramsulfuron as their pharmacological properties and diabetes type 2 may confound with the interpretation of the results.

Industry representatives analysed the evidence of carcinogenic potential of other sulfonylureas used as pesticides. Draft assessment reports published by EFSA were used for this analysis. Results are summarised in the table below:

***Table*:** Carcinogenic potential of other sulfonylureas used as pesticides as analysed by industry representatives

Compounds	**Evidence of carcinogenic potential**
Bensulfuron, Ethamethsulfuron-methyl, halosulfuron, mesosulfuron-methyl, metsulfuron-methyl, rimsulfuron, triasulfuron	None
Chlorsulfuron	↑ Leydig cell tumours in rats
Prosulfuron	↑ Leydig cell tumours and mammary gland adenoma in rats
Trisulfuron-methyl	↑ Leydig cell adenoma in rats
Sulfosulfuron	↑ Transitional cell carcinoma and papilloma in female rats (low incidences) at the top dose. ↑ mesenchymal tumours in the urinary bladder of male mice at highest doses
Thifensulfuron-methyl	↑ Total tumour incidences (mainly due to mammary gland tumours) in female rats
Nicosulfuron	↑ liver adenoma in male mice

RAC notes that the analysis was only performed on a selected number of sulfonylureas used as herbicides. Indeed, amidosulfuron, orthosulfuron, flupyrsulfuron-methyl, tritosulfuron, ethoxysulfuron, azimsulfuron, tribenuron, imazosulfuron, iodosulfuron-methyl, oxasulfuron were not included in the analysis. Few of these compounds have an Annex VI entry in CLP and none of them had been classified for carcinogenicity (amidosulfuron, halosulfuron-methyl,

ethametsulfuron, sulfosulfuron, iodosulfuron-methyl, methsulfuron-methyl, triasulfuron, chlorsulfuron, prosulfuron, sulfosulfuron, thifensulfuron-methyl).

RAC agrees with industry that there is no one clear pattern of carcinogenicity for all sulfonylureas. Moreover, no increase in incidences of brain, thyroid or lymphatic system tumours were reported for other sulfonylureas based on the analysis by industry representatives.

A QSAR analysis was also provided during the consultation using Derek Nexus, Oncologic and the OECD QSAR toolbox. None of these tools flagged a carcinogenic alert for the substance. Data form ToxCast/Tox21 also did not indicate evidence of carcinogenic potential. RAC notes that no details were provided on these analyses. Nevertheless, RAC considers these data of lower weight than the available *in vivo* carcinogenicity studies provided on the substance.

Overall, RAC acknowledges that there are no evidence of a class-specific carcinogenic potential. Nevertheless, RAC considers that this does not invalidate the carcinogenicity data obtained specifically with foramsulfuron.

Comparison with criteria

As there is no evidence of carcinogenicity in human reported in the dossier, category 1A is not appropriate.

The main concern is raised by the increase in malignant brain and spinal cord astrocytomas in rats in both sexes. Spinal cord astrocytomas are rarely seen in this strain of rats. Nevertheless, the absence of dose-response in males, and low incidences raised some uncertainties on the toxicological relevance of the tumours. Therefore, RAC considers that astrocytoma provides limited evidence of carcinogenicity.

In addition, the increase in thyroid tumours in male and female rats and the increase in malignant lymphoma in male rats cannot be fully dismissed and support classification.

In conclusion, RAC agrees with the DS that **classification as Carc. 2, H351 is warranted for foramsulfuron.**

10.10 Reproductive toxicity

Table 73: Summary table of animal studies on adverse effects on sexual function and fertility

Method, guideline, deviations if any, species, strain, sex, no/group	Test substance, dose levels duration of exposure	Results	Reference
Two-generation reproductive toxicity study OECD TG 416 (1983). The study includes also	foramsulfuron, purity 96.1% (w/w) 0, 100, 1225, 15000 ppm (M: 0, 7, 82 and 1038 mg/kg bw/d; F: 0, 10, 115 and 1430 mg/kg	No treatment-related findings on parameters on sexual function and fertility (including oestrous cycling, balanopreputial separation, vaginal opening, spermatogenetic function and capacity).	RAR B.6.6.1, 1999

Method, guideline, deviations if any, species, strain, sex, no/group	Test substance, dose levels duration of exposure	Results	Reference
requirements of the guideline adopted in 2001. According to GLP Rat, Sprague Dawley Crl:CD (SD)BR 30/sex/dose Acceptable	bw/d) Continuous in diet through ≥ 70 days premating, mating, gestation and lactation periods up to lactation day 22.	No parental toxicity	

Table 74: Summary table of other studies relevant for toxicity on sexual function and fertility

Type of study/data	Test substance, dose levels duration of exposure	Observations	Reference
Combined chronic toxicity and oncogenicity study OECD TG 453 (1981) USEPA: 83-5 JMAFF : 4200 According to GLP No deviations from the guideline that would compromise validity of the study Rat, Sprague-Dawley 70/sex/dose(20 of them for chronic phase) Acceptable	foramsulfuron, purity: 94.6% (w/w) 0, 100, 600, 6000 or 20000 ppm (M: 4.5, 25, 246 and 849 mg/kg bw/day; F: 5.6, 34, 339 and 1135 mg/kg bw/day) Continuous in diet through 104 - 108 consecutive weeks	Sexual function and fertility: Histopathological examination of epididymis revealed slightly increased incidence of reduced or absent spermatozoa graded as very severe at 6000 ppm and 20000 ppm when compared to controls. Slightly increased incidence of endometrial stromal polyps in uterus at 20000 ppm when compared to controls and HC range 0-12% (incidences 12%, 14%, 12%, 10% and 20% at 0, 100, 600, 6000 and 20000 ppm, respectively). Other toxicity: No treatment-related effects on survival, clinical signs of toxicity, on palpable masses, body weight, food consumption, biochemistry, haematology, urinalysis, organ weights or macroscopic findings.	RAR B. 6.5.1, 2000
Repeated dose toxicity studies reviewed in section 10.12. and carcinogenicity study in mice reviewed in 10.8.		When examined, there were no remarkable findings in histopathology of testes or epididymis in these studies.	RAR B.6.3, B.6.5.2

10.10.1 Short summary and overall relevance of the provided information on adverse effects on sexual function and fertility

In the two-generation reproductive toxicity study groups of 30 male and 30 female Sprague Dawley Crl:CD rats were treated with phenmedipham doses 0, 100, 1225 and 15000 ppm via diet corresponding to 0, 7, 82 and 1038 mg/kg bw/day in males and 0, 10, 115 and 1430 mg/kg bw/day in females, respectively (**RAR B.6.6.1, 1999**). Although the study has been conducted prior to update of OECD TG 416 in 2001, it also included requirements of this updated guideline. Hence, a range of endocrine sensitive endpoints were investigated: e.g. estrous cycle length and normality, various sperm parameters, age of sexual maturation of offspring and various organ weights including reproductive organs. However, numbers of corpora lutea and implantations were not counted and thyroid was not weighted. Histopathology was conducted on the reproductive and target organs of 10 males and 10 females from the control and highest dose levels of each generation. Parent animals were subjected to detailed necropsy after their pups had been weaned and selected organs were weighed. Spermatogenetic endpoints (sperm motility, morphology and numbers) were recorded for all F0 and F1 males. Vaginal smears were taken for 21 days prior to pairing, during pairing until mating occurred and at necropsy. Litters were examined twice daily for pup mortality, clinical signs and behaviour. Pups were weighed individually and sexed on post-natal Days 0/1, 4, 7, 14 and 21. Balanopreputial separation and vaginal opening were monitored in the F1 generation animals. Further details on the study are given in RAR.

There were no mortalities or remarkable clinical signs or necropsy findings in parental F0 or F1 animals. No effects of the test article were observed on organ weight data of parental animals at any dose. The mean body weights and mean body weight gains of parental animals were unaffected by treatment throughout pre-breeding, post-breeding, gestation and lactation periods. The few statistically significant differences in these parameters between treated parental animals and controls were transient and did not occur in a dose-dependent manner and thus are not attributed to treatment with foramsulfuron. Food consumption and food efficiency were unaffected by the treatment in both parental generations.

The parameters of mating and fertility were comparable between the foramsulfuron treated groups and the controls in both generations (

Table 75). The mean numbers of days between pairing and coitus in the treated groups were comparable to the control group values in both generations; differences were slight and were not statistically significant. Individual variations in the oestrous cycle occurred in all study groups. The regularity and duration of oestrus were not affected by treatment in either generation (data not shown).

Table 75: Summary of reproductive performance in two-generation reproduction study

	foramsulfuron (ppm)							
	F0				**F1**			
	0	**100**	**1225**	**15000**	**0**	**100**	**1225**	**15000**
No. animals	30	30	30	30	30	30	30	30
Male mating index (%)[a]	96.6	93.3	96.7	93.3	90.0	100.0	90.0	93.3
Female mating index (%)[a]	96.7	93.3	96.7	93.3	90.0	100.0	90.0	93.3
Male fertility index (%)[b]	82.8	80	90	93.3	83.3	96.7	73.3	90.0
Female fertility index (%)[c]	83.3	80	90	93.3	83.3	96.7	73.3	90.0

No. animals with evidence of mating	28	28	29	28	27	30	27	28
Mean pre-coital intervals (days)[d]	2.1	2.5	2.2	2.3	2.1	2.6	2.6	2.8
S.D.	1.38	2.33	2.45	2.52	1.44	2.43	1.55	2.37

Positive evidence of mating during breeding period was confirmed by the presence of sperm in a vaginal smear or a copulatory plug. Males were considered to have sired a litter if the paired female was gravid, regardless of delivery status. Pre-coital intervals not significantly different from control group using Dunnetts's test; Mating and fertility indices not significantly different from control group using Chi-Square test.

[a]Male (Female) mating index (%) = No. of males (females) with evidence of mating (or confirmed pregnancy) / Total no. of Males (Females) used for mating X 100. [b]Male fertility index (%) = No. of males siring a litter / Total no. of males used for mating X 100; [c]Female fertility index (%) = No. of females with confirmed pregnancy / Total number of females used for mating X 100.

[d]Animals paired over a 12-hour dark cycle were considered to have been paired for one day.

The mean lengths of gestation were unaffected by foramsulfuron in both generations. The mean gestation lengths ± standard deviation (s.d.) were 21.8±0.37, 21.8±0.51, 21.8±0.51 and 21.7±0.53 days in F0 females and 21.6±0.49, 21.7±0.54, 21.9±0.47 and 21.6±0.49 in F1 females, in 0, 100, 1225 and 15000 ppm groups, respectively. No signs of dystocia were observed.

Foramsulfuron treatment had no effect on spermatogenic parameters in either generation. Differences between the control and treated groups were slight and were not statistically significant (Table 76).

Table 76: Summary of sperm parameters (means) in two-generation reproduction toxicity study

	foramsulfuron (ppm)							
	F0				F1			
	0	100	1225	15000	0	100	1225	15000
N[a]	30	29	30	30	30	30	30	30
Sperm number, testis[b]	87.7	75.2	82.8	82.1	86.9	88.9	85.5	91.8
S.D.	21.45	25.25	17.33	15.23	11.46	19.44	21.77	12.65
Sperm number, epididymis[b]	498.4	448.4	472.5	492.5	482.5	449.7	480.1	435.4
S.D.	99.51	149.04	98.42	90.42	127.63	91.46	124.61	111.46
Sperm production rate[c]	14.4	12.3	13.6	13.5	14.3	14.6	14.0	15.0
S.D.	3.53	4.14	2.84	2.50	1.88	3.18	3.57	2.08
Sperm motility (%)	87.8	88.4	83.9	87.4	72.6	70.3	67.8	67.1
S.D.	6.04	5.73	14.42	5.31	10.25	11.22	14.35	13.99
Sperm morphology, normal (%)	99.2	99.4	99.3	99.5	99.3	99.0	99.0	99.0
S.D.	1.43	0.72	0.90	0.64	0.62	1.02	1.20	0.94
Normally shaped head separated from flagellum (%)	0.3	0.3	0.2	0.2	0.4	0.7	0.6	0.6
S.D.	0.65	0.47	0.37	0.37	0.49	0.79	0.78	0.73
Head absent with normal flagellum (%)	0.5	0.3	0.5	0.3	0.2	0.4	0.4	0.4
S.D.	1.09	0.45	0.84	0.47	0.29	0.44	0.77	0.44

[a] number of animals was 30 for all epididymis samples of F0 and 29 for sperm motility and morphology assessment of F1 1225 ppm group.
[b] no. sperm in millions/g of tissue, [c] no. sperm in millions/g of tissue/day. None statistically significant using Kruskal-Wallis test. There were no incidences of following abnormalities: head absent with abnormal flagellum, misshapen head with normal flagellum, degenerative flagerral defects, other flagellar defects.

Foramsulfuron treatment did not affect mean live litter size or the number of pups born. In F1 generation the mean live litter size and the number of pups pups born (16.1 and 16.3 pups/litter respectively) in the high dose group were slightly increased relative to control group (14.3 and 14.5 pups/litter, respectively, Table 77). However the differences were not statistically significant, and similar effects were not observed in the F2 generation.

Table 77: Summary of litter data in two generation reproduction toxicity study (means)

	foramsulfuron (ppm)							
	F1				F2			
	0	100	1225	15000	0	100	1225	15000

No. (litters)	25	24	27	27	25	29	22	27
No. pups born /litter	14.5	15.1	15.6	16.3	14.4	15.1	14.1	15.3
S.D.	3.68	2.11	3.22	1.51	2.33	2.40	3.27	3.53
Sex ratio (% males)	54.2	53.3	52.4	48.7	48.5	48.1	51.0	48.8
S.D.	12.40	12.21	9.92	10.96	14.58	12.37	12.48	11.45
Live litter size (PND 0)	14.3	14.9	15.4	16.1	14.3	15.0	13.9	15.2
S.D.	3.63	2.17	3.45	1.47	2.42	2.44	3.28	3.51

No statistically significant differences (Kruskal-Wallis, Dunnett´s)

There were no significant differences in sexual maturation landmarks between F1 offspring groups (Table 78).

Table 78: Maturation landmarks and body weights at day of acquisition in F1 pups in two-generation reproductive toxicity sudy (means)

	foramsulfuron (ppm)			
	0	**100**	**1225**	**15000**
Balanopreputial separation, age (days)	43.7	43.8	44.4	44.5
S.D.	3.91	2.28	2.67	3.18
body weight (g)	241.1	238.9	244.8	251.9
S.D.	23.21	18.04	19.83	18.65
Vaginal patency, age (days)	32.9	33.1	33.3	33.3
S.D.	1.74	1.51	1.82	1.48
body weight (g)	122.2	121.3	127.1	128.1
S.D.	14.13	10.95	14.86	16.53

No statistically significant differences (Dunnett´s test). Balanopreputial separation was first observed for all males between PND 40 and PND 59.Vaginal perforation was first observed for all females between PND 30 and PND 39. Number of animals is 30 for all other groups except that the body weight for males was only reported for 29 animals.

In conclusion; no treatment-related effects were observed. There were no treatment-related findings of parental toxicity i.e. no effects on body weight and body weight gain, food consumption, clinical condition, or macroscopic pathology. Furthermore, no effects on sexual function and fertility (mating, days between pairing and mating, gestation length, parturition, litter size, oestrous cycling, balano-preputial separation, vaginal opening, spermatogenetic function and capacity) were observed.

In a combined chronic toxicity and carcinogenicity study in rat (**RAR B. 6.5.1, 2000**) histopathological examination revealed slightly, but not statistically significantly increased incidence of reduced or absent spermatozoa in the epididymis of males exposed to foramsulfuron dose 20000 ppm via diet (Table 79, incidences 20% and 26% in controls and at 20000 ppm, respectively). The increased incidence at 20000 ppm (corresponding to 849 mg/kg bw/day) compared to controls was due to increase in the incidence of reduced or absent spermatozoa graded as very severe (incidences 12% and 18% in controls and at 20000 ppm, respectively), whereas there were no differences in the incidences of this histopathological finding graded as severe (Table 79). A slight, but not statistically significantly increased incidence of this histopathological

finding graded as very severe was also observed at foramsulfuron dose 6000 ppm (246 mg/kg bw/day, 12% and 16% in controls and 6000 ppm, respectively, Table 79). The applicant has submitted historical control data from the performing laboratory (Table 79).

Table 79: Histopathological findings of epididymes in the rat carcinogenicity study

Effect	Sex	foramsulfuron (ppm)					Historical controls* Min–Max
		0	100	600	6000	20000	
Epididymides, reduced or absent spermatozoa **(Total)**	M	10/50 (20%)	9/50 (18%)	5/50 (10%)	9/50 (18%)	13/50 (26%)	6–20%**
Epididymides, reduced or absent spermatozoa, severe	M	3/50 (6%)	2/50 (4%)	0/50 (0%)	1/50 (2%)	2/50 (4%)	2-12%
Epididymides, reduced or absent spermatozoa, very severe	M	6/50 (12%)	5/50 (10%)	4/50 (8%)	8/50 (16%)	9/50 (18%)	n.s.

n.s. = lesion not scored,

* HCD is from 4 studies conducted during 1995-1998 in the performing laboratory (RAR). The combined chronic toxicity and carcinogenicity study (RAR B. 6.5.1, 2000) was conducted 11/1996-11/1998.

** The grading of the HCD lesions remains a bit unclear, i.e. it is not stated in RAR whether the range 6-20% represents the total number of lesions or not. Lesions graded as very severe have not been reported in the HCD.

We note that incidences of reduced or absent spermatozoa, graded as very severe, in the two highest dose groups are only slightly higher than those in the control group and incidences in all groups did not follow a dose-response relationship. The differences to control values were not statistically significant. Unfortunately, deficiences in reporting of the historical control data (see Table 79) do not allow a definite comparison with the reported incidences. However, foramsulfuron dietary dose levels up to 15000 ppm had no effects on spermatogenic endpoints (mean testicular and epididymal sperm numbers, sperm production rate, sperm motility and morphology) in F0 and F1 in the two generation reproductive toxicity study (RAR B.6.6.1, 1999). Nor there were, when examined, any remarkable histological findings in testes in other carcinogenicity study or in repeated dose toxicity studies with foramsulfuron (RAR B.6.3, B.6.5.2). Therefore we consider unlikely that this finding would be treatment-related and consider that it is not relevant for classification.

In the same study (**RAR B. 6.5.1, 2000**) incidences of endometrial stromal polyps in uterus were slightly increased in high dose group (incidences 12%, 14%, 12%, 10% and 20% at 0, 100, 600, 6000 and 20000 ppm, respectively). Endometrial stromal polyps may influence fertility. However, incidence of this tumor type was only slightly increased in high dose group compared to controls whereas the incidence of the control group was in the upper range of the historical control range (0-12%). Taking also into account that incidences were not dose-related, it remains unclear whether this finding is related to foramsulfuron treatment. Overall, no effects on fertility or gestation parameters were observed in two-generation reproduction toxicity study (RAR B.6.6.1, 1999) or any of the other relevant studies. Therefore we do not consider this finding relevant for classification.

10.10.2 Comparison with the CLP criteria

Foramsulfuron had no effects on sexual function and fertility in rat two-generation reproduction toxicity study (RAR B.6.6.1, 1999). There were no remarkable findings related to sexual function and fertility in other studies with foramsulfuron either (i.e. repeated dose toxicity and carcinogenicity/chronic toxicity studies). Therefore, the data regarding effects on sexual function and fertility are conclusive but do not warrant classification.

10.10.3 Adverse effects on development

Table 80: Summary table of animal studies on adverse effects on development

Method, guideline, deviations if any, species, strain, sex, no/group	**Test substance, dose levels duration of exposure**	**Results**	**Reference**
Developmental toxicity (teratogenicity) study OECD TG 414 (1981). Fullfills also the requirements of the updated guideline (2001), except for the exposure period (days 7-16 instead of days 5-20) According to GLP Rat, Wistar Hoe: WISKf(SPF71) 23 mated females/group Acceptable	foramsulfuron, purity 98.4% (w/w) 0, 5, 71 or 1000 mg/kg bw/day Oral by gavage on gestation days 7 to 16 of pregnancy	Maternal toxicity: Maternal body weights and food consumption were not affected, and no other compound-related effects were observed. Developmental toxicity: Foramsulfuron up to 1000 mg/kg bw/day, the limit dose, did not cause developmental toxicity.	RAR B.6.6.2.1, 1997
Developmental toxicity (terato-genicity) range finding study According to GLP Rabbit, Himalayan Chbb: HM SPF Kleinrusse 4 mated females/dose No vehicle control group. The data was compared to HCD of the laboratory. Acceptable as a range finding study	foramsulfuron, purity 98.4% (w/w) 500 and 1000 mg/kg bw/day Oral administration by gavage from day 6 to 18 of pregnancy	Maternal toxicity: 500 mg/kg bw/day: Low mean body weight gain over gestation days 6-13. Temporarily reduced food consumption over gestation days 6-10. 1000 mg/kg bw/day: decreased body weights of dams over gestation days 6–13 compared to historical control, reduced food consumption during the whole treatment period. Developmental toxicity: 1000 mg/kg bw/day: Slightly lower fetal body weights. One dam had 6 slightly small foetuses. Two foetuses of another dam showed bent forepaws.	RAR B.6.6.2.2, 1997
Developmental toxicity (terato-genicity) study OECD TG 414 (1981)	foramsulfuron, purity 98.4% (w/w) 0, 5, 50 or 500 mg/kg bw day	Maternal toxicity: 500 mg/kg bw/day: Reduced body weight gain (98 % lower than controls on GD 6-19), slightly reduced daily food consumption (24% lower than control),	RAR B.6.6.2.2, 1997

Method, guideline, deviations if any, species, strain, sex, no/group	**Test substance, dose levels duration of exposure**	**Results**	**Reference**
According to GLP Rabbit, Himalayan Chbb: HM SPF Kleinrusse 15 mated females/group live foetuses were incubated for 24 hours after delivery to monitor their survival. This was standard practice at the testing facility at the time of this study was conducted Acceptable	Oral administration by gavage from day 6 to 18 of pregnancy	reddish coloured urine in 6 dams during gestation days 10-12, and in one animal on days 15-17. Developmental toxicity: No treatment-related developmental toxicity. One control foetus exhibited microphthalmia and one foetus in each of two litters from the intermediate dose level had aplasia of the lens of the eye.	
Two-generation reproductive toxicity study OECD TG 416 (1983). The study fullfills also requirements of the guideline adopted in 2001). According to GLP Rat, Sprague Dawley Crl:CD (SD)BR 30/sex/dose Acceptable	foramsulfuron, purity 96.1% (w/w) 0, 100, 1225, 15000 ppm (M: 0, 7, 82 and 1038 mg/kg bw/d; F: 0, 10, 115 and 1430 mg/kg bw/d) Continuous in diet through ≥ 70 days premating, mating, gestation and lactation periods up to lactation day 22.	No parental toxicity Developmental toxicity: No-treatment-related developmental toxicity	RAR B.6.6.1, 1999

10.10.4 Short summary and overall relevance of the provided information on adverse effects on development

Two developmental toxicity studies, one in a rat and one in a rabbit, one developmental toxicity (teratogenicity) range finding study in rabbit and a two-generation reproductive toxicity study in rat have been conducted with foramsulfuron. The developmental toxicity studies compile with an older OECD TG 414 (1981), i.e. the dosing is during organogenesis only (gestation days 7-16 and 6-18 in rat and rabbit, respectively). In the rabbit study the number of animals with implantation sites at necropsy, 15, is just under the required count (16-20 does) in the current OECD Test Guideline (2001). The studies are only briefly described here, further details are given in RAR.

In the rat developmental toxicity study (**RAR B.6.6.2, 1997**) groups of 23 mated Wistar Hoe females were exposed to foramsulfuron with dose levels of 0, 5, 71 and 1000 mg/kg bw/day via diet over gestation days 7-16. No treatment-related deaths, clinical signs or effects on body weights in dams occurred. Food consumption was slightly, but statistically significantly higher in high dose group (1000 mg/kg bw/day) on days 7-10 and 14-17. One dam from the control group showed decreased activity, hypothermia, piloerection and drowsiness on days 19-20 and was sacrificed. One dam from the low dose group (5 mg/kg bw/day) had total resorption. No premature deliveries occurred. No compound-related effects were observed at necropsy. Gravid uterus weights, crown-rump lengths, litter size, sex ratios, foetal and placental weights were not affected by treatment, and there was no increase in the number of early or late conceptuses undergoing resorption (Table 81). Morphological examination of the foetuses did not reveal any treatment-related defects. Visceral examination revealed few foramsulfuron treated fetuses with uni- or bilateral distended kidney pelvis (% incidences fetus/litter 2.4/9.5, 1.8/9.5, 0.8/4.8 and 4.6/17.4, at 0, 5, 71 and 1000 mg/kg bw/day, respectively). Incidences of unossified 5 metacarpals were slightly but not statistically significantly increased in foramsulfuron treated groups compared to control group and seemed to follow dose-response (% incidences fetus/litter 6.8/23.8, 6.6/28.6, 11.5/38.1 and 12.7/47.8, at 0, 5 71 and 1000 mg/kg bw/day, respectively). However, all incidences of this variation were within the historical control range of the laboratory. The only statistically significant finding compared to controls was significantly increased incidence of wavy and/or thichend rib in low dose group (% incidences fetus/litter 6.1/19.0, 19.7/42.9, 5.8/28.6 and 5.6/21.7, at 0, 5, 71 and 1000 mg/kg bw/day, respectively. All incidences of these defects in treatment groups were within the historical control range.

Foetal body weights were marginally, but statistically significantly higher in the intermediate and high dose group, and, crown-rump lengths were slightly, but statistically significantly increased in the high-dose group (Table 81). However, these slight findings were considered to be fortuitous and not compound-related, since there was no other evidence of precocious development. Moreover, the values were within the historical control range.

Table 81: Summary of gestation and litter data of rat development toxicity study

	foramsulfuron (mg/kg bw/day)			
	0	**5**	**71**	**1000**
No. pregnancies	22[a]	22[b]	21	23
Dams at term with live fetuses	21	21	21	23
No. corpora lutea (mean ± s.d.)	14.1±1.8	13.9±1.8	14.0±1.2	14.0±1.4
No. implantations (mean ± s.d.)	13.0±1.5	11.9±3.5	13.5±1.3	12.2±2.5
Pre-implantation loss (% mean)	7.14	14.53	3.98	12.64
Post-implantation loss (% mean)[c]	7.15	8.20	5.19	2.77
Live fetuses (mean ± s.d)	12.1±2.3	11.0±3.9	12.7±1.6	11.9±2.6
Sex ratio (males %)	52.2	50.4	50.9	54.4
Pup body weight (g, mean±s.d.)	3.4±0.2	3.5±0.3	3.5±0.2*	3.6±0.3*
Crown/rump length (mm, mean±s.d.)	35.5±1.0	36.2±1.4	36.1±1.0	36.7±1.4*
Placental weight (g, mean±s.d.)	0.46±0.05	0.47±0.05	0.43±0.03	0.44±0.03
Gravid uterus weight (g, mean±s.d.)	61.79±11.29	58.09±18.29	66.60±8.36	63.12±12.94

[a] One dam was killed in extremis on day 20, [b]One dam had total resorption, [c]All intrauterine deaths were early, * Statistically significantly different from the control group

In conclusion, foramsulfuron up to and including 1000 mg/kg bw/day, the limit dose, did not cause maternal, embryonal or foetal toxicity. Therefore, foramsulfuron was not toxic for development in the rat. The NOEL was 1000 mg/kg bw/day for both maternal and developmental toxicity.

In a range finding study for rabbit developmental toxicity study groups of four mated Himalayan rabbit females received orally by gavage foramsulfuron at doses 500 or 1000 mg/kg bw/day from day 6 to 18 of pregnancy (**RAR B.6.6.2.1, 1997**). No vehicle control animals were included in the study. Thus, body weight and food consumption data were compared with historical control data submitted by the applicant (Table 82). The animals were killed on day 29 of pregnancy and the uterus was opened, the number of live and dead foetuses and the number of conceptuses undergoing resorption were determined. There were no mortalities and no clinical signs of intoxication in rabbits of both dose groups. An initial loss of body weight was observed from day 6–13 in the 1000 mg/kg bw/day group (

Table 82). In rabbits given 500 mg/kg bw/day, mean body weight gain appeared to be low during gestation days 6-13 by comparison with pretreatment data (days 0-6). Based on pretreatment feed intakes, food consumption was decreased in the high-dose group during the whole treatment period and in the 500 mg/kg bw/d group temporarily during gestation days 6–10. Fetal body weights were slightly lower at 1000 mg/kg bw/d (34.5 ± 5.7 g) than at 500 mg/kg bw/day (40.2 ± 4.5 g). One high dose (1000 mg/kg bw/day) dam had 6 slightly small foetuses. Two foetuses of another high dose dam showed bent forepaws. Because of the low group size the toxicological significance of this finding is unclear. No effects on embryofetal development were seen at 500 mg/kg bw/day. Based on the results of the range-finding study, 500 mg/kg bw/day was chosen as high dosage level for the main teratogenicity study in rabbits.

Table 82: Mean doe body weight gains in a rabbit developmental toxicity dose ranging study

Body weight gain (g)	**Historical control data***	**Dose level (mg/kg bw/day)**	
	Mean ± STD (MIN–MAX)	**500**	**1000**
Gestation days 0–6	62.0 ± 30.3 (13.2 – 132.1)	110.5 ± 29.3	94.5 ± 26.1
Gestation days 6–13	4.0 ± 17.1 (-31.8 – 27.7)	11.5 ± 28.2	-40.5 ± 23.7
Gestation days 6–19	126.1 ± 52.4 (1.4 – 234.6)	134.7 ± 9.0	10.2 ± 48.9
Gestation days 0-29		445.0 ± 79.7	306.0 ± 66.6

* Historical control data based on 18 studies conducted between 1995–1997 at the same test facility using the same rabbit strain (Himalayan) as the rabbit oral developmental toxicity study with foramsulfuron. The experimental part of the range finding study was conducted 08/1996-09/1996.

In the main rabbit developmental toxicity (teratogenicity) study, groups of 15 mated females were administered with foramsulfuron at doses 0, 5, 50 or 500 mg/kg bw/day from day 6 to 18 of pregnancy (**RAR B.6.6.2.1, 1997**). Animals were sacrificed on day 29 of pregnancy and examined externally and internally for macroscopic abnormalities. No deaths occurred throughout the study. Maternal toxicity was seen at the high dose (500 mg/kg bw/day), as evidenced by statistically significantly reduced body weight gain between GD6-19 (98% lower than controls) and slightly decreased food consumption during the treatment period (24% lower than controls, Table 83). Statistical evaluation revealed decreased body weight gain in all treated groups on day 19 of the study, but there was no dose-related response in the intermediate dose groups (RAR). Relative food intake (/100 g bw) of the high dose does was statistically significantly decreased compared to control group over days 6-8, 8-10, 10-13, and 16-19 (RAR). Moreover, reddish coloured urine was observed in six high dose animals for 1 to 3 days between days 10 and 12, and in one animal on days 15 to 17. No treatment-related clinical signs were observed in animals of the other groups.

Table 83: Body weight gain and food consumption in the rabbit developmental toxicity study

Parameter **(Days 6-19 of gestation)**	**Dose level (mg/kg body weight)**				
	0	**5**	**50**	**500**	**Historical control* Mean ± SD (Min – Max)**
Body weight gain (g) (% control)	81.9 (100)	47.4 (58)	53.8 (66)	1.8 (2)	64.1 ± 32.1 (-20.7 – 117.7) [< 31.4 in 1 of 18 studies]
Food consumption (g/animal/day) (% control)	201.6 (100)	184.0 (91)	193.5 (96)	153.8 (76)	–

* Historical control data based on 18 studies conducted between 1995–1997 at the same test facility using the same rabbit strain (Himalayan) as the rabbit oral developmental toxicity study with foramsulfuron. The experimental part of the main rabbit developmental toxicity study was conducted 10/1996-12/1996.

No compound-related effects were observed at necropsy of the animals. Gravid uterus, the number of live foetuses, foetal and placental weights, crown-rump lengths and sex ratios were not affected by treatment. One doe from the control group and one doe from the high dose group each had total litter loss. This was not considered treatment-related. Pre-implantation loss rate was slightly higher in foramsulfuron treated groups compared to control group (Table 84). According to study report the data on pre-implantation loss was not analysed statistically, but incidences were stated to be within the historical control range. Survival rates of the fetuses over 24 hours were comparable in all groups (97.1, 100, 99.2 and 96.9% in 0, 5, 71 and 1000 mg/kg bw/day, respectively).

Table 84: Summary of gestation and litter data of rabbit developmental toxicity study

	foramsulfuron (mg/kg bw/day)			
	0	**5**	**71**	**1000**
No. pregnancies	15	15	15	15
Does at term with live fetuses	14	15	15	14
No. corpora lutea (mean ± s.d.)	8.9±1.5	7.9±1.5	8.7±1.7	9.1±1.2
No. implantations (mean ± s.d.)	8.4±2.0	6.6±2.6	7.3±1.9	7.4±1.7
Pre-implantation loss (% mean)	6.76	18.63	17.42	18.05
Post-implantation loss (% mean)	6.54	5.05	4.93	10.39
Live fetuses (mean ± s.d)	7.8±2.0	6.3±2.4	6.9±2.0	6.7±2.0
Sex ratio (males %)	63.3	52.1	59.6	48.9
Pup body weight (g, mean±s.d.)	39.6±3.3	41.2±3.0	40.4±4.1	39.8±4.7
Crown/rump length (mm, mean±s.d.)	98.1±3.9	99.2±2.8	98.2±3.8	98.2±4.2
Placental weight (g, mean±s.d.)	4.6±0.063	4.73±0.55	4.70±0.68	4.55±0.62

No compound-related external, visceral or skeletal anomalies were detected in the foetuses at necropsy. One control foetus exhibited microphthalmia and one foetus in each of two litters from the intermediate dose level

had aplasia of the lens of the eye. However, in the absence of any dose-response relationship, the findings in the treated group were considered to be fortuitous.

Foramsulfuron was not toxic to development in rabbits. The NOEL for developmental toxicity was 500 mg/kg bw/d, whereas the NOEL for maternal toxicity in rabbits is considered to be 50 mg/kg bw/d, based on reduced body weight gain and food consumption at 500 mg/kg bw/day.

In the rat two-generation study (**RAR B.6.6.1, 1999**, reviewed in section 10.10.1) no treatment-related effects were observed in physical condition or mortality incidence of F1 or F2 pups (Table 85). Parental foramsulfuron treatment had no effect on pup body weights on postnatal days 1, 4, 7, 14 and 21 in either generation (Table 85). The only statistically significant difference from the control group was an increased mean F1 female pup body weight in the 1225 ppm group on PND 1 ($p<0.05$). Since similar increase was not observed at higher dose or in F1 generation, this was apparently not treatment-related. No treatment-related external, visceral or skeletal abnormalities were observed in necropsy and macroscopic examinations of the pups in either generation. One decedent F1 pup of the control group had a cleft palate and agenesis of the left ureter and kidney. A dilated left renal pelvis was observed in one F1 female pup of 15000 ppm group and a small thymus gland in one female pup of the same group. One male F1 pup of 1225 group had enlarged speleen. One F2 pup of 1225 ppm group (found dead) had spina bifida. Moreover, one F2 pup of each of the 100 ppm and 1225 ppm groups had dilated renal pelvis and the same 100 ppm pup also had a distended ureter. Since these findings were singular there were not attributet to foramsulfuron treatment.

Table 85: Postnatal survival and body weights (means) of offpring in two-generation reproduction study

	foramsulfuron (ppm)							
	F1				**F2**			
	0	**100**	**1225**	**15000**	**0**	**100**	**1225**	**15000**
N (litters)	25	24	27	27	25	29	22	27
Postnatal survival (%/litter)								
PND 0 (relative to number born)	98.7	98.3	97.1	98.7	99.0	99.5	97.9	99.6
S.D.	2.67	3.64	9.82	3.35	2.88	1.98	3.80	2.26
PND 0-4	97.7	97.5	94.3	98.5	95.2	98.7	96.7	98.2
S.D.	3.59	3.85	12.66	3.47	14.35	3.12	4.57	3.81
PND 4-21	99.5	99.5	100.0	99.1	97.5	99.6	100.0	99.5
S.D.	2.50	2.55	0.00	3.34	10.21	2.32	0.00	2.41
body weight (g), males								
PND 1	7.2	7.1	7.1	7.2	7.1	7.2	7.6	7.1
PND 7	16.6	16.7	16.3	16.9	16.9	16.9	18.0	17. 0
PND 21	55.0	55.5	55.2	56.3	54.0	55.1	58.6	55.3
body weight (g), females								
PND 1	6.8	6.8	6.6	6.8	6.7	6.8	7.2*	6.7
PND 7	15.8	15.8	15.3	15.9	15.7	15.8	17.0	16.0

PND 21	52.1	53.0	52.7	53.4	52.3	52.7	55.4	53.1

*significantly different from the control group at 0.05 using Dunnentt´s test

10.10.5 Comparison with the CLP criteria

Foramsulfuron administration during the period of organogenesis in rat and rabbit studies had no effect on the development of the conceptus (including no evidence of teratogenicity) of either rats or rabbits at dose levels up to 1000 mg/kg bw/day (1430 mg/kg bw/day in two generation study) and 500 mg/kg bw/day, respectively. In rats, there were no indications of maternal toxicity up to the international regulatory limit dose (1000 mg/kg bw/day, 1430 mg/kg bw/day). In rabbits, however, maternal toxicity, as indicated by reduced body weight gain and slightly decreased food intake throughout the dosing period at 500 mg/kg bw/day, was observed. No effects on development of foetuses or offspring were reported in the rat two-generation study on foramsulfuron. No classification for developmental toxicity is warranted.

10.10.6 Adverse effects on or via lactation

Short summary and overall relevance of the provided information on effects on or via lactation

There were no treatment-related findings on reproductive parameters during the lactation phases in the rat dietary two-generation reproductive toxicity study (RAR B.6.6.1, 1999). Specifically, F1 and F2 pup survival and weight were not affected during the lactation phases, and also mean body weights, body weight gains and food consumption of P0 and F1 females were not affected by treatment with foramsulfuron. Nor there were effects on maternal care. There are no data available on secretion of foramsulfuron in milk.

10.10.7 Comparison with the CLP criteria

This classification is intended to indicate when a substance may cause harm due to its effects on or via lactation. This can be due to the substance being absorbed by women and adversely affecting milk production or quality, or due to the substance (or its metabolites) being present in breast milk in amounts sufficient to cause concern for the health of a breastfed child.

There are no data available on secretion of foramsulfuron on milk. In the rat dietary two-generation reproductive toxicity study, no treatment-related effects on pup survival, development or body weights were reported. Therefore classification for effects on or via lactation is not appropriate.

10.10.8 Conclusion on classification and labelling for reproductive toxicity

No classification for sexual function and fertility, developmental toxicity or effects on or via lactation is proposed.

RAC evaluation of reproductive toxicity

Summary of the Dossier Submitter's proposal

Sexual function and fertility

The DS based its evaluation on a 2-generation reproductive toxicity study in rats (GLP-compliant, OECD TG 416) from 1999, the combined chronic toxicity and carcinogenicity study in rats and the repeated-dose toxicity studies.

In the 2-generation study and in the repeated-dose toxicity studies, no effects on parameters investigated on sexual function and fertility were observed. In particular, no effects on spermatogenetic parameters were noted at doses up to 20000 ppm (1038 mg/kg bw/day).

In the chronic toxicity study performed in rats, a slight increase, not statistically significant, in the incidence of reduced or absent spermatozoa (total) in the epididymis was noted at the top dose of 20000 ppm (26% vs 20% controls) due to the effect graded very severe (18% vs 12% in controls). A slight increase in the effect of very severe grade was also noted at 6000 ppm (16% vs 12% in controls). The table below describes the histopathological findings of epididymes in the rat carcinogenicity study.

***Table**: Histopathological findings of epididymes in the rat carcinogenicity study*

Effect	**Sex**	**Dose level (ppm)**				
		0	**100**	**600**	**6000**	**20000**
Epididymes, reduced or absent spermatozoa (Total)	M	10/50 (20%)	9/50 (18%)	5/50 (10%)	9/50 (18%)	13/50 (26%)
Epididymes, reduced or absent spermatozoa, severe	M	3/50 (6%)	2/50 (4%)	0/50 (0%)	1/50 (2%)	2/50 (4%)
Epididymes, reduced or absent spermatozoa, very severe	M	6/50 (12%)	5/50 (10%)	4/50 (8%)	8/50 (16%)	9/50 (18%)

As the increase was minimal and as no effects were seen in the 2-generation study or in the repeated-dose toxicity studies, no classification was considered warranted by the DS.

In the same study, an increase in endometrial polyps in the uterus was slightly increased at the top dose (12%, 14%, 12%, 10%, 20% at 0, 100, 600, 6000 and 20000 ppm). The increase was above the historical control data range. As the effects were not dose-related, and as the control was at the upper end of the historical control data range values, the DS considered this effect of doubtful toxicological relevance. As no effects were observed in the 2-generation study on fertility, no classification for this effect was proposed by the DS.

Overall, no classification was proposed by the DS for sexual function and fertility.

Developmental toxicity

Two developmental toxicity studies were considered by the DS, one in rats and one in rabbits (a range-finding study and a main study). The 2-generation reproductive toxicity study was also considered by the DS for this endpoint.

In the rat developmental toxicity study, pup weight and crown/rump length was statistically significantly increased at 71 and 1000 mg/kg. Nevertheless, the increase was marginal and inside the historical control data range.

In the rabbit range-finding study, one high dose dam had 6 slightly small foetuses. Two foetuses of another high dose dam showed bent forepaws. As only few animals were exposed per group (4 mated females/dose), the DS considered this finding of unclear toxicological significance. In the main rabbit developmental toxicity study, foramsulfuron was not toxic to development.

No developmental toxicity was seen in the 2-generation toxicity study.

Overall, the DS proposed no classification for developmental toxicity.

Adverse effects on or via lactation

There were no treatment-related findings during the lactation phases in the 2-generation study in rats. There are no data available on secretion of foramsulfuron in milk. Overall no classification was proposed by the DS for effects on/or via lactation.

Comments received during consultation

One industry representative supported the DS's proposal.

Assessment and comparison with the classification criteria

Sexual function and fertility

In the chronic rat toxicity study, the total incidence of reduced or absent spermatozoa in epididymides (slight to very severe) was increased at the top dose. Although there was no clear dose-response at the lower dose levels, there was an increase in the incidence of reduced or absent spermatozoa, graded very severe, at the higher dose levels (6000, 20000 ppm). While it is not statistical significant, the effect might be of biological significance. Although HCD were provided, the interpretation is difficult as grading of lesions was not done similarly between the HCD and the present study.

Since the difference between the control and highest dose is minimal and since no effects were seen in the 2-generation reproductive toxicity study, RAC considers the progression in severity of the effect on epididymis (reduced or absent spermatozoa) at the high dose levels insufficient for classification.

The increased incidences in uterine lesions (endometrial stromal polyps), do not provide clear evidence of a treatment-related effect as no dose-response relationship was observed.

Overall, RAC agrees with the DS that **no classification is warranted for foramsulfuron for sexual function and fertility.**

Developmental toxicity

RAC agrees with the DS that there were no treatment-related effects that could be considered relevant were observed and therefore **no classification of Formasulfuron for developmental toxicity is warranted.**

Adverse effects on or via lactation

RAC agrees with the DS that there were no treatment-related effects during the lactating phase of the 2-generation toxicity study that could be considered relevant for classification for effects on or via lactation **and therefore, no classification for lactation is warranted.**

10.11 Specific target organ toxicity-single exposure

Table 86: Summary table of animal studies on STOT SE

Method, guideline, deviations if any, species, strain, sex, no/group	**Test substance, route of exposure, dose levels, duration of exposure**	**Results**	**Reference**
Acute oral toxicity study in rat OECD TG 401, GLP	foramsulfuron single oral dose by gavage of 5000 mg/kg bw	Treatment-related clinical signs seen in all animals included piloerection, hunched posture and white, soft to liquid faeces. Recovery was complete in all cases by day 4. LD_{50} > 5000 mg/kg bw.	RAR B.6.2.1., 1997
Acute dermal toxicity study in rat OECD TG 402, GLP	foramsulfuron a single occlusive 24-h dermal application of 2000 mg/kg bw active substance 75% w/v in 1% w/v aqueous methylcellulose.	No signs of systemic reaction to the treatment were seen. LD_{50} > 2000 mg/kg bw.	RAR B.6.2.2., 1997
Acute inhalation toxicity study in rat OECD TG 403, GLP	foramsulfuron nose-only system to an achieved dust aerosol atmosphere of 5.04 mg/l. 4 hours	All animals exhibited wet fur. Increased or decreased respiratory rate was seen occasionally. Several animals had red/brown staining around the eyes, snout or head. Recovery of all animals was complete on day 1 after exposure. LC_{50} >5.04 mg/L (the highest achievable concentration).	RAR B.6.2.3., 1998

Table 87: Summary table of other studies relevant for STOT SE

Type of study/data	**Test substance, route of exposure, dose levels, duration of exposure**	**Observations**	**Reference**
28-day dietary neurotoxicity study OECD TG 424 GLP Rat, Wistar Han 12/sex/group	foramsulfuron, batch number AE F130360-01-01 (origin batch no. ELIR004130), Purity: 97.6 % (w/w) 0, 3750 and 15000 ppm corresponding to 0, 307.0 and 1208 mg/kg bw/day for males and 362.4 and 1415 mg/kg bw/day for females via diet for 28 days	No treatment-related clinical signs or indications for neurotoxicity. No treatment-related effects in any of the neurotoxicologic endpoints up to 15000 ppm corresponding to 1208 and 1415 mg/kg bw/day for males and females, respectively.	RAR B.6.7.1., 2009

10.11.1 Short summary and overall relevance of the provided information on specific target organ toxicity – single exposure

Specific target organ toxicity after single exposure of foramsulfuron has been studied in rat acute toxicity studies via oral, inhalation and dermal routes (RAR B.6.2.1.-6.2.3., 1997, 1998). These studies have been reviewed in in the sections 10.1.- 10.3. of this clh report. In addition, a subacute neurotoxicity study is available (RAR B.6.7.1., 2009).

The studies demonstrated a low acute toxic potential of foramsulfuron with LD50 and LC50 values above the classification criteria. In oral acute toxicity study (RAR B.6.2.1.,1997) only non-specific clinical signs were observed (piloerection, hunched posture and white, soft to liquid faeces). In the 4-hour inhalation acute toxicity study (RAR B.6.2.2., 1998) the main clinical signs were also non-specific: wet fur, hunched posture and piloerection. No systemic clinical signs were observed in the dermal acute toxicity study. There were no indications for acute neurotoxicity or narcotic effects in the subacute neurotoxicity study (RAR B.6.7.1., 2009).

10.11.2. Comparison with the CLP criteria

According to CLP criteria: “specific target organ toxicity (single exposure) is defined as specific, non lethal target organ toxicity arising from a single exposure to a substance or mixture. All significant health effects that can impair function, both reversible and irreversible, immediate and/or delayed STOT-SE should be considered where there is clear evidence of toxicity to a specific organ especially when it is observed in the absence of lethality…”.

Acute toxicity studies with foramsulfuron demonstrated low toxicity and only nonspecific clinical signs were reported. In addition, no signs of acute neurotoxicity or narcotic effects were observed in subacute neurotoxicity study with foramsulfuron. Thus, no specific target organ toxicity, or other significant health effects that can impair function, both reversible and irreversible, immediate and/or delayed, arising from a single exposure were seen in these studies with foramsulfuron. Therefore classification for STOT-SE Category 1 or Category 2 is not appropriate.

Classification as STOT-SE 3 is reserved for transient target organ effects and is limited to substances that have narcotic effects or cause respiratory tract irritation.

Classification of foramsulfuron for STOT-SE 3 is not appropriate, since no sings of transient target organ effects i.e signs of respiratory tract irritation or narcotic effects were observed in the studies available.

10.11.3 Conclusion on classification and labelling for STOT SE

A comparison of these toxicological effects in acute oral, dermal and inhalation toxicity studies and the lack of acute effects in a subacute neurotoxicity rat study with the classification criteria reveals that the results are conclusive and that a STOT-SE Category 1, 2 and 3 classification of foramsufuron is not warranted.

RAC evaluation of specific target organ toxicity – single exposure (STOT SE)

Summary of the Dossier Submitter's proposal

The DS concluded that foramsulfuron was of low acute toxicity and that there was no basis for STOT SE category 1 or 2 classification. Moreover, no evidence or indication of transient respiratory tract irritation or narcosis, which would meet the criteria for STOT SE 3, was observed in the available studies. Therefore, the DS proposed no classification for STOT SE.

Comments received during consultation

One industry representative agreed with the DS's proposal.

Assessment and comparison with the classification criteria

There was no relevant human data in the dossier. In the acute inhalation toxicity study, clinical signs suggesting respiratory tract irritation such as occasional increase or decrease respiration and red/brown staining around the eyes, snout or head were observed in several animals. These clinical signs were reversible by day 1 and no abnormalities were observed at necropsy. As the substance is a solid, the mechanical effect of solid particles may have contributed to the irritation observed. The substance was without irritant effect in the eyes or the skin of rabbits. No gross pathological findings in the lung were observed at necropsy. Therefore, RAC agrees with the DS's proposal not to classify foramsulfuron STOT SE 3 for respiratory tract irritation.

Overall, RAC agrees with the DS that **no classification for STOT SE is warranted for foramsulfuron**.

10.12 Specific target organ toxicity-repeated exposure

Table 88: Summary table of animal studies on STOT RE

Method, guideline, deviations if any, species, strain, sex, no/group	**Test substance, route of exposure, dose levels, duration of exposure**	**Results**	**Reference**
Rat 28-day dietary repeat dose study OECD TG 407, 12 May 1981 Acceptable to RMS as a range-finding study Sprague Dawley CRL:CD (SD) BR rats 5/sex/dose	Foramsulfuron, (purity: 90.0% (w/w)) Administration via diet at 0, 1000, 5000 or 20000 ppm corresponding to 0, 95, 462 and 1837 mg/kg bw/d for the combined sexes for 29 or 30 days.	No deaths occurred. At 20000 ppm, there was a decrease in body weight gain of 26% in females only over the course of the treatment period. Food consumption was decreased by an average of 8% in females only over the treatment period compared with controls, whilst water consumption by females was increased by 16%. Food conversion ratios were decreased in females from weeks 2 to 4 of treatment. No toxicologically significant effect of treatment was observed in haematology or blood biochemistry parameters or following histopathological examination of tissues. No effects were seen in females at 5000 or 1000 ppm or in males at any dose level. Thus, the NOAELs are 20000 ppm and 5000 ppm in males and females, respectively. These doses of 462 and 1837 mg/kg bw/d are above the trigger doses for STOT-RE classification.	1998 KCA5.3.1 /01
Mouse 28-day dietary toxicity study OECD TG 407, 12 May 1981 Acceptable to RMS as a range-finding study CRL:CD-1 (ICR) BR mice 5/sex/dose	Foramsulfuron, (purity: 90.0% (w/w)) Administration via diet at 0, 400, 1600 or 6400 ppm corresponding to 0, 51.5, 312 and 1164 mg/kg bw/d for males and 62.5, 401 and 1695 mg/kg bw/d for females for 28 or 29 consecutive days.	No treatment-related mortalities or clinical signs of toxicity occurred during the study. Dietary administration of foramsulfuron to mice at dose levels up to 6400 ppm caused no treatment-related effects. The no observed effect level (NOEL) and no observed adverse effect level (NOAEL) for both sexes was 6400 ppm of foramsulfuron, the highest dose level and equivalent to a daily intake of 1164 mg/kg bw/d for males, 1695 mg/kg bw/d for females and 1430 mg/kg bw/d for both sexes. These doses are above the trigger doses for STOT-RE classification.	1998 KCA5.3.1 /02
Dog 28-day oral toxicity study OECD TG 409, 12 May 1981 Acceptable to RMS Beagle dogs 2/sex/dose	Foramsulfuron, (purity: 98.4% (w/w)) Daily oral gavage dose of 0, 40, 200 or 1000 mg/kg bw/d for 28 or 29 consecutive days	In this study, no treatment-related effects occurred. The no observed effect level (NOEL) and no observed adverse effect level (NOAEL) for both sexes was 1000 mg/kg bw/day. For a subsequent 90-day oral toxicity study in the dog the limit dose of 1 000 mg/kg bw/day was selected based on this dose range finder.	1998 KCA5.3.1/ 03

Rat 90-day dietary toxicity study with 4 week off dose period OECD TG 408, 12 May 1981 Acceptable to RMS Sprague Dawley CRL:CD (SD) BR rats 10/sex/dose	Foramsulfuron, (purity: 97.4% (w/w)) Administration via diet at 0, 20, 200, 5000, 20000 ppm for 13 consecutive weeks	No treatment-related effects were seen in rats of either sex, at dose levels of up to and including 20000 ppm, following 13 weeks dietary administration of foramsulfuron. The no observed effect level (NOEL) for the combined sexes was 20000 ppm (1677 mg/ kg bw/day), which is above the international limit dose of 1000 mg/kg bw/day over a chronic period. This dose is above the trigger dose for STOT-RE classification.	1998 KCA5.3.2/ 01
Mouse 90-day dietary toxicity study OECD TG 408, 12 May 1981 Acceptable to RMS CRL:CD-1 (ICR) BR mice 10/sex/dose	Foramsulfuron, (purity: 98.4% (w/w)) Administration via diet at 0, 64, 3200 or 6400 ppm for 13 consecutive weeks	There were no deaths or treatment-related clinical signs in any of the treatment groups in either sex. The mean achieved dietary intake of foramsulfuron for the combined sexes was 12.6, 660 and 1090 mg/kg bw/day at 64, 3200 and 6400 ppm, respectively. The no observed effect level (NOEL) for the combined sexes was 6400 ppm (1090 mg/kg bw/day), equivalent to a daily intake of approximately 1000 mg/kg bw/day over a subchronic period. This dose is above the trigger dose for STOT-RE classification.	1998 KCA5.3.2/ 02
Dog 90-day oral toxicity study OECD TG 409, 12 May 1981 Acceptable to RMS Beagle dogs 4/sex/dose	Foramsulfuron, (purity: 94.1% (w/w)) Oral administrat-ion by gavage at 0, 10, 250 or 1000 mg/ kg bw/day for 13 consecutive weeks	At the administered doses of 10, 250 and 1000 mg/kg bw/day, no mortalities or clinical signs, and no treatment-related ophthalmic changes or effects on body weight, food consumption, organ weights, macroscopic pathology and histopathology occurred. It is concluded that foramsulfuron was well tolerated by dogs and that the NOAEL for both sexes was 1000 mg/kg bw/day, the international dose limit. This dose is above the trigger dose for STOT-RE classification.	1998 KCA5.3.2/ 03

Dog 12 month oral toxicity study OECD TG 452, 12 May 1981 Acceptable to RMS Beagle dogs 4/sex/dose	Foramsulfuron, (purity: 96.4% (w/w)) Oral administrat-ion by gavage of 0, 5, 100 or 1000 mg/kg bw/day for 52 consecutive weeks	No mortalities occurred, only a slight increase in the incidence of beige faeces (beige was the colour of foramsulfuron) of females given 1000 mg/kg bw/day was seen, particularly during the first week of treatment. Isolated incidents of beige vomit were also seen throughout the study in both sexes at this dose level. No treatment-related ophthalmic changes or effects on body weight, food intake, haematology, bio-chemistry, urinalysis, organ weights, macroscopic pathology and histopathology were observed. The NOAEL for both sexes was 1000 mg/kg bw/day, the international regulatory limit dose. This dose is above the trigger dose for STOT-RE classification.	1999 KCA5.3.2/ 04
Rat 28 days dermal, OECD TG 410 May 1981, 5/sex/dose	Foramsulfuron, (purity: 94.2% (w/w)) 0, 10, 100 or 1000 mg/kg bw/d for a total of 28 or 29 consecutive days for males and females respectively, excluding weekends.	At 1000 mg/kg bw/d, the highest dose level, yellow staining was observed at the treatment site in both sexes from Day 1 until termination, whilst slight redness was noted in 1/5 females in week 4. The yellow staining was due to the colour and concentration of the material. At 100 mg/kg bw/d slight yellow staining was seen in 1/5 males during week 4. There were no other findings at these dose levels and no findings at 10 mg/kg bw/d.	1997
Chronic and carcinogenicity studies in rats and mice	See 10.9.1-10.9.3	See 10.9.1-10.9.3	See 10.9.1-10.9.3
Reproduction and developmental toxicity studies in rats and rabbits	See 10.10.1-10.10.10	See 10.10.1-10.10.10	See 10.10.1-10.10.10

Table 89: Summary table of human data on STOT RE

Type of data/report	Test substance	Route of exposure Relevant information about the study (as applicable)	Observations	Reference
No human data available.				

Table 90: Summary table of other studies relevant for STOT RE

Type of study/data	Test substance	Relevant information about the study (as applicable)	Observations	Reference
28-Day Dietary Neurotoxicity Study in Wistar Rats OECD TG 424, 21 July 1997 Acceptable to RMS Wistar rat 12/sex/dose	Foramsulfu-ron (purity 97.6 % (w/w)) Oral admini-stration of 0, 3750, 15,000 ppm via diet	Foramsulfuron was mixed in the diet and given for 28 days to young-adult male and female Wistar rats. All test diets (including control) were provided for ad libitum consump-tion throughout the study except during neurobehavioral testing.	There were no treatment-related effects attributed to exposure to foramsulfuron at any dietary level in either sex. Most importantly, there were no neurotoxic effects at any dietary level in either sex. The NOAEL was established at the highest dose of 15000 ppm, equivalent to 1208 mg/kg bw/day in males and to 1415 mg/kg bw/day in females. Thes doses are clearly above the trigger doses for STOT-RE classification.	2009 KCA 5.7.1/ 01

28 days, rat (OECD TG 407)

Material and Methods:

Groups of 5 male and 5 female Sprague Dawley rats, housed in groups of 5 by sex and dose level, were given dietary concentrations of either 0, 1000, 5000 or 20000 ppm foramsulfuron for 29 or 30 consecutive days. The conduct of the study generally followed the current OECD TG 407, with the exceptions listed above. Water intake was measured for each cage over a 4-day period during week 3 of treatment.

Findings:

The mean achieved intakes were 0, 95, 462 and 1837 mg foramsulfuron /kg bw/d for the combined sexes at 0, 1000, 5000 and 20000 ppm, respectively. The corresponding values for the two sexes were 92, 434 and 1789 mg/kg bw/d for males and 97, 490 and 1884 mg/kg bw/d for females at 1000, 5000 and 20000 ppm, respectively.

There were no mortalities and no clinical signs of toxicity.

At 20000 ppm, female body weight gain was decreased by 26% compared to control animals over the treatment period, whilst water intake was increased by 16%.

Food consumption in these females was also reduced over this period by an average of 8% compared with controls. Their mean food conversion ratio was also decreased by 20% from weeks 2 to 4. The only possible treatment-related change at 5000 ppm was a marginally reduced body weight gain in females (-12%). Thus, no adverse effects were seen in females at 1000 ppm or in males at any dose level.

No toxicologically significant treatment-related effect was observed in haematology or blood chemistry indices. Similarly there were no macroscopic abnormalities at necropsy that were ascribed to treatment and no histopathological findings.

Conclusion

The 28-day rat study, being a range-finding study, has used a limited number of animals and therefore the lack of statistical significance of the decreased body weight gain in females at the two high dose levels can be questioned.

Based on the decreased body weight gain (<90% of control) at 20000 and 5000 ppm in females, the NOAEL is 1000 ppm (97 mg/kg bw/day in females).

28 days, mouse (OECD TG 407)

Material and Methods:

Groups of 5 male and 5 female CD-1 mice, 34 days old and weighing between 23 to 27.1 g (males) and 21.7 to 24.5 g (females) on the first day of treatment, were given diet containing either 0, 400, 1600 or 6400 ppm of foramsulfuron for 28 or 29 consecutive days. The mean achieved daily intakes of foramsulfuron were 0, 57 (adjusted according to the achieved concentration which was 32% of nominal concentration for weeks 3 and 4), 357 and 1430 mg/kg bw/d for the combined sexes at 0, 400, 1600 and 6400 ppm, respectively. The corresponding values for each sex were 0, 51.5, 312 and 1164 mg/kg bw/d for males and 62.5, 401 and 1695 mg/kg bw/d for females at 0, 400, 1600 and 6400 ppm, respectively.

They were housed in groups of 5 by sex and dose level.

Animals were observed daily (once on weekends and on public holidays) for clinical signs and mortality. Individual body weights and cage group food consumption were measured weekly. Haematology and clinical chemistry investigations on all animals were conducted at termination. At necropsy, animals were examined thoroughly for macroscopic abnormalities, the weights of selected organs recorded and a range of tissues preserved. Tissues from all control and high dose animals and gross lesions from all other mice were subsequently examined histopathologically.

Findings:

No treatment-related mortalities or clinical signs of toxicity occurred during the study.

Dietary administration of foramsulfuron to mice at dose levels up to 6400 ppm caused no treatment-related effects.

Conclusion:

The no observed effect level (NOEL) and no observed adverse effect level (NOAEL) for both sexes was 6400 ppm of foramsulfuron, the highest dose level and equivalent to a daily intake of 1164 mg/kg bw/d for males, 1695 mg/kg bw/d for females and 1430 mg/kg bw/d for both sexes.

28 days, dog (OECD TG 409)

Material and Methods:

Groups of 2 male and 2 female beagle dogs, 4 months old and weighing between 5.9 to 8.0 kg (males) and 5.3 to 7.6 kg (females) at the start of dosing, were used. Each was given a single daily oral dose, by gavage, of either 0, 40, 200 or 1000 mg/kg bw/d for 28 or 29 consecutive days. The test material was administered as a suspension in 0.5% w/v methylcellulose in distilled water at a constant volume of 5 ml/kg bw/d. Controls received the vehicle alone.

Animals were examined thoroughly prior to the start of and at the end of treatment. They were observed for clinical signs twice daily (once on weekends and on public holidays). Individual body weights were recorded weekly throughout the treatment period and at necropsy. Food consumption was measured daily and water intake determined over four days in the third/fourth week of treatment. Ophthalmoscopy was conducted on all animals prior to the start of treatment and on the control and highest dose group animals prior to termination. An electrocardiogram was recorded for each dog one week prior to the start of treatment and on Study Day 28, pre-dose and post-dose (approximately 2 hours after dosing). Haematology and blood biochemistry investigations were conducted 8 and 1 day before the start of the treatment period and on Days 14 and 27 of dosing. Urinalysis parameters were measured at termination from a urinary bladder sample. At necropsy, all animals were examined thoroughly for gross abnormalities, the weights of selected organs were recorded and

an extensive range of tissues was preserved. Subsequently, the range of tissues required by the testing guidelines was examined histopathologically.

Findings:

There were no mortalities and no treatment-related effects at any dose level.

Conclusion:

The no observed effect level (NOEL) and no observed adverse effect level (NOAEL) for both sexes was 1000 mg foramsulfuron /kg bw/d.

90 days, rat (OECD TG 408)

Material and Methods:

Groups of 10 male and 10 female Sprague Dawley rats were fed diet containing either 0, 20, 200, 5000 or 20000 ppm of foramsulfuron for 13 consecutive weeks. The mean achieved daily intakes for the combined sexes were 0, 1.68, 17.4, 432 and 1677 mg foramsulfuron/kg bw/d at 0, 20, 200, 5000 and 20000 ppm, respectively. The corresponding values for the two sexes were 1.54, 15.4, 388 and 1568 mg/kg bw/d for males and 1.81, 19.4, 475 and 1786 mg/kg bw/d for females at 20, 200, 5000 and 20000 ppm, respectively. Two further groups (off-dose animals), each consisting of 10 males and 10 females were fed either 0 or 20000 ppm for 13 weeks and then maintained on untreated (control) diet for a further 4 weeks to examine the reversibility of any effects seen. At the start of treatment the animals were just over 5 weeks of age and weighed 121 to 170 g (males) and 110 to 170 g (females). They were housed by sex and dose level in groups of 5 and had been acclimatised for 7 days.

Animals were observed for clinical signs twice daily (once on weekends and on public holidays). Individual body weights were recorded weekly throughout the treatment period and at necropsy. Cage group food consumption was also measured weekly. Water intake was recorded for each cage group over 4-day periods (monday to friday) during weeks 4, 8 and 12. Ophthalmoscopy was performed on all animals prior to the start of treatment and on all control and high dose level rats in week 13. Biochemistry, haematology and urinalysis were carried out in week 13 of treatment. At necropsy, all animals were examined thoroughly for macroscopic abnormalities, the weights of selected organs recorded and a comprehensive range of tissues preserved. All organs and tissues from the control and high dose level groups and both kidneys, livers and lungs from animals of the remaining dose levels sacrificed in week 13 and all organs and tissues from any animal sacrificed during the study were examined histopathologically.

Findings:

There were no treatment-related mortalities. At 20 ppm, one male was sacrificed *in extremis* on Study Day 58. In view of its isolated occurrence, this death was considered to be fortuitous. One female given 20 ppm died during blood sampling on Study Day 92.

No treatment-related effects were seen at any dose level.

Conclusion:

The no observed effect level (NOEL) and no observed adverse effect level (NOAEL) for the combined sexes was 20000 ppm, equivalent to a daily intake of 1677 mg/kg bw/d, which is in excess of the 1000 mg/kg bw/d international limit dose.

Mouse, 90 days (OECD TG 408)

Material and Methods:

Groups of 10 male and 10 female CD-1 mice were fed diet containing either 0, 64, 3200 or 6400 ppm of foramsulfuron for 13 consecutive weeks. The achieved mean daily intakes of foramsulfuron were 0, 12.6, 660 and 1090 mg/kg bw/d for the combined sexes at 0, 64, 3200 and 6400 ppm, respectively. The corresponding values for the separate sexes were 10.5, 498 and 1002 mg/kg bw/d for males and 14.6, 822 and 1178 mg/kg bw/d for females at 64, 3200 and 6400 ppm, respectively.

At the start of treatment, the animals were approximately 6 weeks of age and weighed 23.9 to 34.4 g (males) and 23.8 to 30.1 g (females). They were housed in groups of 5 by sex and dose level and had been acclimatised for 12 days.

Animals were observed for clinical signs twice daily (once on weekends and on public holidays). Detailed observations were conducted prior to weighing once weekly until day 71 and daily thereafter. During these observations swellings/lumps were noted in several males in the urinogenital region. Therefore mass tracking was implemented from day 85 to termination. Individual body weights were recorded weekly throughout the treatment period and at necropsy. Food consumption was also measured weekly. Biochemistry and haematology were carried out in week 14. At necropsy, all animals were examined thoroughly for macroscopic abnormalities, the weights of selected organs were recorded and a comprehensive range of tissues was preserved. Subsequently all tissues from the control and high dose level animals sacrificed in week 13 and any mice sacrificed during the study were examined histopathologically.

Findings:

There were no treatment-related deaths.

No treatment-related effects were found in mice at any dose level, including no effects on the incidence of swelling in the urinogenital region.

Conclusion:

The no observed effect level (NOEL) and no observed adverse effect level (NOAEL) were 6400 ppm (equivalent to 1002 mg/kg bw/d for males, 1178 mg/kg bw/d for females and 1090 mg/kg bw/d for the combined sexes, which is approximately the international limit dose of 1000 mg/kg bw/d).

Dog, 90 days (OECD TG 409)

Material and Methods:

Groups of 4 male and 4 female beagle dogs were given a single daily oral dose, by gavage, of either 0, 10, 250 or 1000 mg/kg bw/d for 13 consecutive weeks. The test material was administered as an aqueous suspension in 0.5% w/v methylcellulose at a constant volume of 5 ml/kg bw. Controls received the vehicle alone. At the start of treatment the dogs were approximately 7 to 8 months old and weighed 8.4 to 11.8 kg (males) and 8.0 to 9.5 kg (females). They had been acclimatised for 42 days prior to treatment and were housed in pens of 2 by sex and dose group, except during dosing and feeding when they were housed individually.

Each animal was given a thorough clinical examination prior to and at the end of the treatment period. Animals were observed for clinical signs twice daily (once on weekends and on public holidays). Veterinarian visits/advice was obtained as necessary. Ophthalmoscopy was conducted on each dog prior to the first dose and on all control and high dose animals during the last week of treatment. Individual body weights were recorded at the start of treatment, at weekly intervals thereafter and at necropsy. Individual food consumption was also measured weekly. Biochemistry and haematology were carried out on Days 41 and 92. Urinalysis was performed on a bladder sample at necropsy (Days 93 and 94 for males and on Days 97 and 98 for females). At necropsy, all animals were examined thoroughly for macroscopic abnormalities, the weights of selected organs recorded and a comprehensive range of tissues preserved. Subsequently, tissues from all animals were examined histopathologically.

Findings:

There were no mortalities and no clinical signs directly related to treatment. Occasional beige faeces (beige being the colour of the test material) were noted at 1000 mg/kg bw/d from week 3 of treatment, particularly in females. Isolated incidences of this finding were also observed in one male in each of the 10 mg/kg bw/d and 250 mg/kg bw/d groups.

No treatment-related adverse effects were observed at any dose level.

Conclusion:

The no observed adverse effect level (NOAEL) for both sexes was 1000 mg/kg bw/d, the international limit dose.

1 year, dog (OECD TG 452)

Material and Methods:

Groups of 4 male and 4 female Beagle dogs were given a single daily oral dose, by gavage, of either 0, 5, 100 or 1000 mg/kg bw/d, suspended in 0.5 or 1.0% w/v methylcellulose in distilled water for 52 consecutive weeks. The control group received the vehicle alone. A constant volume of 5 ml/kg bw was used. The dogs were approximately 8 months old and weighed 8.1 to 12.6 kg (males) and 7.6 to 11.6 kg (females) at the start of treatment. They were housed in pairs by sex and dose group, except during feeding and dosing when they were housed individually.

Each animal was given a thorough clinical examination prior to the treatment period. Animals were observed for clinical signs twice daily (once on weekends and on public holidays). Veterinarian visits/advice was obtained as necessary. Ophthalmoscopy was conducted on each dog prior to the first dose and on all control and high dose animals during the last week of treatment. Individual body weights were recorded at the start of treatment, at weekly intervals thereafter and at necropsy. Individual food consumption was measured daily throughout the treatment period. Biochemistry and haematology were carried out at 3, 6, and 12 months of treatment. Urinalysis was performed on a bladder sample taken by catheterisation at 3 and 6 months and directly from the bladder at necropsy. Animals were sacrificed by exsanguination under deep anaesthesia induced by sodium pentobarbitone. Each animal was examined thoroughly for macroscopic abnormalities, the weights of the discrete organs recorded and a comprehensive range of tissues preserved. A bone marrow smear was also taken. Subsequently, all prepared tissues from all animals were examined histopathologically.

Findings:

There were no mortalities. A slight increase in the incidence of beige faeces (beige was the colour of foramsulfuron) of females given 1000 mg/kg bw/d was seen, particularly during the first week of treatment. In addition, isolated incidents of beige vomit were seen throughout the study in both sexes at this dose level.

No treatment-related ophthalmic changes or effects on body weight, food intake, haematology, biochemistry, urinalysis, organ weights, macroscopic pathology and histopathology were observed.

Conclusion:

The no observed adverse effect level (NOAEL) for both sexes was 1000 mg/kg bw/d, the international regulatory limit dose.

Other routes

Dermal

Rat, 28 days

Material and Methods:

Groups of five male and five female Sprague-Dawley rats were given a daily, topical 6-hour application of either 0, 10, 100 or 1000 mg/kg bw/d for a total of 28 or 29 consecutive days for males and females respectively, excluding weekends. The test material was suspended in the vehicle, 1% w/v methylcellulose in distilled water. Control animals received the vehicle alone over the same period. On the first day of treatment, the animals were approximately 8 weeks of age (54 days old) and weighed between 247 g and 276 g (males) and between 208 g and 249 g (females).

Animals were observed for clinical signs twice daily (once on weekends and on public holidays). The treated skin site was examined macroscopically for local irritation prior to the first topical application and between about 30 and 60 minutes at the end of each exposure period. Individual body weights were recorded at the start of treatment, twice weekly thereafter and at necropsy. Cage group food consumption was measured weekly throughout the treatment period. Biochemistry and haematology were carried out on Day 29. At necropsy, all animals were examined thoroughly for macroscopic abnormalities. Particular attention was paid to the site of application. The weights of selected organs were recorded and a limited range of tissues preserved. The liver, kidneys, treated and untreated skin sites from the control and high dose level groups were examined histopathologically.

Findings:

There were no treatment-related mortalities or systemic clinical signs of toxicity.

At 1000 mg/kg bw/d, the highest dose level, yellow staining was observed at the treatment site in both sexes from Day 1 until termination, whilst slight redness was noted in 1/5 females in week 4. The yellow staining was due to the colour and concentration of the material.

At 100 mg/kg bw/d slight yellow staining was seen in 1/5 males during week 4.

There were no other findings at these dose levels and no findings at 10 mg/kg bw/d.

Conclusion:

The no observed effect level (NOEL) and the no observed adverse effect level (NOAEL) of foramsulfuron for systemic effects in both sexes was 1000 mg/kg bw/d, the regulatory limit dose.

10.12.1 Short summary and overall relevance of the provided information on specific target organ toxicity – repeated exposure

The short-term toxicity studies were performed and reported in accordance with OECD and EU testing guidelines and were compliant with GLP.

In a 28-day study in rats with doses of 0, 1000, 5000 or 20000 ppm for 29 or 30 days, no mortality occurred. At 20000 ppm, there was a decrease in body weight gain of 26% in females during the treatment period. Food consumption was decreased by an average of 8% in females compared with controls, whilst water consumption by females was increased by 16%. Food conversion ratios were decreased in females from weeks 2 to 4 of treatment. No toxicologically significant effects were observed in haematology or blood biochemistry parameters in the histopathological examination of tissues. The achieved dietary intakes for the combined sexes were equivalent to daily consumption of 95, 462 and 1837 mg/kg bw for 1000, 5000 and 20000 ppm, respectively. No effects were seen in females at 5000 or 1000 ppm or in males at any dose level. Thus, the NOAELs are 20000 ppm in males (equivalent to 1789 mg/kg bw/day), and 5000 ppm in females (equivalent to 490 mg/kg bw/day). These NOAELs are above the trigger value of 300 mg/kg bw/day for STOT-RE classification of 28-day studies.

In a rat 90-day dietary toxicity study with 4 week off dose period, with doses of 0, 20, 200, 5000, 20000 ppm via the diet for 13 consecutive weeks, no treatment-related effects were seen in rats of either sex, at dose levels of up to and including 20000 ppm. The no observed effect level (NOEL) for the combined sexes was 20000

ppm (1677 mg/ kg bw/day), which is above the international limit dose of 1000 mg/kg bw/day and also above the trigger value of 100 mg/kg bw/day for STOT-RE classification of 90-day studies.

In a mouse 28-day dietary toxicity study with administration of foramsulfuron via diet at 0, 400, 1600 or 6400 ppm for 28 or 29 consecutive days, no treatment-related mortalities or clinical signs of toxicity or other treatment-related effects occurred during the study. The no observed effect level (NOEL) and no observed adverse effect level (NOAEL) for both sexes was 6400 ppm of foramsulfuron, the highest dose level and equivalent to a daily intake of 1430 mg/kg bw/d for both sexes.

In a mouse toxicity study with dietary doses of 0, 64, 3200 or 6400 ppm for 13 consecutive weeks, no deaths or treatment-related clinical signs occurred in any of the treatment groups in either sex. The mean achieved dietary intake of foramsulfuron for the combined sexes was 12.6, 660 and 1090 mg/kg bw/day at 64, 3200 and 6400 ppm, respectively. The no observed effect level (NOEL) for the combined sexes was 6400 ppm (1090 mg/kg bw/day), equivalent to a daily intake of approximately 1000 mg/kg bw/day, the limit dose, over a chronic period. These NOAELs in mice are above the trigger value of 100 mg/kg bw/day for STOT-RE classification of 90-day studies.

In a subacute dog toxicity study, with daily oral gavage doses of 0, 40, 200 or 1000 mg/kg bw/d for 28 or 29 consecutive days, no treatment-related effects occurred. The no observed adverse effect level (NOAEL) and also the no observed effect level (NOEL) for both sexes was 1000 mg/kg bw/day.

In a subchronic dog toxicity study with oral gavage doses of 0, 10, 250 or 1000 mg/kg bw/day for 13 consecutive weeks, no mortalities or clinical signs occurred. There were no treatment-related ophthalmic changes or effects on body weight, food consumption, organ weights, macroscopic pathology and histopathology. Thus, it is concluded that foramsulfuron was well tolerated by dogs and that the NOAEL for both sexes was 1000 mg/kg bw/day, the international dose limit.

In a 12-month oral toxicity study in dogs with gavage doses of of 0, 5, 100 or 1000 mg/kg bw/day for 52 consecutive weeks, no mortalities occurred. Only a slight increase in the incidence of beige faeces (beige was the colour of foramsulfuron) of females given 1000 mg/kg bw/day was seen, particularly during the first treatment week, with isolated incidents of beige vomit also throughout the study in both sexes at this dose level. No treatment-related ophthalmic changes or effects on body weight, food intake, haematology, biochemistry, urinalysis, organ weights, macroscopic pathology and histopathology were observed. The NOAEL for both sexes was 1000 mg/kg bw/day, the international regulatory limit dose. The dog NOAELs are also above the STOT-RE trigger levels.

In the dietary combined chronic toxicity and carcinogenicity study in rats, there was no indication that foramsulfuron induced chronic toxicity meeting the criteria for STOT RE classification in the rat at any dose level, so that from this study no evidence of STOT-relevant findings can be derived.
Also in the mouse carcinogenicity study, and there were no clinical signs of toxicity and no treatment related effects on survival, body weight, food consumption, haematology, organ weights, macroscopic or microscopic non-neoplastic findings which could be considered STOT-relevant.

In a 28-day dietary neurotoxicity study in Wistar rats no treatment-related effects including neurotoxic effects at any dietary level in either sex occurred. The NOAEL was established at the highest dose of 15000 ppm, equivalent to 1208 mg/kg bw/day in males and to 1415 mg/kg bw/day in females and thus above the limit dose of 1000 mg/kg bw/day.

In summary, it is concluded that foramsulfuron was well-tolerated in the repeated dose rat, mouse and dog studies, including a 12-month dog study, with high NOELs, except in the 28-day rat study, in all toxicity studies even up to the international limit dose of 1000 mg/kg bw/day. Especially, no mortalities and no functional changes in the central and peripheral nervous system or in other organs were seen. This is supported

by the results of a 28-day neurotoxicity study in rats in which no evidence of neurotoxic effects was seen. Furthermore, from the chronic toxicity and carcinogenicity studies in rats and mice no STOT-relevant findings occurred.

Table 91: Extrapolation of equivalent effective dose for toxicity studies of greater or lesser duration than 90 days [if adequate, otherwise please delete]

Study reference	Effective dose (mg/kg/d)	Length of exposure	Extrapolated effective dose when extrapolated to 90-day exposure	Classification supported by the study
No extrapolation necessary	All NOAELs in all species are above the guidance value range for STOT RE classification			

10.12.2 Comparison with the CLP criteria

It can be summarized that in the described subacute and subchronic studies in rats, mice and dogs, and in the subacute neurotoxicity study in rats no severe or critical effects, also no consistent changes in clinical biochemistry, hematology or urinalysis parameters that indicate severe organ dysfunction were seen. Also severe organ damage noted in microscopic examination following autopsy was not observed. In most studies even up to and including the highest dose no effect at all occurred. Therefore, effects which would be relevant for STOT-RE classification, like irreversible organ effects, effects on the central or peripheral nervous system or other functional changes were absent.

All NOAELs were above the classification criteria for STOT-RE classification which are summarized in the following table.

Table: STOT-RE criteria

Study type	Species	Administration	Category 1	Category 2
28-day	Rat	Oral (mg/kg bw/d)	≤ 30	≤ 300
90-day	Rat	Oral (mg/kg bw/d)	≤ 10	≤ 100

10.12.3 Conclusion on classification and labelling for STOT RE

In rodents, effects which could be relevant for STOT-RE classification did neither occur in the short-term toxicity studies nor in the chronic toxicity and oncogenicity studies or in the reproduction and developmental toxicity studies, nor in a subacute neurotoxicity study in rats with foramsulfuron.

Also in dogs no adverse severe or critical findings were reported in a subacute, subchronic or 1-year toxicity study with foramsulfuron. Therefore also the dog study results do not trigger a STOT-RE classification.

Overall, therefore, the data are conclusive, but do not warrant a STOT-RE classification according to the CLP.

RAC evaluation of specific target organ toxicity – repeated exposure (STOT RE)

Summary of the Dossier Submitter's proposal

The evaluation of STOT RE endpoint was based on nine repeated-dose toxicity studies. The studies consisted of three oral studies in dogs (28-day, 90-day and 1-year), two oral studies in mice (28-day and 90-day), two oral studies in rats (28-day and 90-day), one 28-day dermal toxicity study in rats and one 28-day neurotoxicity study in rats. In addition, the carcinogenicity studies in rats and mice and the reproductive toxicity studies in rats and rabbits were considered relevant for this endpoint. The studies were performed according to OECD TGs and were GLP-compliant.

In these studies, no effects which could be relevant for STOT RE classification occurred and no classification was proposed by the DS.

Comments received during consultation

One industry representative agreed with the DS's proposal. One MSCA noted an inconsistency in the reporting of the NOAEL for the 28-day oral toxicity study in rat in the CLH dossier, but did not comment on the classification proposal itself.

Assessment and comparison with the classification criteria

No changes in biochemical, haematological or urinalysis parameters, organ weights or histopathological parameters were seen in the repeated-dose toxicity studies in any species. In most studies, no effects occurred up to the highest dose tested (above guidance values relevant for classification). In rats, the only reported treatment-related finding was a decrease in body weight gain and an increase in water uptake in the 28-day oral toxicity study in females.

Overall, RAC agrees with the DS that **no classification for STOT RE is warranted for foramsulfuron.**

10.13 Aspiration hazard

Table 92: Summary table of evidence for aspiration hazard

Type of study/data	Test substance,	Relevant information about the study (as applicable)	Observations	Reference
No specific studies on aspiration hazard are				

Type of study/data	Test substance,	Relevant information about the study (as applicable)	Observations	Reference
available, no evidence of this hazard for foramsulfuron				

10.13.1Short summary and overall relevance of the provided information on aspiration hazard

An aspiration hazard is indicated at a kinematic viscosity of ≤ 20.5 mm^2/s at 40°C. The assumption is that the hazard exist around 20°C at application/storage temperature. The trigger value will be 20.5 mm^2/s at 20°C. Measurements are not available, however, on the basis of existing animal studies and expert judgment that takes into account surface tension, water solubility, boiling point, volatility and chemical structure (foramsulfuron is not an hydrocarbon, primary alcohol or ketone) aspiration hazard is not expected.

10.13.2Comparison with the CLP criteria

On the basis of existing animal studies and expert judgment that takes into account surface tension, water solubility, boiling point and volatility and because foramsulfuron is no hydrocarbon, no aspiration hazard is expected.

10.13.3Conclusion on classification and labelling for aspiration hazard

Since foramsufuron is not a hydrocarbon, no aspiration hazard is expected, and a classification according to the CLP is not warranted.

RAC evaluation of aspiration toxicity

Summary of the Dossier Submitter's proposal

No classification was proposed by the DS as the substance is not a hydrocarbon. Moreover, no aspiration hazard was expected based on an expert judgement taking into account the physico-chemical properties of the substance.

Comments received during consultation

One industry representative agreed with the DS's proposal.

Assessment and comparison with the classification criteria

No measurement of viscosity was available. Nevertheless, RAC agrees with the DS that **no classification is warranted for foramsulfuron,** as the substance is not a solid and is not a hydrocarbon.

11 EVALUATION OF ENVIRONMENTAL HAZARDS

11.1 Rapid degradability of organic substances

Summary of relevant studies from the Renewal Assessment Report on degradation are reported briefly below (RAR annexed to this CLH proposal). Only relevant and valid studies for the proposed classification of foramsulfuron have been included from the RAR.

Table 93: Summary of relevant information on rapid degradability

Method	Results	Remarks	Reference
Hydrolysis			
OECD: 111 USEPA: 161-1 GLP	Hydrolysis half-lives: 3.7 d at pH 4, 10.1 d at pH 5, 128 d at pH 7 and 132 d at pH 9 (25°C). 2 main hydrolysis products were formed.		RAR B.8.4.1.1, 2000
Degradation in Water			
OECD 309 GLP	No degradation observed with mineralisation to CO_2 <0.1% after 58 days. No major transformation products were observed.	At 22 °C. pH: 7.5	RAR B.8.4.2.2, 2013
Aerobic Transformation/Degradation in Soil			
USEPA: Section N, 162-1 Canada PMRA: T-1-255 SETAC-Europe 1.1 in line with OECD 307 GLP	DT50 (FOMC): 1.0 - 11.5 d. Mineralisation to CO_2 max. 17.3% after 143 days. NER: 76.9% - 88.1% after 203 d (sandy loam). NER: 65.3% - 93.8% after 196 - 199 d (clay loam). 5 degradates were observed in the soil.	Aerobic conditions 20 °C, three European soils.	RAR B.8.1.1.1/1, 2000
USEPA: Section N, 162-1 Canada PMRA: T-1-255 EU: Annex II, Point 7.1. 1.1 in line with OECD 307 GLP	DT50 (FOMC): 6.7 - 9.2 d Mineralisation to CO_2 max. 21.5% after 366 d. NER: 56% - 88% after 188 days. 4 degradates were observed in the soil.	Aerobic conditions 25 °C, two U.S soils.	RAR B.8.1.1.1/2, 1999
USEPA: Section N, 162-1 Canada PMRA: T-1-255 EU: SETAC- Europe 1.1 in line with OECD 307 GLP	DT50 (DFOP): 18.5 – 20.5 d Mineralisation to CO_2 max. 1.7%. NER: 72.2% - 83.9% after 133 d 5 degradates were observed in the soil.	Aerobic conditions at 10 °C, one European soil.	RAR B.8.1.1.1/3, 2000
Aerobic Transformation/Degradation in Sediment/Water Systems			
USEPA: Section N, 162-4 Canada PMRA: T-1-255 EU: Annex II, Section 7, Point 7.2.1.3.2 GLP	<u>Degradation (whole system)</u> DT50 (SFO): 26.0 - 28.7 d (silty clay loam) DT50 (SFO): 37.9 - 41.4 d (sand) Mineralisation to CO_2 max. 6.2% after 365 d. NER: 77.3 - 93.1% (silty clay loam) after 363 d. NER: 40.4 - 53.8% (sand) after 365 d.	Aerobic conditions at 20 °C. pH: 5.7 - 6.2 (silty clay loam) pH: 7.8 - 8.4 (sand)	RAR B.8.4.2.3, 2000

Method	Results	Remarks	Reference
	2 main degradates were formed.		
Photolytic degradation at soil surface			
Directives 95/36/EEC EPA-540/9-82-021, Section 161-3 GLP	Photolytic half-life >300 d corresponding to > 431 d for conditions of Florida summer sunlight. One degradation product observed < 10%.	Photolysis on soil surface	RAR B.8.1.3/1, 2000
US EPA Fate, Transport and Transformation Guidelines. OPPTS 835.2410 OECD Guidelines for the Testing of Chemicals. 2002 Draft Document GLP	DT50 was determined as 15.9 d which is equivalent to 30.5 environmental days under Arizona (US) light conditions. One main transformation product observed (10.4%) resulting from photo-degradation. Photolytically induced degradation is significantly slower when being compared to biotic processes of degradation.	Phototransformation on soil surface	RAR B.8.1.3/2, 2012
Photolytic degradation in water			
USEPA: § 161-2 line with OECD 316 GLP	Photolytic half-life: 500 - 538 d (12 hours day/night interval)	At 25° pH: 7 sterile aqueous buffer	RAR B.8.4.1.2.1/1, 1999
US EPA Guidelines OPPTS 835.2240 EC guidelines 94/37/EC and 95/36/EC GLP	Photolytic half-life: 11.6 - 14.9 d (Athens, Greece) 4 degradation products were observed.	At 25°C pH: 7 sterile aqueous buffer solution, two radiolabels	RAR B.8.4.1.2.1/2, 2012
OECD 316 GLP	DT50: 48.7 - 2280 d depending on the latitude. DT50: 58 - 14000 d depending on season. Quantum yield: 6.18 x 10^{-4} Φ		RAR B.8.4.1.2.1/3, 2013
US EPA Subdivision N, Section 161-2 GLP	DT50: 10.7 d (light conditions of Athens, Greece). 3 main transformation products were observed.	At 25°C pH: 8.3 Indirect phototransformation Sterilised natural water 1 radiolabel	RAR B.8.4.1.2.2/1, 2009
US EPA Subdivision N, Section 161-2 GLP	DT50: 9.6 d (light conditions of Athens, Greece) 3 main transformation products were observed.	At 25°C pH: 7.9 Indirect phototransformation Sterilised natural water 1 radiolabel	RAR B.8.4.1.2.2/2, 2008

11.1.1 Ready biodegradability

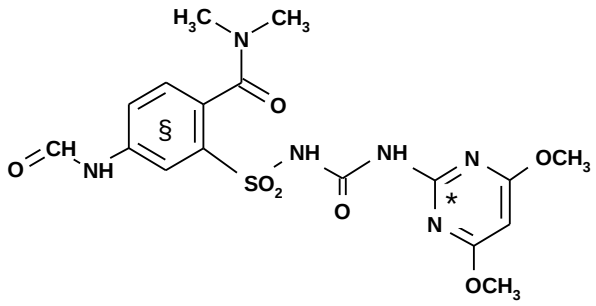
No data available.

11.1.2 BOD_5/COD

No data available.

11.1.3 Hydrolysis

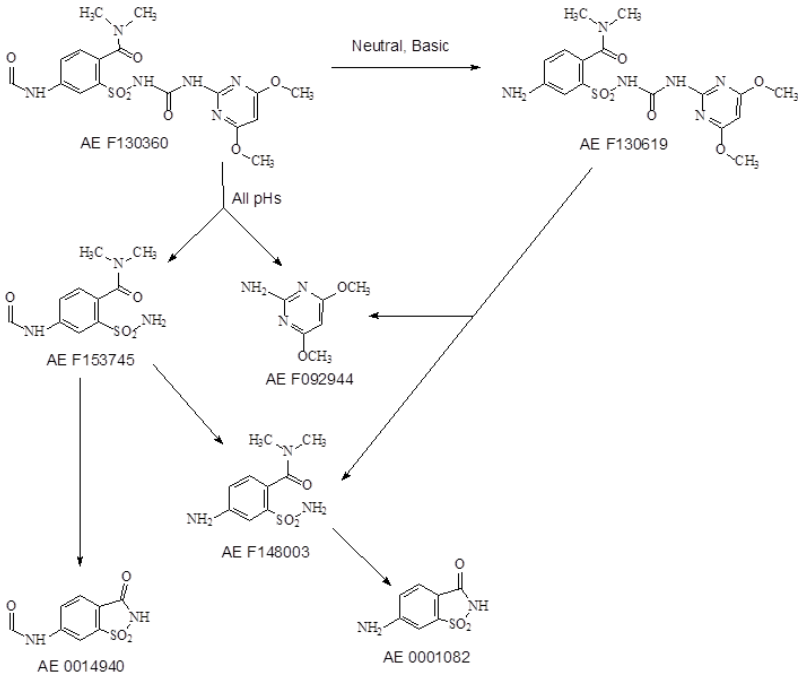
The studies investigating the environmental fate of foramsulfuron were performed with the following positions of 14C-radiolabel in the active substance:



(§) Label 1: [phenyl-UL-^{14}C]
(*) Label 2: [pyrimidyl-2-^{14}C]

The abiotic hydrolysis of foramsulfuron was investigated in a study according to the OECD guidance 111 and GLP (RAR B.8.4.1.1, 2000). Sterile aqueous buffer at pH 4, 5, 7 and 9 was used and the ^{14}C-labelled foramsulfuron was applied and incubated at 25 °C and 40 °C in the dark. Hydrolysis of the substance was shown to be dependent on pH resulting in half-lives of 3.7 d at pH 4, 10.1 d at pH 5, 128 d at pH 7 and 132 d at pH 9 (25°C). Dependent on position of radiolabel, the substance was found to form 2-amino-4,6-dimethoxypyrimidine (AE F092944) and 4-formylamino-N,N-dimethyl-2-sulfamoylbenzamide (AE F153745) as main (>10% AR) hydrolysis products at 83.3% AR (pH 5, day 30, 25°C) and 71.3% (pH 5, day 30, 25°C) in the course of the study accompanied by the formation of 4-amino-2-[3-(4,6-dimethoxypyrimidin-2-yl)ureidosulfonyl]-N,N-dimethylbenzamide (AE F130619), 4-amino-N,N-dimethyl-2-sulfamoylbenzamide (AE F148003), N-(1,1-dioxido-3-oxo-2,3-dihydro-1,2-benzothiazol-6-yl)formamide (AE 0014940) and AE 0001082 as minor (i.e. <10% AR) hydrolysis products.

Figure 1. Proposed hydrolysis pathway of foramsulfuron (AE F130360) in sterile aqueous buffer.



11.1.4 Other convincing scientific evidence

11.1.4.1 Field investigations and monitoring data (if relevant for C&L)

No data available.

11.1.4.2 Inherent and enhanced ready biodegradability tests

No data available.

11.1.4.3 Water, water-sediment and soil degradation data (including simulation studies)

Kinetic evaluation of the degradation behaviour of foramsulfuron was conducted following FOCUS kinetics in the RAR.

Degradation in surface water

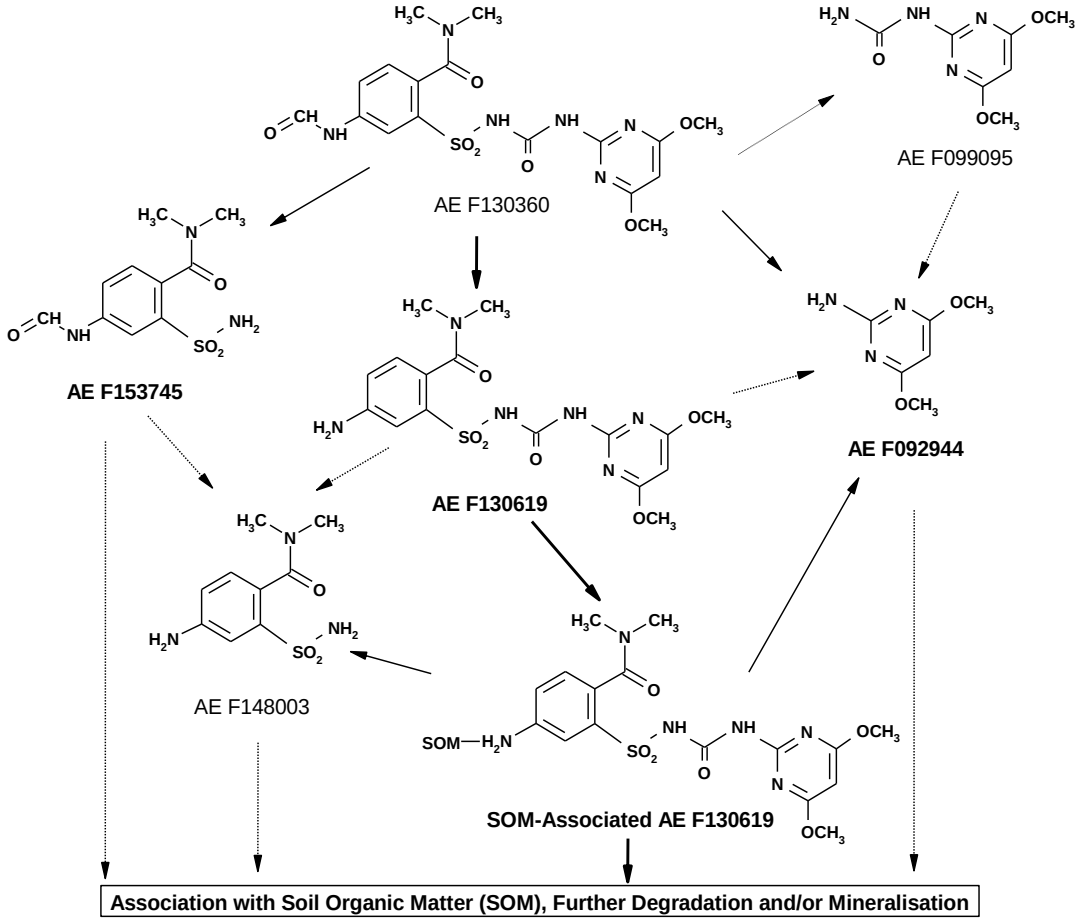
The aerobic degradation of foramsulfuron in surface water was investigated according to the OECD guideline 309 and GLP standards (RAR B.8.4.2.2, 2013). Freshly sampled lake water was exposed to 10.9 µg/L (low dose) and 108.5 µg/L (high dose) of foramsulfuron. A flow-through system was used. The experiment was conducted at 21.7 ± 0.6 °C at pH 7.5 in the dark for 58 days in maximum. Biological activity of the test water was confirmed by the degradation of reference substance UL-^{14}C-benzoic acid within 14 days of incubation. The mean material balances were 99.8% ± 0.9% AR for low dose samples and 100.4% ± 1.7% for the high dose. Degradation of phenyl-labeled foramsulfuron was very slow to result in values of 96.2% AR at day 0 to 93.8% after 58 days for the low dose and 98.3% AR at day 0 to 94.3% after 58 days for the high dose. Degradation was very slow in sterile controls as it is documented by a value of 95.9% for foramsulfuron after 78 days of incubation. No major transformation products were thus observed requiring consideration in environmental risk assessments. No experimental value was calculated for the DT50 of foramsulfuron in water

under conditions of aerobic mineralisation testing as the degradation was insignificant. Formation of ^{14}C-carbon dioxide or other volatile components was negligible to account for less than 0.1% of the substance for both concentrations tested at the end of the study.

Degradation in soil

The degradation of foramsulfuron was found to proceed via two routes, i.e. firstly by hydrolysis of the formamide group of the parent compound to result in the formation of the amino-aryl derivative AE F130619 as the predominant pathway. The second pathway involved cleavage of the 'sulfonylurea bridge' to form AE F153745 and AE F092944.

Figure 2. Proposed pathway of degradation of foramsulfuron (AE F130360) in aerobic soil



Three studies are available evaluating the degradation of the ^{14}C-labelled foramsulfuron in different soils (EU and non-EU soils) under aerobic conditions. All studies were conducted according to the USEPA guidance, which is in line with the OECD guidance 307. In all studies, samples were analysed for the presence of the test substance at the beginning of the test and regular time intervals.

In the first study (RAR B.8.1.1.1/1, 2000) the degradation of ^{14}C-labelled foramsulfuron was studied in 3 European soils (sandy loam and clay loam). The treatments were incubated in the dark at 20 °C ± 1 °C for a maximum of 203 d. [U-^{14}C-phenyl]-foramsulfuron or [2-^{14}C-pyrimidyl]-foramsulfuron in acetonitrile was applied to soil equivalent to a field rate of 90 g/ha. The radioactive residue was characterized as extractable, non-extractable or volatile. Mass balance (consisting of radioactivity recovered in the volatile, extractable, and non-extractable residue fractions) was 85.2% to 115.9% (one exception of 125.0% of applied) in all samples for both experiments. Measured degradation products in the soil were 4-amino-2-[3-(4,6-dimethoxypyrimidin-2-yl)ureidosulfonyl]-N,N-dimethylbenzamide (AE F130619), 4-formylamino-N,N-dimethyl-2-sulfamoylbenzamide (AE F153745) and 2-amino-4,6-dimethoxypyrimidine (AE F1092944) while 4-amino-N,N-dimethyl-2-sulfamoylbenzamide (AE F148003) and 4,6-dimethoxypyrimidin-2-ylurea (AE F099095) occurred at trace level.. The dissipation half-lives were between 1.0 and 11.5 d. Mineralisation reached a maximum of 1.2% after 107 days in samples treated with [U-^{14}C-phenyl]-foramsulfuron, whereas mineralisation reached a maximum of 17.3% after 143 days in samples treated with [2-^{14}C-pyrimidyl]-foramsulfuron. Non-extractable residues (NER) were 76.9% to 88.1% AR for the sandy loam soil after 203 days of incubation. For the two clay loam soils, maximum NER of 73.1% to 103.2% was reached after 107 days followed by a decline to 65.3% to 93.8% at the end of the study (day 196 and day 199, respectively). In sterile sandy loam soil maximum NER of 46.4% to 68.1% was reached at the end of the study (day 134).

In the second study (RAR B.8.1.1.1/2, 1999) the degradation of foramsulfuron in two U.S soils under aerobic conditions and 25 °C (incubated in the dark) was tested. The test was conducted with a silty clay loam and a loamy sand and foramsulfuron was applied at a concentration of 60 g/ha. The treatments were incubated for maximum of 366 days. Soil extracts were analysed by reversed phase HPLC and confirmed by normal and reverse phase TLC. Mass balances ranged from 94.2 to 105.4% for all samples except 88.6% AR at day 188. The dissipation half-lives were between 6.7 - 9.2. Mineralisation to carbon dioxide was about 1% after 366 d for samples treated with [U-^{14}C-phenyl]-foramsulfuron, while it ranged from 11.7% to 21.5% in maximum for samples treated with [2-^{14}Cpyrimidyl-foramsulfuron. Degradates observed in the soil were 4-amino-2-[3-(4,6-dimethoxypyrimidin-2-yl)ureidosulfonyl]-N,N-dimethylbenzamide (AE F130619), 2-amino-4,6-dimethoxypyrimidine (AE F1092944), 4-formylamino-N,N-dimethyl-2-sulfamoylbenzamide (AE F153745) and 4-amino-N,N-dimethyl-2-sulfamoylbenzamide (AE F148003). Non-extractable residues (NER) were maximum of 87 - 88% at day 188 for both soils ([U-14C-phenyl]-foramsulfuron) and 56 - 76% following treatment with pyrimidyl-labelled active substance for the silty clay loam and loamy sand soil at day 188 and day 90, respectively.

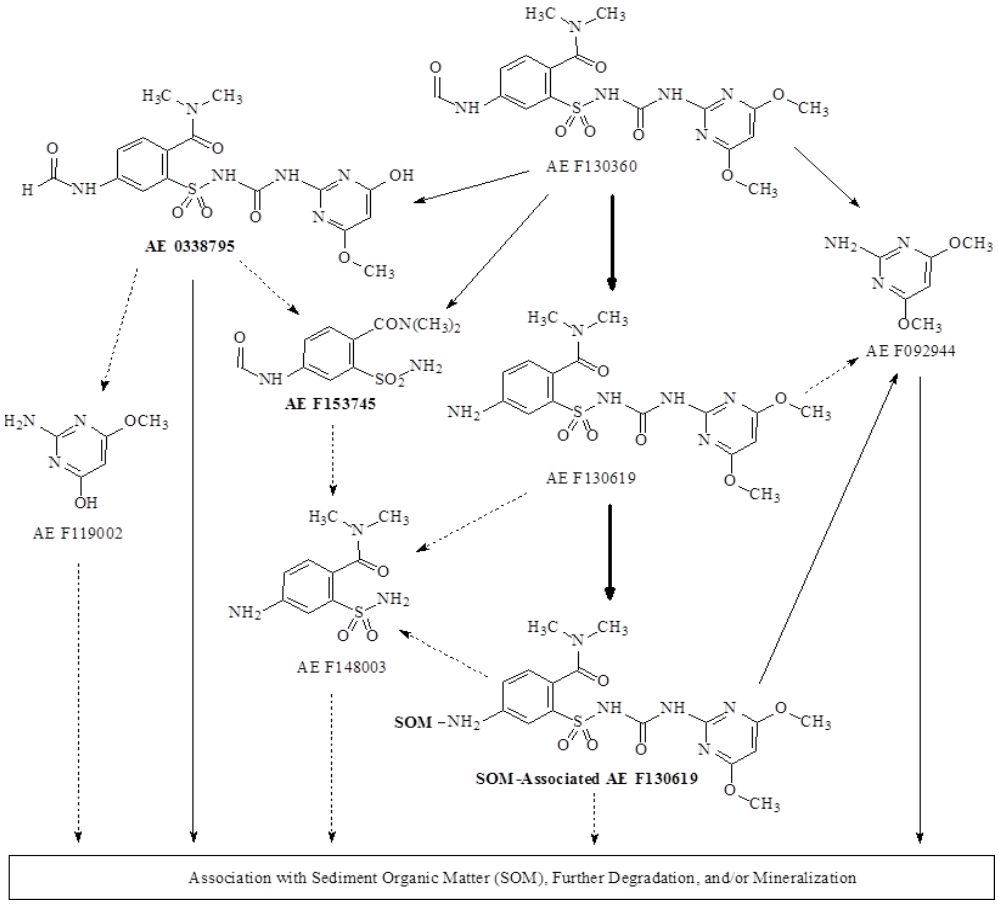
The third available study (RAR B.8.1.1.1/3, 2000) was conducted with one European soil (sandy loam) and 10 °C for 133 days. Foramsulfuron was applied to the soil at a concentration equivalent to 90 g/ha and incubated under aerobic and dark conditions for 250 d. Mass balance (consisting of radioactivity recovered in the volatile, extractable, and non-extractable residue fractions) was 91.1% to 110.2% in all samples. Foramsulfuron degraded forming five main degradates (AE F130619, AE F1153745, AE F148003, AE F092944 and AE F099095). The dissipation half-lives were between 18.5 and 20.5 d. However, mineralisation reached a maximum of 0.4% to 1.7%. Total NER at the end of the study were between 72.2% - 83.9% after 133 d.

In conclusion, the degradation of foramsulfuron proceeded via rapid loss of the formyl group at the benzamine moiety of the active substance to result in the formation of 4-amino-2-[3-(4,6-dimethoxypyrimidin-2-yl)ureidosulfonyl]-N,N-dimethylbenzamide (AE F130619). In the following hydrolysis at the sulfonyl urea structural element resulted mainly in formation of 4-formylamino-N,N-dimethyl-2-sulfamoylbenzamide (AE F153745) and 2-amino-4,6-dimethoxypyrimidine (AE F092944). Foramsulfuron degrades rapidly in soil by hydrolysis forming several degradation products. However, only minor mineralisation of foramsulfuron was observed under the test conditions.

Degradation in water/sediment system

The kinetics and degradation of [U-14C-phenyl]-foramsulfuron and [2-14C-pyrimidyl]-foramsulfuron were studied in two sediment-water systems, a silty clay loam (363 days) and a sand sediment (365 days) and their respective overlying water (RAR B.8.4.2.3, 2000). The study was conducted according to the US EPA: 162-4 guideline which is in line with the OECD guideline 308 and GLP standards. The silty clay loam water/sediment system was more acidic (pH 5.7 – 6.2) than the sand sediment (pH 7.8 – 8.4). A solution of radiolabelled foramsulfuron in acetonitrile was applied to surface of the water overlying sediment at a target rate of 36.6 µg a.i./flask. Flasks were incubated in the dark at 20 °C ± 1 °C. The half-life in the total system (sediment plus water) in silty clay loam sediment system was 26.0 - 28.7 days and in sand sediment system 37.9 - 41.4 days. Mineralisation to carbon dioxide was observed and accounted at a maximum of 6.2% of applied radioactivity by day 365. Total non-extractable residues (NER) at the end of the test were 77.3 - 93.1% in the silty clay loam sediment and 40.4 - 53.8% in sand sediment. Degradation of foramsulfuron proceeded via three pathways in total with de-methylation at an oxygen atom resulting in 4-formylamino-2-[3-(4-hydroxy-6-methoxypyrimidin-2-yl)ureidosulfonyl]-N,N-dimethylbenzamide (AE 0338795) to be the major route. Foramsulfuron also degraded via hydrolysis at the formamide moiety to form 4-amino-2-[3-(4,6-dimethoxypyrimidin-2-yl)ureidosulfonyl]-N,N-dimethylbenzamide (AE F130619) while hydrolysis at the ‘sulfonyl urea bridge’ resulted in the formation of 4-formylamino-N,N-dimethyl-2-sulfamoylbenzamide (AE F153745) and 2-amino-4,6-dimethoxypyrimidine (AE F092944). Main degradates at more than 10% AR in water/sediment testing were 4-formylamino-2-[3-(4-hydroxy-6-methoxypyrimidin-2-yl)ureidosulfonyl]-N,N-dimethylbenzamide (AE 0338795) and 4-formylamino-N,N-dimethyl-2-sulfamoylbenzamide (AE F153745).

Figure 3. Proposed pathway of degradation of foramsulfuron (AE F130360) in water/sediment systems.



11.1.4.4 Photochemical degradation

According to the guidance on the application of the CLP criteria (2017) the actual degree of photochemical degradation in the aquatic environment depends on local conditions e.g. water depth, suspended solids, turbidity as well as seasonal influences, and the hazard of the degradation products is usually not known. However, consideration of photochemical degradation is not precluded by the guidance and therefore for completeness reasons photochemical degradation data were included in the classification proposal.

Photodegradation in soil

Two studies are available and were performed with foramsulfuron at two positions of radiolabel RAR B.8.1.3/1, 2000 and RAR B.8.1.3/2, 2012). The tests indicated slow transformation by photolytic processes on soil surfaces. The contribution of photolytic transformation is thus insignificant to the elimination of the substance residues from the soil environment.

Phototransformation in water

The phototransformation of foramsulfuron in water was studied in a test similar to the OECD 316 and GLP standards (RAR B.8.4.1.2.1/1, 1999). The ^{14}C-labelled foramsulfuron was applied in sterile aqueous buffer at

pH 7 following irradiation with artificial sunlight (xenon light, 290 nm cutoff) at 25°. The study revealed that photolytic degradation of the substance was negligible. Half-lives of 500 days (Suntest I) or 538 days (Suntest II) were determined when being referenced to natural sunlight and considering a 12 hours day/night interval.

A further test is available testing the phototransformation of [phenyl-UL-^{14}C] and [pyrimidine-2-^{14}C] foramsulfuron in water (RAR B.8.4.1.2.1/2, 2012). The study was conducted at 25 °C in sterile buffer (pH 7) at an initial concentration of approximately 1.0 mg a.i./L under artificial irradiation (xenon lamp, >290 nm, quartz and SupraxÒ filter) for 6 to 7 days (corresponding to 18-21 environmental days). The degradation of foramsulfuron in sterile aqueous buffer solution was moderate to result in half-lives of 11.6 and 14.9 days (Athens, Greece) for phenyl and pyrimidyl labelled active substance, respectively. Irradiation resulted in two main label-specific transformation products at maximum values of 10.2 – 16.6% of AR in phenyl-labelled foramsulfuron (4-amino-N-methylbenzamide and 4-formamido-N-methylbenzamide) and 14.2 – 35.2% of AR in pyrimidine-labelled foramsulfuron (foramsulfuron sulfamic acid and 4,6-dimethoxypyrimidin-2-ylurea).

Based on the findings of the second study photolysis may contribute to the overall elimination of foramsulfuron from the aquatic environment.

Direct Photolysis in water

A study according to OECD 316 testing the direct photo-transformation of foramsulfuron in aqueous solution is available (RAR B.8.4.1.2.1/3, 2013). The UV-VIS adsorption spectra for solutions of foramsulfuron in purified water and the corresponding buffer solutions were recorded by a spectrophotometer. The solution was irradiated for 500 minutes. A decline of approximately 12 to 14% was found for foramsulfuron in aqueous solutions. The actinometric determination of light intensity resulted in a mean value of 6.18 x 10^{-4} for the quantum yield Φ. Direct photo-transformation has a limited contribution to the overall elimination of foramsulfuron in the environment. DT50 values range between 48.7 – 2280 d depending on the latitude. In conclusion, the results of quantum yield determination and its associated estimation of direct photo-transformation in aqueous solution indicate that this potential route of degradation may contribute to the overall elimination of the substance in the environment.

Indirect phototransformation in water

The indirect phototrasformation of foramsulfuron in sterile natural water was tested following OECD test guideline 316 in two studies following application of ^{14}C-labelled active substance and irradiation (xenon light, 290 nm cutoff) at 25°C under light conditions equivalent to Tokyo.

In the first study (RAR B.8.4.1.2.2/1, 2009) indirect phototransformation of foramsulfuron was tested in natural water at pH 8.1. The ^{14}C labelled substance was applied to a concentration of 1 mg/L in a lake water. The solution was filter sterilised and irradiated for 5 d (34 environmental days, Tokyo Japan). In irradiated samples, foramsulfuron showed a decrease from 94.4% AR at time zero to 11.0% after 5 days while degradation of foramsulfuron was negligible in dark controls. Irradiation resulted in a complex pattern of transformation products with formation of at least 16 minor components with foramsulfuron amine, 4-formamido-N-methylbenzamide and 4-amino-N-methylbenzamide formed as major products at maximum values of 10.7% (day 1), 19.7% (day 3) and 12.8% (day 4), respectively. Additionally, foramsulfuron sulfonic acid was found as a minor product at 6.7% AR in maximum (day 4). The indirect photolytic transformation of the substance in sterile natural water was moderate and a half-life of 10.7 environmental days (Athens, Greece) was detected.

In the second study (RAR B.8.4.1.2.2/2, 2008) indirect phototransformation of foramsulfuron was tested in natural water at pH 7.9. The test was performed with pyrimidinyl-2-^{14}C-foramsulfuron at an initial concentration of 1.00 mg/L. In irradiated samples, foramsulfuron showed a decrease from 97.5% AR at time zero to 13.5% after 5 days. Degradation of foramsulfuron was negligible in dark controls. Irradiation resulted in a complex pattern of transformation products with formation of at least 13 minor components. Major degradation products were foramsulfuron urea, foramsulfuron sulfamic acid and foramsulfuron

pyrimidinamine at maximum values of 19.7% (day 5), 17.6% (day 5) and 26.5% (day 5), respectively. Additionally, foramsulfuron amine was found as a minor product at 6.1% AR in maximum (day 1). Half-life of 9.6 environmental days (light conditions of Athens, Greece) was detected.

11.1.5 Conclusion on rapid degradability

Results from the simulation studies demonstrate that foramsulfuron is not ultimately degradable (≥ 70 % mineralised) in water, soil or sediment simulation tests. According to the guidance on the application of the CLP criteria (2017), preferred data types for the decision on rapid degradability are ready biodegradability studies and surface water simulation tests. When these preferred data types are not available rapid degradation may be demonstrated by soil or aquatic water/sediment simulation tests. For foramsulfuron ready biodegradation studies are not available and therefore the assessment of rapid degradability is primarily based on the test of aerobic mineralisation in surface water (RAR B.8.4.2.2, 2013) and the test on hydrolysis (RAR B.8.4.1.1, 2000). The test on aerobic mineralisation in surface water showed that degradation in non-sterile natural water was insignificant and no major degradation products were observed. No experimental DT50 value was calculated in the study. Soil and sediment simulation studies further support that ultimate degradation of foramsulfuron is slow also in these compartments.

According to the guidance on the application of the CLP criteria (2017), data on hydrolysis can be considered for classification purposes but only when the longest half-life t½ determined within the pH range 4-9 is shorter than 16 days. Hydrolysis is not considered as an ultimate degradation and various intermediate degradation products may be formed, some of which may be only slowly degradable. Only when it can be satisfactorily demonstrated that the hydrolysis products formed do not fulfil the criteria for classification as hazardous for the aquatic environment, data from hydrolysis studies can be considered. Hydrolysis half-lives at pH 7-9 (25°C) of foramsulfuron were over 16 days (RAR B.8.4.1.1, 2000).

Photochemical degradation processes can contribute to some extent to degradation of foramsulfuron in the environment. However, photochemical degradation of foramsulfuron in the environment is not considered relevant to be taken into account for the classification purposes of foramsulfuron when more preferred data are available. Photochemical degradation in the environment is dependent on local conditions eg. water depth and suspended solids.

Consequently, foramsulfuron is considered to be **not rapidly degradable** because:

- it was not demonstrated that foramsulfuron is ultimately degraded > 70 % within 28 days in the aquatic environment. Mineralisation to CO_2 was negligible (<0.1 %) with insignificant primary degradation in non-sterile natural water after 58 days (RAR B.8.4.2.2, 2013).
- hydrolytic degradation half-lives were not under 16 days in the whole pH range of 4.0-9.0 and the hydrolysis product AE F130619 fulfils the classification criteria as hazardous for the aquatic environment.

11.2 Environmental transformation of metals or inorganic metals compounds

Not applicable.

11.2.1 Summary of data/information on environmental transformation

11.3 Environmental fate and other relevant information

11.4 Bioaccumulation

11.4.1 Estimated bioaccumulation

No data available.

11.4.2 Measured partition coefficient and bioaccumulation test data

No experimental bioaccumulation data is available. Due to the low measured log Kow (log Kow value 1.44 at pH 2 and -0.78 at pH 7) measured in OECD 107 (shaking flask method) foramsulfuron has a low potential for bioaccumulation. The log Kow of foramsulfuron does not met the CLP criteria of log Kow ≥ 4 indicating a potential to bioaccumulate.

11.5 Acute aquatic hazard

Evaluation of acute aquatic hazard for foramsulfuron is based on studies which are considered valid in the Renewal Assessment Report of foramsulfuron (RAR annexed to this CLH proposal). All valid studies are presented in the table below and relevant studies for the classification purposes are also briefly summarised below. More details can be found in the annexed RAR. Ecotoxicological information is based on technical foramsulfuron (AE F130360) with a minimum purity of 94.2 % in the following studies.

Table 94: Summary of relevant information on acute aquatic toxicity

Method	Species	Test material	Results	Remarks	Reference
Fish					
OECD 203 GLP 96 h semi-static test	*Oncorhynchus mykiss* (rainbow trout)	Foramsulfuron (98.6 % purity)	LC50 (96 h) > 100 mg/L	Based on nominal but analyt. verified concentrations	RAR B.9.2.1.1, 1997
OECD 203 GLP 96 h semi-static test	*Lepomis macrochirus* (bluegill sunfish)	Foramsulfuron (98.6 % purity)	LC50 (96 h) > 100 mg/L	Based on nominal but analyt. verified concentrations	RAR B.9.2.1.2, 1997
OECD 203 GLP 96 h static test	*Cyprinodon variegatus* (sheephead minnow)	Foramsulfuron (94.2 % purity)	LC50 (96 h) > 100 mg/L	Based on nominal but analyt. verified concentrations	RAR B.9.2.1.3, 1998
OECD 203 GLP 96 h static test	*Oncorhynchus mykiss* (rainbow trout)	Degradate AF F092944 (> 99 % purity)	LC50 (96 h) 254 mg/L	Based on nominal but analyt. verified concentrations	RAR B.9.2.1.4, 1993
Aquatic invertebrates					
OECD 202 GLP 48 h semi-static test	*Daphnia magna*	Foramsulfuron (98.4% purity)	EC50 (48 h) > 100 mg/L	Based on nominal but analyt. verified concentrations	RAR B.9.2.4.1, 1997
OECD 202 GLP 48 h static test	*Daphnia magna*	Degradate AF F092944 (> 99 % purity)	EC50 (48 h) = 223 mg/L	Based on nominal but analyt. verified concentrations	RAR B.9.2.4.2, 1993
Algae					
OECD 201 GLP 96 h static test	*Pseudokirchneriella subcapitata* (green alga)	Foramsulfuron (94.2 % purity)	ErC50 (72 h) = 75.0 mg/L (growth) E_bC50 (72 h) = 10.9 mg/L (biomass) ErC50 (96 h) = 86.2 E_bC50 (96 h) = 12.5 mg/L	Based on nominal but analyt. verified test concentrations	RAR B.9.2.6.1, 1998
OECD 201 GLP 72 h static test	*Navicula pelliculosa* (diatom)	Foramsulfuron (94.2 % purity)	ErC50/E_bC50 (72h) > 112 mg/L	Based on mean measured concentrations	RAR B.9.2.6.2, 1999
OECD 201 GLP	*Anabaena flos-aquae* (blue-green alga)	Foramsulfuron (94.6 % purity)	ErC50 (72/96 h) = 8.1 mg/L	Based on nominal but analyt.	RAR B.9.2.6.3, 1999

96 h static test			E_bC50 (96 h) = 3.3 mg/L	verified concentrations	
OECD 201 GLP 96 h static test	*Skeletonema costatum* (marine diatom)	Foramsulfuron (94.6 % purity)	ErC50 (96 h) >105 mg/L	Based on mean measured concentrations	RAR B.9.2.6.4, 1999
OECD 201 GLP 72 h static test	*Desmodesmus subspicatus (green alga)*	Degradate F092944 (> 99 % purity)	ErC50 (72 h) >560 mg/L	During the study analytical measurements were carried out only in one test item concentration (18 mg/L). Based on nominal but analyt. verified concentrations.	RAR B.9.2.6.5, 1993
OECD 201 GLP 72 h static test	*Pseudokirchneriella subcapitata* (green alga)	Degradate F099095 (99.6 % purity)	ErC50 (72 h) >100 mg/L	Based on nominal but analyt. verified concentrations.	RAR B.9.2.6.6, 2005
Aquatic macrophytes					
US EPA 122-2 in line with OECD 221 GLP 7 d static test	*Lemna gibba* (duck weed)	Foramsulfuron (96.1 % purity)	ErC50 (7 d) = 1.01 µg/L EbC50 (7 d) = 0.65 µg/L	Based on nominal concentrations but analyt. verified at day 0 and day 7. Mean measured concentrations in range of 87 to 121 % of nominal.	RAR B.9.2.7.1, 1998
EU Directive 91/414/EEC GLP 42 d semi-static test with static conditions at days 0-7.	***Lemna gibba* (duck weed)**	**Foramsulfuron (97.3 % purity)**	**ErC50 (7 d) = 0.96 µg/L (growth rate, frond area) ErC50 (7 d) = 1.22 µg/L (growth rate frond number)**	**Higher tier prolonged growth inhibition study (6 weeks), 1st week equal to *Lemna* standard test OECD 221. Based on nominal but analytically verified concentrations**	**RAR B.9.2.7.4, 2013 Key study**
EU directive 91/414/EEC in line with OECD 221 GLP 7d static test	*Lemna gibba* (duck weed)	Foramsulfuron (97.3 % purity)	peak-ErC50 > 56.8 µg/L	Growth Inhibition, peak exposure (1 d exposure + 6 d recovery)	RAR B.9.2.7.3, 2013

				Based on nominal but analyt. verified concentrations Supportive study	
OECD 221 GLP 21 d	*Lemna gibba* (duck weed)	Foramsulfuron (97.3 % Purity)	No acute endpoint derived. EC50 value is approximately the lowest test concentration 0.625 µg/L	Growth Inhibition + Recovery (7 d + 14 d)	RAR B.9.2.7.2, 2005
No guideline GLP 6 weeks	ten aquatic plant species	Foramsulfuron WG (52.2 % purity)	Lowest growth rate ErC50 (6 weeks, *Elodea canadensis*) = 0.85 µg a.s./L	Outdoor growth inhibition (6 weeks) and recovery study (2 d + 5.5 weeks) Based on geom. mean measured concentrations Supportive study	RAR B.9.2.7.5, 2012
OCSPP Guideline Number 850.SUPP GLP 14 d static test	*Myriophyllum spicatum*	Foramsulfuron (97.6% purity)	EyC50 (14 d) for all endpoints > 84 µg/L	Based on the study results *Myriophyllum spicatum* is not considered the most sensitive aquatic macrophyte Calculations based on mean measured concentrations	RAR B.9.2.7.6, 2012
US EPA 123-2 GLP 7d semi-static test	*Lemna gibba* (duck weed)	Degradate F153745 (97.8 % purity)	EC50 > 100 mg/L	Based on nominal but analyt. verified concentrations	RAR B.9.2.7.7, 2000
US EPA 123-2 GLP 7d semi-static test	*Lemna gibba* (duck weed)	Degradate F0338795 (90.2 % purity)	ErC50 (7 d) = 27.2 mg/L E_bC_{50} (7 d) = 14.8 mg/L	Based on nominal but analyt. verified concentrations.	RAR B.9.2.7.8, 2000
US EPA 123-2 GLP 7d semi-static test	*Lemna gibba* (duck weed)	Degradate F092944 (98.8 % purity)	EC50 > 100 mg/L	Based on nominal but analyt. verified concentrations	RAR B.9.2.7.9, 2000

OECD 221 GLP 7 d	*Lemna gibba* (duck weed)	Degradate F099095 (99.6 % purity)	EC50 > 100 mg/L	Based on nominal but analyt. verified concentrations	RAR B.9.2.7.10, 2005
OECD 221 GLP 7 d static test	*Lemna gibba* (duck weed)	Degradate F130619 (94 % purity)	ErC50 (7 d) = 0.889 µg/L (frond area) ErC50 (7 d) = 1.50 µg/L (frond number)	Based on nominal but analyt. verified concentrations.	RAR B.9.2.7.11, 2013
EU directive 91/414/EEC GLP 7 d static test	*Lemna gibba* (duck weed)	Degradate 4-amino-N-methylbenzamide (BCS-CV29520) (97.6 % purity)	No effects observed	limit test at 10 mg/L	RAR B.9.2.7.12, 2013
OECD 221 GLP 7 d static test	*Lemna gibba* (duck weed)	Degradate 4-Formamido-N-methylbenzamide (BCS-CW90756) (99 % purity)	No effects observed	limit test at 10 mg/L	RAR B.9.2.7.13, 2013
OECD 221 GLP 7d static test	*Lemna gibba* (duck weed)	Degradate Foramsulfuron-sulfamic acid (BCS-AW41401) (89.7 % purity)	No effects observed	limit test at 10 mg/L	RAR B.9.2.7.14, 2013
Other aquatic organisms					
OECD 203 GLP 96 h static test	*Palaemonetes pugio* (grass shrimp)	Foramsulfuron (94.2% purity)	LC50 (96 h) > 100 mg/L	Based on nominal but analyt. verified concentrations	RAR B.9.2.8.1, 1998
USEPA (=EPA): FIFRA 72-3, SEP 540/9-85-011 GLP 96 h flow-through test	*Crassostrea virginica* (eastern oyster)	Foramsulfuron	EC50 (96 h) = 118 mg/L	Based on mean measured concentrations	RAR B.9.2.8.2, 1998

11.5.1 Acute (short-term) toxicity to fish

Three studies testing the acute toxicity of foramsulfuron towards three different fish species are available. All tests were conducted according to the OECD test guideline 203 and GLP. They are all considered relevant for the classification purposes. The 96h LC_{50} is > 100 mg/L (nominal) for all three species as no mortality or sublethal effects were observed in the studies. Analytical verification confirmed the nominal concentrations.

One acute toxicity study (RAR B.9.2.1.4, 1993) is available for degradation product AE F092944 (2-amino-4,6-dimethoxypyrimidine) for fish (*Oncorhynchus mykiss*). The study was conducted according to the OECD test guideline 203 and GLP. Based on analytical verification the biological endpoints are reported as nominal concentrations. The 96h LC_{50} is 254 mg/L for degradate AE F092944. This end point is based on nominal concentrations even though the measured concentration in the highest treatment group is below 80 % of the nominal. However, since the toxicity of the degradate AE F092944 is not driving the risk assessment of foramsulfuron this is considered acceptable in the RAR by RMS.

11.5.2 Acute (short-term) toxicity to aquatic invertebrates

One study is available evaluating the toxicity of foramsulfuron to aquatic invertebrates (RAR B.9.2.4.1, 1997). The study was conducted according to the OECD test guideline 202 and GLP standards. No mortality or sublethal effects were observed in the study. The EC_{50} (48 h) is > 100 mg/L (nominal), analytical verification confirmed the nominal concentrations. This study is relevant for the classification purposes.

One acute toxicity study (RAR B.9.2.4.2, 1993) is available for degradation product AE F092944 (2-amino-4,6-dimethoxypyrimidine) for aquatic invertebrates. The study was conducted according to the OECD test guideline 202 and GLP. During the study analytical measurements were carried out only in the lowest test item concentration, which is not in line with the test guideline OECD 202. The analysis of the test substance with a nominal concentration of 10 mg/L resulted in a value of 100.4% of the nominal value. Nonetheless, this study is considered valid in the RAR. The 48 h EC50 value of 223 mg/L was observed in the test based on nominal concentrations.

11.5.3 Acute (short-term) toxicity to algae or other aquatic plants

Potential effects of foramsulfuron on algal growth were investigated with four different algae species, a green alga, a blue-green alga and a freshwater and a marine diatom. All four studies were conducted according to the OECD guideline 201 and GLP standards and are considered valid in the RAR. E_rC_{50} from these 4 studies are relevant for the classification of aquatic acute toxicity. The lowest E_rC_{50} based on growth inhibition is 8.1 mg/L and the lowest EbC_{50} based on biomass inhibition is 3.3 mg/L on the blue-green alga *Anabaena flos-aquae* in RAR B.9.2.6.3, 1999 for foramsulfuron indicating low toxicity to algae. Results that were based on nominal concentrations were analytically verified and the measured concentrations were in the range of 80 – 120 % of the initial nominal concentrations. It is considered acceptable to present these results as nominal concentrations as studies testing algae species do not represent key studies for the aquatic classification of foramsulfuron. No significant toxicity was observed for the degradation products F092944 (2-amino-4,6-dimethoxypyrimidine) and F099095 (4,6-dimethoxy-2-pyrimidinyl)urea) in two available studies for algae in the RAR.

Several studies testing the toxicity of foramsulfuron towards macrophytes are available in the RAR. These studies include standard guideline studies with the standard species *Lemna gibba* as well as higher tier studies with *Lemna* or other macrophyte species.

Aquatic plants are clearly the most sensitive taxonomic group and *Lemna gibba* can be considered as the most sensitive plant species tested. From the different studies performed with *Lemna gibba*, the following most relevant E_rC_{50} values can be derived for the classification purposes of foramsulfuron:

7d-E_rC_{50} = 1.01 µg/L from the Lemna OECD TG 221 study (RAR B.9.2.7.1, 1998)

7d-E_rC_{50} = 0.96 µg/L from the 1st week of the Lemna 6-weeks bioassay (RAR B.9.2.7.4, 2013)

The first week of the 6-weeks bioassay (RAR B.9.2.7.4, 2013) with stepwise reduced test concentrations over time was basically a standard 7d *Lemna gibba* study (OECD TG 221) and the 7d endpoints are therefore suitable for the classification purposes. For the first week of the test temperature was between 23.8 and 24.1°C and the pH was between 7.6-7.7 at day 0 and 8.6-8.9 at the day 7. The mean light intensity of the first week was 8107 lux. Validity criterion for doubling time of frond number in the controls was met for week 1 and for the rest of the test periods. Test concentrations of foramsulfuron were 0.20, 0.40, 0.80, 1.60 and 3.20 µg/L from day 0 to day 7. Analytical findings revealed that the test concentrations were between 103 - 114% at day 0 and 108 - 116% at day 7. Thus, the endpoints were referred to nominal initial test concentrations. E_rC_{50} value of 1.22 µg/L for total frond number and 0.96 µg/L for total frond area growth rate inhibition were observed for week 1 (days 0-7). In contrast, the 6-weeks endpoints provided in the report of this study are higher tier endpoints and were specifically derived for comparison with 6 weeks results of the outdoor pond study by RAR B.9.2.7.5 (2012). Since *Lemna gibba* cannot be investigated in outdoor pond studies directly due to its high nutrient demands, decreasing concentrations of foramsulfuron over time as observed in the pond study were mimicked in the laboratory and delivered a specific *Lemna gibba* 6-weeks endpoint only for higher tier use in the RAR. Only endpoints from steady test concentrations at the first week of this study are used for the

classification purposes of foramsulfuron. RAR B.9.2.7.4 (2013) is the key study for the aquatic acute toxicity classification of foramsulfuron.

7 day growth inhibition test in line with OECD TG 221 was conducted in RAR B.9.2.7.1 (1998). Three replicates of aquatic plants were exposed to nominal concentrations of 0 (control), 0.13, 0.22, 0.36, 0.60, and 1.00 µg/L of foramsulfuron. The results of analyses of the test solutions showed that the mean measured foramsulfuron concentrations were 0.1575, 0.2556, 0.3309, 0.5216, and 0.9554 µg/L (87 to 121%) for Day 0 and Day 7 samples. Base on this all endpoints were calculated based on nominal concentrations. The 7 day E_rC_{50} (frond growth rate) value of 1.01 µg/L and 7 day E_bC_{50} value of 0.65 µg/L based on frond growth (biomass) were determined in the study for foramsulfuron. Validity criteria in the OECD TG 221 were met.

For the 7d exposure phase of the *Lemna gibba* recovery study according to OECD TG 221 and GLP in RAR B.9.2.7.2 (2005) no E_rC_{50} value has been derived in the RAR. During first 7 day exposure to foramsulfuron growth rate inhibition were 49 % based on total frond count and 52 % based on total frond area compared to control at the lowest nominal test concentration of 0.625 µg/L. A robust E_rC_{50} calculation was thus not possible as the lowest test concentration already had a significant effect on growth of *Lemna gibba*. However, the growth inhibition was approximately 50 % at the lowest test concentration so it could be assumed that E_rC_{50} value is close to the lowest nominal test concentration of 0.625 µg/L. As there is more reliable E_rC_{50} value available in the range of 0.1-1.0 µg/L this study is not considered as a key study for the aquatic acute classification of foramsulfuron.

The 7d *Lemna gibba* peak exposure study (1 day exposure and 6 day recovery phase) by RAR B.9.2.7.3 (2013) is not suitable to derive an appropriate endpoint for classification because exposure in this study was only for 24 hours. Also no effects at the highest test concentration were seen in the study. This is considered as only supportive study for the classification of foramsulfuron.

The multispecies pond study in RAR B.9.2.7.5 (2012) on aquatic plant species other than *Lemna gibba* is not suitable to derive a standard acute endpoint for classification because growth effects were only determined after 6 weeks, which significantly deviates from evaluations in standard laboratory studies (e.g. after 14 days in a *Myriophyllum* study). Also, exposure concentrations in this study decreased to about 30% of nominal over the 6 weeks of total study duration and the analysed purity of the foramsulfuron WG 50 % tested was only 52.2 %. Seven of the ten aquatic plants exposed to foramsulfuron WG 50% in outdoor ponds indicated sensitivity in reduced plant biomass or morphological abnormalities over the range of concentrations tested. The lowest EC_{50} was 0.85 µg/L for *Elodea canadensis* based on geometric mean concentrations over 6 week test period. This is considered as only supportive study for the classification of foramsulfuron.

No significant toxicity for aquatic plant *Lemna gibba* was observed for any other degradate than F130619 (4-amino-2-[3-(4,6-dimethoxypyrimidin-2-yl)ureidosulfonyl]-N,N-dimethylbenzamide). The most sensitive endpoint in this OECD TG 221 study was 7d E_rC_{50} value of 0.889 µg (growth rate for frond area) for F130619 based on nominal but analytically verified test concentrations in RAR B.9.2.7.11 (2013). Analytical findings on day 0 were between 84 and 110% (average 100%) of nominal. On day 7 there were analytical findings between 83 and 112% (average 101%) of nominal. Toxicity of degradate F130619 for aquatic plants is within similar order of magnitude than it is for foramsulfuron. Thus, it is preferred to classify foramsulfuron based on the data on the active substance itself.

In conclusion, the 7d E_rC_{50} value of 0.96 µg/L from the first week of *Lemna gibba* 6-weeks bioassay (nominal but analytically verified) by RAR B.9.2.7.4 (2013) is proposed as the lowest reliable and relevant aquatic acute endpoint. There are available lower valid acute toxicity endpoint for *Lemna gibba*, a 7 day E_bC_{50} value of 0.65 µg/L (RAR B.9.2.7.1, 1998). However, endpoints based on growth rate reduction rather than growth (biomass) are preferred for algae in the classification according to the guidance on the application of the CLP criteria (2017). Thus, this same principle is applied for the aquatic macrophytes. It is noted that both of these acute endpoints are in the range of 0.1-1.0 µg/L and would result in the same acute aquatic classification with the same M-factor for foramsulfuron. This is further supported by the study (RAR B.9.2.7.2, 2005) where no E_rC_{50} value was determined but based on the study results it would be in the same range of 0.1-1.0 µg/L.

11.5.4 Acute (short-term) toxicity to other aquatic organisms

The acute toxicity of foramsulfuron to grass shrimp and potential growth effects of the substance on the eastern oyster were investigated in RAR B.9.2.8.1 (1998) & RAR B.9.2.8.2 (1998). The EC_{50} (96 h) on grass shrimp is > 100 mg/L and the EC_{50} (96 h) is 118 mg/L on the oyster.

11.6 Long-term aquatic hazard

Evaluation of chronic aquatic hazard for foramsulfuron is based on studies which are considered valid in the Renewal Assessment Report of foramsulfuron (RAR annexed to this CLH proposal). All valid studies are presented in the table below and relevant studies for the classification purposes are also briefly summarised below. More details can be found in the annexed RAR. Ecotoxicological information is based on technical foramsulfuron (AE F130360) with a minimum purity of 94.2 % in the following studies.

Table 95: Summary of relevant information on chronic aquatic toxicity

Method	Species	Test material	Results	Remarks	Reference
Fish					
OECD 210 GLP 35 d Early Life Stage flow-through test	*Pimephales promelas* (fathead minnow)	Foramsulfuron (purity 97.3%)	NOEC (35 d) = 10.5 mg/L	Based on mean measured concentrations	RAR B.9.2.2.2, 2004
OECD 204 GLP 28 d flow-through test	*Oncorhynchus mykiss* (rainbow trout)	Foramsulfuron (purity 95.8%)	NOEC (28 d) = 100 mg/L	Based on nominal but analyt. verified concentrations	RAR B.9.2.2.1, 1999
Aquatic invertebrates					
OECD 211 GLP 21 d semi-static test	*Daphnia magna*	Foramsulfuron (purity 95.8%)	NOEC (21 d) >100	Based on nominal but analyt. verified concentrations	RAR B.9.2.5.1.1, 1999
Algae					
OECD 201 GLP 96 h static test	*Pseudokirchneriella subcapitata* (green alga)	Foramsulfuron (94.2% purity)	NOEbC (72 h) < 13.0 mg/L	Based on nominal but analyt. verified concentrations	RAR B.9.2.6.1, 1998
OECD 201 GLP 72 h static test	*Navicula pelliculosa* (diatom)	Foramsulfuron (94.2% purity)	NOEC (72 h) ≥ 112 mg/L	Based on mean measured concentrartions	RAR B.9.2.6.2, 1999
OECD 201 GLP 96 h static test	*Anabaena flos-aquae* (blue-green alga)	Foramsulfuron (94.6% purity)	NOErC (72/96 h) <2.6 mg/L	Based on nominal but analyt. verified concentrations	RAR B.9.2.6.3, 1999
OECD 201 GLP 96 h static test	*Skeletonema costatum* (marine diatom)	Foramsulfuron (94.6% purity)	NOErC (72 h) = 105 mg/L	Based on mean measured concentrations	RAR B.9.2.6.4, 1999
OECD 201 GLP	*Desmodesmus subspicatus*	Degradate F092944	NOErC (72 h) = 25 mg/L	During the study analytical	RAR B.9.2.6.5, 1993

72 h static test	*(green alga)*	(> 99 % purity)		measurements were carried out only in one test item concentration (18 mg/L)	
OECD 201 GLP 72 h static test	*Pseudokirchneriella subcapitata* (green alga)	Degradate F099095 (99.6 % purity)	NOErC (72 h) = 25 mg/L	Based on nominal but analyt. verified concentrations	RAR B.9.2.6.6, 2005
Aquatic macrophytes					
US EPA 122-2 in line with OECD 221 GLP 7 d static test	*Lemna gibba* (duck weed)	Foramsulfuron (96.1% purity)	NOEC (7 d) = 0.36 µg/L (biomass and growth rate)	Based on nominal concentrations but analyt. verified at day 0 and day 7. Mean measured concentrations in range of 87 to 121 % of nominal.	RAR B.9.2.7.1, 1998
EU Directive 91/414/EEC GLP semi-static test with static conditions at days 0-7.	***Lemna gibba*** (duck weed)	**Foramsulfuron (97.3 % purity)**	**ErC_{10} (7d) = 0.125 µg/L (growth rate ,frond number) ErC_{10} (7d) = 0.164 µg/L (growth rate, frond area)**	**Higher tier prolonged growth inhibition study (6 weeks), 1st week equal to *Lemna* standard test OECD 221 based on nominal but analytically verified concentrations**	**RAR B.9.2.7.4, 2013** **Key study**
EU directive 91/414/EEC in line with OECD 221 GLP 7d static test	*Lemna gibba* (duck weed)	Foramsulfuron (97.3 % purity)	NOEC for growth between day 2-7 = 2.42 µg/L NOEC for growth between day 0-7 = 0.5 µg/L	Growth Inhibition, (1 d exposure + 6 d recovery phase) based on nominal but analyt. verified concentrations Supportive study	RAR B.9.2.7.3, 2013
OECD 221 GLP Growth Inhibition + recovery (7 d + 14 d) static test, growth medium was renewed on day 7.	*Lemna gibba* (duck weed)	Foramsulfuron (97.3 % Purity)	NOEC (14 d) < 0.625 µg/L	The analytical findings in all test levels on day 0 in reference to nominal concentrations ranged between 89 and 113 %. In aged test levels on day 7 there were analytical findings between 94 and 112 % of nominal.	RAR B.9.2.7.2, 2005

				Based on nominal but analyt. verified concentrations	
No guideline GLP 6 weeks	ten aquatic plant species	Foramsulfuron (52.2 % purity)	The lowest NOEC (6 weeks, *Elodea canadensis*) = 0.058 µg a.s./L	Outdoor growth inhibition (6 weeks) and recovery study (2 d + 5.5 weeks). Based on geometric mean measured concentrations Supporting study	RAR B.9.2.7.5, 2012
OCSPP Guideline Number 850.SUPP GLP 14 d static test	*Myriophyllum spicatum*	Foramsulfuron (97.6% purity)	NOEyC (14 d) = 84 µg/L for all endpoints	Based on the study results *Myriophyllum spicatum* is not considered the most sensitive aquatic macrophyte. Calculated based on geometric mean measured concentrations	RAR B.9.2.7.6, 2012
US EPA 123-2 GLP 7d semi-static test	*Lemna gibba* (duck weed)	Degradate F153745 (97.8 % purity)	NOEC = 100 mg/L	No effects observed at the highest test concentration. Based on geometric mean measured concentrations	RAR B.9.2.7.7, 2000
US EPA 123-2 GLP 7d semi-static test	*Lemna gibba* (duck weed)	Degradate F0338795 (90.2 % purity)	NOEC = < 13 mg/L	based on nominal but analyt. verified concentrations.	RAR B.9.2.7.8, 2000
US EPA 123-2 GLP 7d semi-static test	*Lemna gibba* (duck weed)	Degradate F092944 (98.8 % purity)	NOEC = 100 mg/L	no effects observed at the highest test concentration.	RAR B.9.2.7.9, 2000
OECD 221 GLP 7 d	*Lemna gibba* (duck weed)	Degradate F099095 (99.6 % purity)	NOEC = 100 mg/L	no effects observed at the highest test concentration.	RAR B.9.2.7.10, 2005
OECD 221 GLP 7 d static test	*Lemna gibba* (duck weed)	Degradate F130619 (94 % purity)	NOErC = 0.179 µg/L	based on nominal but analyt. verified concentrations.	RAR B.9.2.7.11, 2013

11.6.1 Chronic toxicity to fish

The long-term toxicity of foramsulfuron to fish was investigated with fathead minnow (*Pimephales promelas*) embryos and larvae in a 35 d toxicity test under flow-through conditions according to the OECD guideline 210 (GLP) (RAR B.9.2.2.2, 2004). No treatment related effects occurred in the early life stage exposure of the

fathead minnow to foramsulfuron, the NOEC is 10.5 mg/L (mean measured) for all endpoints. This study is relevant for the classification purposes.

Furthermore, a prolonged toxicity test on rainbow trout was performed with foramsulfuron (RAR B.9.2.2.1, 1999). The study was conducted according to the OECD guideline 204 and GLP. Based on survival and growth of fish during this study (no statistically significant effects were observed in the study), the NOEC (28 d) is the nominal concentration of 100 mg/L (analytically verified). It should be noted that following the OECD Council decision, the Test Guideline 204 'Fish, Prolonged Toxicity Test: 14-Day Study' was deleted on 2nd April 2014. However, the conducted study was prolonged to 28 days and no toxic effects were observed supporting the conclusion that foramsulfuron is not significantly harmful to fish species.

11.6.2 Chronic toxicity to aquatic invertebrates

One study is available testing the chronic toxicity of foramsulfuron towards the water flea, *Daphnia magna* (RAR B.9.2.5.1.1, 1999). The test was conducted according to the OECD guideline 211 and GLP standards. No treatment related effects were observed in the study. The NOEC (21 d) is ≥ 100 mg/L based on nominal concentrations. The concentrations of the test substance were confirmed by analytical measurement. This study is relevant for the classification purposes.

11.6.3 Chronic toxicity to algae or other aquatic plants

Potential effects of foramsulfuron on algal growth were investigated with four different algae species, a green alga, a blue-green alga and a freshwater and a marine diatom. All four studies were conducted according to the OECD guideline 201, GLP standards and were considered valid in the RAR. No robust NOEC could be derived for the most sensitive algae (*Anabaena flos-aquae*) since effects were observed at the lowest nominal concentration tested at 2.6 mg/L (RAR B.9.2.6.3, 1999). Studies that were based on nominal concentrations were analytically verified and the measured concentrations were in the range of 80 – 120 % of the initial nominal concentrations. This is considered acceptable as studies testing algae species do not represent key studies for the aquatic classification of foramsulfuron. NOE_rC value of 25 mg/L were observed for the degradation products F092944 (2-amino-4,6-dimethoxypyrimidine) and F099095 (4,6-dimethoxy-2-pyrimidinyl)urea) for algae in the RAR.

Several studies testing the toxicity of foramsulfuron towards macrophytes are available in the RAR. These studies include standard studies with the standard species *Lemna gibba* as well as higher tier studies with *Lemna gibba* or other macrophyte species.

As for acute toxicity, also for chronic toxicity aquatic plants are clearly the most sensitive taxonomic group and *Lemna gibba* can be considered as the most sensitive plant species tested. From the different studies performed with *Lemna gibba*, the following most relevant NOEC/E_rC_{10} values can be derived for the chronic classification purposes of foramsulfuron:

7d-NOEC = 0.36 µg/L from the *Lemna gibba* OECD TG 221 study (RAR B.9.2.7.1, 1998)

7d-E_rC_{10} = 0.125 µg/L from the *Lemna gibba* 6-weeks bioassay (RAR B.9.2.7.4, 2013)

Summaries of the studies by RAR B.9.2.7.4 (2013) and RAR B.9.2.7.1 (1998) were already presented in the section 11.5.3. In the original study report 7 d E_rC_{10} values of 0.125 µg/L (frond number growth rate inhibition) and 0.164 µg/L (frond area growth rate inhibition) are available for week 1 based on nominal but analytically verified test concentrations (RAR B.9.2.7.4, 2013). This is the key study for the aquatic chronic toxicity classification of foramsulfuron.

For the 7d exposure phase of the *Lemna gibba* recovery study (14 day recovery phase without foramsulfuron) in RAR B.9.2.7.2 (2005) no NOEC or EC_{10} have been be derived in the RAR because high test concentrations were selected for this type of study and growth rate reductions at the lowest concentration were already about 50%. During first 7 days exposure to foramsulfuron growth rate inhibition were 49 % based on total frond count and 52 % based on total frond area compared to control at the lowest nominal test concentration of 0.625

µg/L. Based on this NOEC value cannot be adequately determined but it is concluded that NOEC value is < 0.625 mg/L for growth inhibition during 7 day exposure phase. The growth rates for frond number and total frond area fully recovered for all test levels (up to 20 µg a.s./L) within the first phase of the recovery period (study days 7 – 14) and fronds fully recovered from all visual effects (reduction of size, deformation, decolouration and necrosis) up to 5 µg/L (highest observed test level) after 14 days.

The 7d *Lemna gibba* peak exposure study (1 day exposure and 6 day recovery phase) by RAR B.9.2.7.3 (2013) is not suitable to derive an appropriate endpoint for classification because exposure in this study was only for 24 hours. This is considered as only supportive study for the classification of foramsulfuron.

The multispecies pond study (RAR B.9.2.7.5, 2012) on aquatic plant species other than *Lemna gibba* is not suitable to derive a standard chronic endpoint for classification because growth effects were only determined after 6 weeks which significantly deviates from evaluations in standard lab studies (e.g. after 14 days in a *Myriophyllum* study). Also, exposure concentrations in this study decreased to about 30% of nominal over the 6 weeks of total study duration and the analysed purity of the tested foramsulfuron WG 50 % was only 52.2 %. Thus, this is only presented as supporting study for the classification purposes. Seven of the ten aquatic plants exposed to foramsulfuron WG 50% in outdoor ponds indicated sensitivity in reduced plant biomass or morphological abnormalities over the range of concentrations tested. The lowest NOEC was 0.058 µg/L for *Elodea canadensis* based on geometric mean concentrations over 6 week test period.

No significant toxicity for aquatic plant *Lemna gibba* was observed for any other degradate than F130619 (4-amino-2-[3-(4,6-dimethoxypyrimidin-2-yl)ureidosulfonyl]-N,N-dimethylbenzamide) in OECD TG 221 study. The lowest NOErC value of 0.179 µg (nominal) was based on statistical data analysis of growth rate inhibition (frond number and the total frond area of plants) for F130619 in RAR B.9.2.7.11 (2013). Toxicity of degradate F130619 for aquatic plants is within similar order of magnitude than it is for foramsulfuron. Thus, it is preferred to classify foramsulfuron based on the data on active substance itself.

In conclusion, the 7d-E_rC_{10} value of 0.125 µg/L from the first week of *Lemna gibba* 6-weeks bioassay (nominal but analytically verified concentrations) by RAR B.9.2.7.4 (2013) is proposed as the lowest reliable and the most relevant aquatic chronic endpoint.

11.6.4 Chronic toxicity to other aquatic organisms

No data available.

11.7 Comparison with the CLP criteria

11.7.1 Acute aquatic hazard

Acute aquatic toxicity data for foramsulfuron are available for fish, aquatic invertebrates, algae and aquatic plants. Aquatic plants are clearly the most sensitive taxonomic group and *Lemna gibba* can be considered as the most sensitive plant species tested. The **7d-E_rC_{50}** value of **0.96 µg/L** by RAR B.9.2.7.4 (2013) from the first week of *Lemna gibba* 6-weeks bioassay (nominal but analytically verified concentrations) is proposed as the lowest and the most reliable acute endpoint. There are available lower valid acute toxicity endpoint for *Lemna gibba*, a 7 day E_bC_{50} value of 0.65 µg/L. However, endpoints based on growth rate reduction rather than growth (biomass) are preferred for algae in the classification according to the guidance on the application of the CLP criteria (2017). Thus, this same principle is applied for the aquatic macrophytes. It is noted that both of these acute endpoints are in the range of 0.1-1.0 µg/L and would result in the same acute aquatic classification and M-factor for foramsulfuron. This is further supported by RAR B.9.2.7.2 (2005) for *Lemna gibba* where no E_rC_{50} value was determined but based on the study results E_rC_{50} value would be in the same range of 0.1-1.0 µg/L.

For acute aquatic hazards, on the basis of these acute aquatic macrophyte endpoints being in the range 0.0001 mg/l < L(E)C_{50} ≤ 0.001 mg/l, foramsulfuron should be classified as Aquatic Acute 1 (H400) with M-factor of 1000.

11.7.2 Long-term aquatic hazard (including bioaccumulation potential and degradation)

Results from the simulation studies demonstrate that foramsulfuron is not ultimately degradable (≥ 70 % mineralised) in water, soil or sediment simulation tests. For foramsulfuron ready biodegradation studies are not available and therefore the assessment of rapid degradability is primarily based on the test of aerobic mineralisation in surface water (RAR B.8.4.2.2, 2013) and the test on hydrolysis (RAR B.8.4.1.1, 2000). The test on aerobic mineralisation in surface water showed that degradation in non-sterile natural water was insignificant and no major degradation products were observed. No experimental DT50 value was calculated in the study. Soil and sediment simulation studies support that ultimate degradation of foramsulfuron is slow also in these compartments.

Hydrolysis half-lives at pH 7-9 (25°C) of foramsulfuron were over 16 days (RAR B.8.4.1.1, 2000).

Photochemical degradation of foramsulfuron in the environment is not considered relevant to be taken into account for the classification purposes of foramsulfuron when more preferred data are available.

Consequently, foramsulfuron is considered to be **not rapidly degradable** because:

- it was not demonstrated that foramsulfuron is ultimately degraded > 70 % within 28 days in the aquatic environment. Mineralisation to CO_2 was negligible (<0.1 %) with insignificant primary degradation in non-sterile natural water after 58 days (RAR B.8.4.2.2, 2013).
- hydrolytic degradation half-lives were not under 16 days in the whole pH range of 4.0-9.0 and the hydrolysis product AE F130619 fulfils the classification criteria as hazardous for the aquatic environment.

Furthermore, foramsulfuron has **a low potential to bioaccumulate** based on log Kow (-0.78 at pH 7). No experimental data on bioaccumulation is available.

Long-term aquatic toxicity data for foramsulfuron are available for fish, aquatic invertebrates, algae and aquatic plants. As for acute, also for long-term aquatic toxicity aquatic plants are clearly the most sensitive taxonomic group and *Lemna gibba* can be considered as the most sensitive plant species tested. The **7d-E_rC_{10} value of 0.125 µg/L** by RAR B.9.2.7.4 (2013) from the first week of *Lemna gibba* 6-weeks bioassay (nominal but analytically verified concentrations) is proposed as the lowest and the most reliable chronic endpoint.

Since foramsulfuron is non-rapidly degradable and adequate chronic toxicity data are available for all trophic levels, foramsulfuron can be classified according to the criteria set out in CLP in Table 4.1.0(b)(i). In this case classification of Aquatic Chronic 1 is applicable for foramsulfuron based on the lowest **E_rC_{10}** value of **0.125 µg/l** for *Lemna gibba* (≤ 0.1 mg/l) with a chronic M-factor of 100 (0.0001 < NOEC ≤ 0.001 mg/l).

For long-term aquatic hazards, foramsulfuron should be classified according to Regulation EC 1272/2008 as Aquatic Chronic 1 (H410) with M-factor of 100.

11.8 CONCLUSION ON CLASSIFICATION AND LABELLING FOR ENVIRONMENTAL HAZARDS

Conclusions on classification and labelling for environmental hazards of foramsulfuron.

Hazard Class and Category code(s)	M factor	Hazard Statement
Aquatic Acute Category 1, H400	1000	Very toxic to aquatic life

Aquatic Chronic Category 1, H410	100	Very toxic to aquatic life with long lasting effects

RAC evaluation of aquatic hazards (acute and chronic)

Summary of the Dossier Submitter's proposal

Foramsulfuron is an active substance in plant protection products, namely a sulfonyl-urea herbicide mainly used in corn and sugar beet. The substance is currently not listed in Annex VI of Regulation (EC) No 1272/2008.

The Dossier Submitter (DS) proposed to classify the substance as:

- **Aquatic Acute 1 (H400) with M-factor of 1000** based on a 7d-E_rC_{50} value of 0.96 µg/L for the *Lemna gibba.* In the CLP report there are also other studies with aquatic macrophytes available which provide toxicities within the same range.
- **Aquatic Chronic 1 (H410) with M-factor of 100** based on lack of rapid degradation and a 7d-E_rC_{10} value of 0.125 µg/L for the *Lemna gibba.*

Degradation

A hydrolysis study according to OECD TG 111 and in compliance with GLP was run at pH 4, 5, 7 and 9 and at 25 °C and 40 °C in the dark in sterile aqueous buffered solutions. Hydrolysis was pH dependent and resulted in half-lives of 3.7 days at pH 4, 10.1 days at pH 5, 128 days at pH 7 and 132 days at pH 9 (25°C). Depending on the position of the radiolabel, the substance was found to form 2-amino-4,6-dimethoxypyrimidine (AE F092944) and 4-formylamino-N,N-dimethyl-2-sulfamoylbenzamide (AE F153745) as main (>10 % AR) hydrolysis products at 83.3 % AR (pH 5, day 30, 25°C) and 71.3 % (pH 5, day 30, 25°C) in the course of the study. This was accompanied by the formation of 4-amino-2-[3-(4,6-dimethoxypyrimidin-2- yl)ureidosulfonyl]-N,N-dimethylbenzamide (AE F130619), 4-amino-N,N-dimethyl-2- sulfamoylbenzamide (AE F148003), N-(1,1-dioxido-3-oxo-2,3-dihydro-1,2-benzothiazol-6-yl) formamide (AE 0014940) and AE 0001082 as minor (i.e. <10 % AR) hydrolysis products.

There were five photolytic degradation in water studies available on foramsulfuron. The studies have shown that photochemical degradation processes can contribute to some extend to degradation of foramsulfuron in the environment.

There were two soil photodegradation studies available. The studies indicated slow transformation by photolytic processes on soil surfaces. The contribution of photolytic transformation is thus insignificant to the elimination of the substance residues from the soil environment.

No ready biodegradation test is available for foramsulfuron.

In an aerobic mineralization study performed according to OECD TG 309 and GLP, no degradation of foramsulfuron was observed after 58 days. Mineralization was negligible (formation of carbon dioxide less than 0.1 %). No major transformation products were observed.

The kinetics and degradation of radiolabelled foramsulfuron were studied in two sediment-water systems, a silty clay loam (363 days) and a sand sediment (365 days). The study was conducted according to the US EPA: 162-4 guideline which is in line with the OECD TG 308. The half-life in the total system in silty clay loam sediment system was 26.0 - 28.7 days and in sand sediment system 37.9 - 41.4 days. Mineralisation to carbon dioxide was observed and accounted at a maximum of 6.2 % of applied radioactivity by day 365. Total non-extractable residues (NER) at the end of the test were 77.3 - 93.1 % in the silty clay loam sediment and 40.4 - 53.8 % in sand sediment. Main degradants at levels above 10 % AR in water/sediment testing were 4-formylamino-2-[3-(4-hydroxy-6-methoxypyrimidin-2-yl)ureidosulfonyl]-N,Ndimethylbenzamide(AE 0338795) and 4-formylamino-N,N-dimethyl-2-sulfamoylbenzamide (AE F153745).

There were three aerobic soil degradation studies available. The studies indicated that foramsulfuron degrades rapidly in soil by hydrolysis forming several degradation products. However, only minor mineralisation of foramsulfuron was observed under the test conditions.

Overall, the DS concluded that foramsulfuron is considered to be not rapidly degradable because it was not demonstrated that foramsulfuron is ultimately degraded > 70 % within 28 days in the aquatic environment. Mineralisation to carbon dioxide was negligible (<0.1 %) with insignificant primary degradation in water after 58 days (RAR B.8.4.2.2., 2013). Furthermore, hydrolytic degradation half-lives were not under 16 days in the whole pH range of 4.0-9.0 and the hydrolysis product AE F130619 fulfils the classification criteria as hazardous for the aquatic environment.

Bioaccumulation

In the CLP report, no experimental bioaccumulation data is available. Measured octanol-water partition coefficient (log K_{OW}) determined according to OECD TG 107 (shaking flask method) was 1.44 at pH 2 and -0.78 at pH 7. Based on the data presented, the DS concluded that foramsulfuron has a low potential for bioaccumulation as log K_{OW} of foramsulfuron does not meet the CLP criterion of log $K_{OW} \geq 4$, indicative of a potential to bioaccumulate.

Aquatic Toxicity

In addition to aquatic toxicity studies using foramsulfuron with a minimum purity of 94.2 %, studies using different degradation products are presented in the CLP report. The toxicity studies with different degradation products generally derive effect values much higher (namely, much lower toxicity) than for foramsulfuron.

Acute toxicity

The summary of the relevant information on acute aquatic toxicity for foramsulfuron and its degradation products are provided by the DS in Table 94 of the CLH report. Acute aquatic toxicity data are available for fish, invertebrates, algae and aquatic plants.

For fish, three studies with three different fish species were available for foramsulfuron with purities 94.2-98.6 % in the CLH report. In all three studies, a nominal 96-h LC_{50} value of above 100 mg/L was reported, namely no effects were observed in these studies.

For foramsulfuron (98.4 % purity), there was only one study available for aquatic invertebrates (*Daphnia magna*) with a nominal 48-h EC_{50} value of above 100 mg/L, namely no effects were observed in the study.

Four acute toxicity studies with four different algae species and six studies with different aquatic plant species were available using foramsulfuron. The blue-green alga *Anabaena flos-aquae* was the most sensitive species tested in algae acute studies, with a nominal 96-h E_rC_{50} of 8.1 mg/L and 96-h E_bC_{50} of 3.3 mg/L.

The most sensitive plant species tested in aquatic plants acute studies was duck weed *Lemna gibba*, with a nominal 7-d E_rC_{50} of 0.96 µg/L and nominal 7-d E_rC_{50} of 1.01 µg/L. No significant toxicity for *Lemna gibba* was observed for any other degradant than F130619. The toxicity of degradant F130619 (7d-E_rC_{50} of 0.889 µg/L) was within a similar order of magnitude as for foramsulfuron.

There were data available for other aquatic organisms, i.e. a 96-h EC_{50} of above 100 mg/L for grass shrimp (*Palaemonetes pugio*) and a 96-h EC_{50} of 118 mg/L for eastern oyster (*Crassostrea virginica*).

From the available aquatic toxicity data for foramsulfuron, the DS concluded that aquatic plants are the most acutely sensitive taxonomic group, therefore the acute aquatic classification proposed by the DS was based on the duck weed *Lemna gibba* (7-d E_rC_{50} of 0.96 µg/L). The DS proposed **Aquatic Acute 1** (H400) with an **M-factor of 1000**.

Chronic toxicity

The summary of the relevant information on chronic aquatic toxicity for foramsulfuron and different degradation products is provided in Table 95 of the CLP report. Chronic aquatic toxicity data are available for fish, invertebrates, algae and aquatic plants.

For foramsulfuron (97.3 % purity), there is one long-term toxicity study for fish available with a mean measured 35-d NOEC value of 10.5 mg/L for fathead minnow (*Pimephales promelas*). There is also a prolonged toxicity test (OECD TG 204) on rainbow trout (*Oncorhynchus mykiss*) available, but the test is not considered equivalent to a chronic study for classification purposes.

There was only one study available for aquatic invertebrates (*Daphnia magna*) with a nominal 21-d NOEC value of above 100 mg/L, namely no effects were observed in the study.

Four chronic toxicity studies with four different algae species and six studies with different plant species were available using foramsulfuron. The blue-green alga *Anabaena flos-aquae* was the most sensitive species tested in algae chronic studies, with a nominal 96-h NOE_rC of < 2.6 mg/L. The most sensitive plant species tested was duck weed *Lemna gibba*. From the different studies performed with *Lemna gibba* the following most relevant values were derived, a nominal 7-d NOEC of 0.36 µg/L (biomass and growth rate) and nominal 7-d E_rC_{10} of 0.125 µg/L (growth rate and frond number). There are other studies on the foramsulfuron (97.3 % purity) that derive toxicities within the same range. No significant toxicity for *Lemna gibba* was observed for any other degradant than for F130619. The toxicity of degradant F130619 (7d-NOE_rC of 0.179 µg/L) was within a similar order of magnitude as for foramsulfuron.

Based on the results from the long-term aquatic toxicity studies using foramsulfuron, the DS concluded that aquatic plants are the most sensitive taxonomic group. Therefore, the chronic aquatic classification proposed by DS was based on the duck weed *Lemna gibba* toxicity study (7-d E_rC_{10} of 0.125 µg/L (RAR B.9.2.7.4, 2013)). The DS proposed **Aquatic Chronic 1**, with an **M-factor of 100** (0.0001 < NOEC ≤ 0.001 mg/L) for a not rapidly degradable substance.

Comments received during consultation

Three Member States (MS) and one company-manufacturer provided comments, and all agreed with the proposed by the DS classification for environmental hazards. One MS also agreed with the DS not to use the toxicity values of the degradants for classification of the substance.

Assessment and comparison with the classification criteria

Degradation

RAC agrees with the DS's proposal to consider foramsulfuron as **not rapidly degradable**:

- Foramsulfuron undergoes hydrolysis which is pH dependant. Hydrolysis DT_{50} values are 3.7 day (pH 4), 10.1 day (pH 5), 128 day (pH 7) and 132 day (pH 9) at 25°C. Two main degradants were found, AE F092944 and AE F153745. Data on hydrolysis might be considered for classification purposes only when the longest half-life determined within the pH range 4-9 is less than 16 days (corresponding to a degradation of > 70 % within 28 days). Accordingly, foramsulfuron is hydrolytically stable. Furthermore, according to DS the minor hydrolysis product AE F130619 (<10 % AR) fulfils the criteria for classification as hazardous to the aquatic environment.
- There was no ready biodegradability study available.
- In the surface water simulation test no degradation was observed and mineralisation was negligible.

- The half-life in the total system in a water/sediment system study was 26.0 - 28.7 days (silty clay loam sediment) and 37.9 - 41.4 days (sand sediment). Low mineralization was observed (6.2 %). Two main degradants were formed, namely AE 0338795 and AE F153745.

As supportive information, it was also not demonstrated that foramsulfuron is ultimately degraded in a soil simulation tests with a half-life of < 16 days (dissipation DT_{50}: 1.0 to 20.5 days; mineralisation from 1.7 % to 21.5 %).

Bioaccumulation

RAC agrees with the DS that foramsulfuron has a low potential for bioaccumulation. In the absence of measured BCF data, the basis for this conclusion is the measured log K_{OW} values of 1.44 and -0.78 that are well below the decisive CLP Regulation threshold of 4.

Aquatic toxicity

RAC is of the opinion that reliable acute and long-term toxicity data for foramsulfuron are available for fish, invertebrates, algae and aquatic plants and also agrees with using the nominal values, as these values were analytically verified. RAC agrees with the DS to use the endpoint based on growth rate reduction for algae and aquatic plants as this is in line with the current CLP Guidance (Version 5.0, July 2017).

Acute toxicity

Aquatic plants are the most sensitive taxonomic group and the lowest result is a 7d-E_rC_{50} value of 0.96 µg/L for duck weed *Lemna gibba*. RAC notes that also other studies with aquatic microphytes provide toxicities within the same range (see Table 94 of the CLH report). Consequently, RAC concludes that foramsulfuron warrants classification as **Aquatic Acute 1 (H400) with M-factor of 1000** ($0.0001 < L(E)C_{50} \leq 0.001$ mg/L) for acute aquatic hazards.

Chronic toxicity

Aquatic plants are the most sensitive taxonomic group and the lowest result is a 7d-E_rC_{10} value of 0.125 µg/L for duck weed *Lemna gibba*. Foramsulfuron was not rapidly degradable and had a low potential for bioaccumulation. Consequently, RAC concludes that foramsulfuron warrants classification as **Aquatic Chronic 1 (H410) with M-factor of 100** ($0.0001 < NOEC \leq 0.001$ mg/L) for chronic aquatic hazards.

12 EVALUATION OF ADDITIONAL HAZARDS

12.1 Hazardous to the ozone layer

12.1.1 Short summary and overall relevance of the provided information on ozone layer hazard

The degradation of the substance in the atmosphere was calculated by the software AOPWIN. Foramsulfuron is not expected to remain stable in the air (half-life of 0.07 days in maximum). Due to its low half-life in the

atmosphere combined with a low vapour pressure (4.2 x 10^{-11} Pa at 20 °C) indicating non-volatility to result in a low value for the Henry constant (5.8 x 10^{-12} Pa x m^3 x $mole^{-1}$ at 20 °C), foramsulfuron is not subject to transport via air or cause hazard to ozone layer.

12.1.2 Comparison with the CLP criteria

A substance shall be classified as Hazardous to the Ozone Layer (Category 1) if the available evidence concerning its properties and its predicted or observed environmental fate and behaviour indicate that it may present a danger to the structure and/or the functioning of the stratospheric ozone layer.

The very low volatility of the substance precludes an ozone-layer-depleting potential.

12.1.3 Conclusion on classification and labelling for hazardous to the ozone layer

Not classified – conclusive but not sufficient for classification.

RAC evaluation of hazards to the ozone layer

Summary of the Dossier Submitter's proposal

The degradation of the substance in the atmosphere was calculated by the software AOPWIN. Foramsulfuron is not expected to remain stable in the air (half-life of 0.07 days in maximum). Due to its low half-life in the atmosphere combined with a low vapour pressure (4.2 x 10^{-11} Pa at 20 °C) indicating non-volatility and resulting in a low value for the Henry's Law constant (5.8 x 10^{-12} Pa m^3/mole at 20 °C), foramsulfuron is considered not to be subject to transport via air or cause hazard to ozone layer.

Comments received during consultation

One Member State and one company-manufacturer provided public comments, and both agreed with the DS proposal not to classify the substance as hazardous to the ozone layer.

Assessment and comparison with the classification criteria

Atmospheric transport of foramsulfuron in is considered to be negligible due to its low vapor pressure and Henry´s Law constant, whilst its photodegradation in air is expected to be rapid. Therefore, exposure of ozone to foramsulfuron is expected to be negligible.

Thus, RAC agrees with the DS´s proposal that **no classification is warranted for hazards to the ozone layer.**

13 ADDITIONAL LABELLING

14 REFERENCES

Hill RN, Erdreich LS, Paynter OE, Roberts PA, Rosenthal SL, Wilkinson CF (1989) Thyroid follicular cell carcinogenesis. Fundam Appl Toxicol 12: 629-97.

Nagatani M, Kudo S, Yamakawa S, Ohira T, Yamaguchi Y, Ikezaki S, Suzuki I, Saito T, Hoshiya T, Tamura K, Uchida K (2013) Occurrence of spontaneous tumors in the central nervous system (CNS) of F344 and SD rats. J Toxicol Pathol 26: 263-273

15 ANNEXES

Finland, 2016. Draft Renewal Assessment Report (dRAR) on foramsulfuron prepared by the rapporteur MemberState Finland in the framework of Commission Implementing Regulation (EU) No 844/2012, January 2016.