Committee for Risk Assessment

RAC

Annex 1

Background document

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

ethametsulfuron-methyl (ISO); methyl 2-[(4-ethoxy-6-methylamino-1,3,5-triazin-2-yl)carbamoylsulfamoyl]benzoate

EC Number: 619-290-0

CAS Number: 97780-06-8

CLH-O-0000006714-71-01/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

20 September 2019

CLH report

Proposal for Harmonised Classification and Labelling

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

International Chemical Identification:

Ethametsulfuron-methyl (ISO); Methyl 2-[(4-ethoxy-6-methylamino-1,3,5-triazin-2-yl)carbamoylsulfamoyl]benzoate

EC Number: Not assigned

CAS Number: 97780-06-8

Index Number: Not assigned

Contact details for dossier submitter: **UK Competent Authority**
Chemicals Regulation Division
Health and Safety Executive
United Kingdom

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ANNEX 1 - BACKGROUND DOCUMENT TO RAC OPINION ON ETHAMETSULFURON-METHYL (ISO); METHYL 2-({[4-ETHOXY-6-(METHYLAMINO)-1,3,5-TRIAZIN-2-YL]CARBAMOYL}SULFAMOYL)BENZOATE

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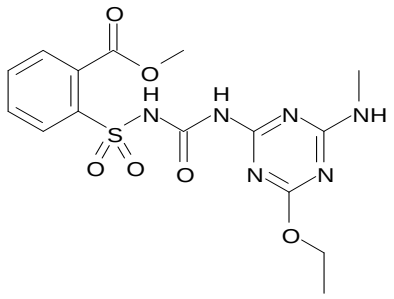
1 IDENTITY OF THE SUBSTANCE

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)	Methyl 2-[(4-ethoxy-6-methylamino-1,3,5-triazin-2-yl)carbamoylsulfamoyl]benzoate
Other names (usual name, trade name, abbreviation)	Ethametsulfuron-methyl (ISO)
ISO common name (if available and appropriate)	Ethametsulfuron-methyl
EC number (if available and appropriate)	-
EC name (if available and appropriate)	-
CAS number (if available)	97780-06-8
Other identity code (if available)	CIPAC Number: 834.201
Molecular formula	$C_{15}H_{18}N_6O_6S$
Structural formula	
SMILES notation (if available)	-
Molecular weight or molecular weight range	410.41 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)	≥97% (w/w)

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)**

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)
Ethametsulfuron-methyl 97780-06-8	>97% (w/w)	-	H319 – Causes serious eye irritation H400 – Very toxic to aquatic life H410 – Very toxic to aquatic life with long lasting effects.

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
-	-	-	-	-	-

The batches used in the relevant studies were considered equivalent to the substance as described above.

2 PROPOSED HARMONISED CLASSIFICATION AND LABELLING

2.1 Proposed harmonised classification and labelling according to the CLP criteria

Table 5:

	Index No	International Chemical Identification	EC No	CAS No	Classification		Labelling			Specific Conc. Limits, M-factors and ATE	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	No existing entry in Annex VI of CLP										
Dossier submitters proposal	TBD	ethametsulfuron-methyl (ISO); Methyl 2-[(4-ethoxy-6-methylamino-1,3,5-triazin-2-yl)carbamoylsulfamoyl]benzoate	-	97780-06-8	Eye Irrit. 2 Aquatic Acute 1 Aquatic Chronic 1	H319 H400 H410	GHS07 GHS09 Wng	H319 H410		M (acute) = 1000 M (chronic) = 100	
Resulting Annex VI entry if agreed by RAC and COM	TBD	ethametsulfuron-methyl (ISO); Methyl 2-[(4-ethoxy-6-methylamino-1,3,5-triazin-2-yl)carbamoylsulfamoyl]benzoate	-	97780-06-8	Eye Irrit. 2 Aquatic Acute 1 Aquatic Chronic 1	H319 H400 H410	GHS07 GHS09 Wng	H319 H410		M = 1000 M = 100	

Table 6: 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, substance is a solid	No
Oxidising gases	Hazard class not applicable, substance is a solid	No
Gases under pressure	Hazard class not applicable, substance is a solid	No
Flammable liquids	Hazard class not applicable, substance is a solid	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, substance is a solid	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, substance is a solid	No
Oxidising solids	Data conclusive but not sufficient for classification	Yes
Organic peroxides	Hazard class not applicable, substance does not exhibit a peroxide moiety	Yes
Corrosive to metals	Data conclusive but not sufficient for classification substance is a solid and unlikely to become liquid in transport	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	Harmonised classification proposed	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	Data conclusive but not sufficient for classification	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
Aspiration hazard	Data lacking	No
Hazardous to the aquatic environment	Harmonised classification proposed	Yes

Hazard class	Reason for no classification	Within the scope of public consultation
Hazardous to the ozone layer	Data conclusive but not sufficient for classification	Yes

3 HISTORY OF THE PREVIOUS CLASSIFICATION AND LABELLING

Ethametsulfuron-methyl is an active substance in the scope of Regulation 1107/2009. It has not been considered for harmonised classification and labelling in the EU previously.

The EFSA conclusion (EFSA Journal 2014;12(7):3787) on the peer review of the pesticide risk assessment for ethametsulfuron-methyl included the following classification;Eye Irritation 2: H319, Reproductive Toxicity 2: H361d, Aquatic Acute 1: H400 and Aquatic Chronic 1: H410.

The above classification has been mostly reflected in self-classification in the C&L Inventory, with the exception of H361d which is not applied.

RAC general comment
Ethametsulfuron-methyl is an active substance in the scope of Regulation 1107/2009. It is used as insecticide and has not been previously considered for harmonised classification and labelling in the EU.

4 JUSTIFICATION THAT ACTION IS NEEDED AT COMMUNITY LEVEL

Ethametsulfuron-methyl is a pesticidal active substance in the scope of Regulation (EU) No 1107/2009. As such, it is subject to the harmonised classification and labelling process in accordance with Article 36 (2) of CLP.

5 IDENTIFIED USES

Ethametsulfuron-methyl is an active substance used in the formulation of the plant protection product ‘Salsa’ (also known as ‘Ethametsulfuron-methyl 75WG’ or ‘Muster 75WG’), which is used as a herbicide.

6 DATA SOURCES

This evaluation relies on data submitted in the context of the application for approval as an active substance under Regulation (EU) No 1107/2009: the Draft Assessment Report (DAR, 2013) compiled by the rapporteur Member State (rMS); original study reports submitted to the rMS by the applicant.

Information is also available in the *EFSA Conclusion on the peer review of the pesticide risk assessment of the active substance ethametsulfuron (evaluated variant ethametsulfuron-methyl)* (EFSA Journal 2014;12(1):3508).

Full references are available in Section 14.

At the time of submission, there is one full registration for ethametsulfuron methyl under REACH.

7 PHYSICOCHEMICAL PROPERTIES

The information used to compile the following table has been taken directly from the Draft Assessment Report (DAR, 2013). This is consistent with the information provided in the REACH registration.

Table 7: Summary of physicochemical properties

Property	Value	Reference	Comment (e.g. measured or estimated)
Physical state at 20°C and 101,3 kPa[A]	Odourless, off-white solid	P. N. Kalyankar (2009)	Purity: 99.2%
Melting/freezing point[B]	196.5°C ± 0.3°C Triplicate measurement by photocell detection	P. N. Kalyankar (2009)	Purity: 99.2% OECD 102 (capillary method)
Boiling point[B]	316.8 ± 0.3°C Triplicate measurement by photocell detection	P. N. Kalyankar (2009)	Purity: 99.2% OECD 103
Relative density[B]	D_4^{20} = 1.4519 The relative density was determined using a pycnometer. A wetting solution containing 0.25% w/v of the surfactant polystryrl phenol polyethoxylate was used to completely fill the pycnometer, relevant corrections for the density of the wetting solution were made	P. N. Kalyankar (2009)	Purity: 99.2% OECD 109
Vapour pressure[A, B]	6.41×10^{-7} Pa (4.81×10^{-9} mm Hg) at 25°C Vapour pressure was determined by the gas saturation method at 25°C, 35°C and 45°C. A vapour pressure curve was used to estimate that the vapour pressure at 25°C	K. N. Manikandan (2010)	Purity: 99.2% OECD Guideline No. 104
Surface tension[A, B]	68.8 mN/m Surface tension of a 90% saturated solution in water at 20°C	H. Sannappa (2009)	Purity: 99.2% OECD 115
Water solubility[A, B]	Milli-Q water: 16.8 mg/L pH 5: 0.56 mg/L pH 7: 223 mg/L pH 9: 1858 mg/L All at 20°C	B. Jagadish (2010)	Purity: 99.2% OECD 105 (flask method)
Partition coefficient n-octanol/water[A, B]	Distilled water: $Log_{10}P_{OW}$	K. G. Pushpalataha	Purity: 99.2%

Property	Value	Reference	Comment (e.g. measured or estimated)
	= 0.53 pH 4.0: $Log_{10}P_{OW}$ = 2.01 pH 7.0: $Log_{10}P_{OW}$ = -0.28 pH 9.0: $Log_{10}P_{OW}$ = -1.83 All at 20°C	(2010)	OECD 107 (shake flask method)
Flash point	-	-	No data submitted. Test not required as melting point >40°C
Flammability	Test item did not support combustion and is not considered flammable	R. L. Gravell and C. M. Hirata (2009)	Purity: 98.7% EEC method A.10 GLP
Explosive properties	Test item was not explosive when subjected to thermal or physical shock.	R. L. Gravell and C. M. Hirata (2009)	Purity: 98.7% EEC method A.14 GLP
Self-ignition temperature	No exotherm was observed up to the melting point (~190°C). Therefore the test item is not considered auto-flammable	R. L. Gravell and C. M. Hirata (2009)	Purity: 98.7% EEC method A.16 GLP
Oxidising properties	The burning rate of the test item was lower than that of a barium nitrate reference, therefore test item not oxidising	R. L. Gravell and C. M. Hirata (2009)	Purity: 98.7% EEC method A.17 GLP
Granulometry	87% of particulate matter was ≥250 µm 12% of particlulate matter was ≤250 µm Negligible amount of particlulate matter was ≤20 µm	Anonymous (2017)	Purity: 98.7% OECD 110
Stability in organic solvents and identity of relevant degradation products	-	-	No data available
Dissociation constant[A, B]	pKa = 4.20 at 20°C Dissociation constant determined spectroscopically due to low water solubility	H. S. Anand (2010)	Purity: 99.2% OECD 112
Viscosity	-	-	No data available. Not relevant as substance is a solid.

A number of studies listed in Table 8 were conducted on commercially manufactured technical material rather than pure active substance. The high purity of the tested material means it is considered to be representative of pure material and commercial technical material. This is indicated by an [A] adjacent to the relevant endpoint.

Furthermore, a number of studies were conducted to GLP principles in an Indian laboratory inspected by a GLP authority from the OECD MAD group; these were considered to be acceptable by the rapporteur Member State under Regulation (EU) No 1107/2009. This is indicated by a [B] adjacent to the relevant endpoint.

8 EVALUATION OF PHYSICAL HAZARDS

8.1 Explosives

Table 9: Summary table of studies on explosive properties

Method	Results	Remarks	Reference
EEC A.14	Test item was not explosive when subjected to thermal or physical shock, nor with respect to friction.		R. L. Gravell and C. M. Hirata (2009)

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

The test substance did not exhibit any thermal or mechanical (shock and friction) sensitivity under the conditions of the test.

8.1.2 Comparison with the CLP criteria

A substance is considered for classification as an explosive substance where a positive result is obtained in the test series indicated in figure 2.1.2 of Annex I of the CLP regulation. Ethametsulfuron-methyl was not found to be sensitive to the effects of heat, shock or friction. Consequently, it does not meet the criteria for classification as an explosive substance.

8.1.3 Conclusion on classification and labelling for explosive properties

Not classified – conclusive but not sufficient for classification.

8.2 Flammable gases (including chemically unstable gases)

Not relevant as the active substance is a solid.

8.3 Oxidising gases

Not relevant as the active substance is a solid.

8.4 Gases under pressure

Not relevant as the active substance is a solid.

8.5 Flammable liquids

Not relevant as the active substance is a solid.

8.6 Flammable solids

Table 10: Summary table of studies on flammable solids

Method	Results	Remarks	Reference
EEC A.10	Ethametsulfuron-methyl melted but did not ignite, and is not considered to be a flammable solid since there was no propagation of the flame.		R. L. Gravell and C. M. Hirata (2009)

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

The test substance was not found to support combustion in the initial screening test during two minutes exposure to the flame as described in the Test Method EEC A.10; only local melting at the point of flame application was observed. The substance is not considered to be a flammable solid since there was no propagation.

8.6.2 Comparison with the CLP criteria

A substance (non-metal) is classified as a flammable solid when the burning time is < 45 seconds or the burning rate is > 2.2 mm/s. On attempted ignition, the test substance exhibitied some melting, but did not ignite – there was no burning time to report. Therefore, the criteria for classification as a flammable solid are not met.

8.6.3 Conclusion on classification and labelling for flammable solids

Not classified – conclusive but not sufficient for classification.

8.7 Self-reactive substances

Table 11: Summary table of studies on self-reactivity

Method	Results	Remarks	Reference
-	-	No data available	-

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

No data available.

8.7.2 Comparison with the CLP criteria

A substance is considered to be self-reactive where the self-accelerating decomposition temperature (SADT) is less than or equal to 75°C when transported in a 50 kg package; or if the heat of decomposition is less than 300 J/g.

No specific data was available for this endpoint.

Test Method A.16 (for autoflammability) showed no exotherms up to the melting temperature of approximately 190 °C; Test Method A.10 (flammability) indicated no thermal instability or degradation after a two minute exposure of the test substance to a flame.

Considering the chemical structure of ethametsulfuron-methyl and the above information on the physcio-chemical properties, there is no evidence that ethametsulfuron-methyl is a self-reactive substance. Therefore, the criteria for classification are not met.

8.7.3 Conclusion on classification and labelling for self-reactive substances

Not classified – conclusive but not sufficient for classification.

8.8 Pyrophoric liquids

Not relevant as the active substance is a solid.

8.9 Pyrophoric solids

Table 12: Summary table of studies on pyrophoric solids

Method	Results	Remarks	Reference
-	-	No data available	-

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

No data available.

8.9.2 Comparison with the CLP criteria

A substance is classified as a pyrophoric solid if it ignites within 5 minutes of coming into contact with air.

No specific data was available for this endpoint.

From the other physicochemical tests conducted, there has been no evidence of the test substance igniting after contact with air or water.

Furthermore, considering the chemical structure, there is no indication that ethametsulfuron-methyl is a pyrophoric substance. Therefore, the criteria for classification are not met.

8.9.3 Conclusion on classification and labelling for pyrophoric solids

Not classified – conclusive but not sufficient for classification.

8.10 Self-heating substances

Table 13: Summary table of studies on self-heating substances

Method	Results	Remarks	Reference
EEC A.16	No exotherm was observed up to the melting point (~190°C). Therefore the test item is not considered auto-flammable		R. L. Gravell and C. M. Hirata (2009)

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

The temperature/time curve relating to conditions in the center of the sample showed no exothermic activity up to its melting point (small endotherm on the time/temperature plot at approximately 190°C).

8.10.2 Comparison with the CLP criteria

A substance is classified as self-heating when a positive result is obtained in the test method out-lined in subsection 33.3.1.6 of the UNRTDG Manual of Tests and Criteria. No data are available as per this method.

A study was conducted according to Test Method A.16; no self-ignition was detected at temperatures below the melting point of ~190°C.

Furthermore, considering the chemical structure and data from Testg Method A.10, there is no evidence that ethametsulfuron-methyl possesses self-heating properties. Therefore, the criteria for classification are not met.

8.10.3 Conclusion on classification and labelling for self-heating substances

Not classified – conclusive but not sufficient for classification.

8.11 Substances which in contact with water emit flammable gases

Table 14: Summary table of studies on substances which in contact with water emit flammable gases

Method	Results	Remarks	Reference
OECD 111	The hydrolytic stability of ethametsulfuron-methyl was investigated in sterile buffer solutions at pH 4 (10, 25, 35, 50°C); pH 7 (50, 60, 70°C) and pH 9 (50, 60, 70°C). From Arrhenius analysis of the data, the half life of ethametsulfuron-methyl at 20°C was estimated: pH 4: DT50 = 28 days. pH 7: Stable. pH 9: Stable.		P. Reibach (2010)

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

No specific data was available for this endpoint. However, hydrolysis rate and data regarding the stability of the active substance in water is available. Ethametsulfuron-methyl appears to be generally stable in contact with water, with hydrolysis occurring primarily in acidic environments.

8.11.2 Comparison with the CLP criteria

Substances which react with water to emit flammable gases are considered for classification in this hazard class.

No specific data was available for this endpoint. Nevertheless, there has been no evidence of the evolution of flammable gases from contact of the test substance with water in the other physicochemical tests conducted, nor through general handling. Using Test Method OECD 111, ethametsulfuron-methyl was found to be generally hydrolytically stable.

Furthermore when considering the chemical structure of ethametsulfuron-methyl, and the hydrolysis breakdown products (from OECD 111), it appears unlikely that flammable gases are released upon contact with water. Therefore, the criteria for classification are not met.

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

Not classified – conclusive but not sufficient for classification.

8.12 Oxidising liquids

Not relevant as the active substance is a solid.

8.13 Oxidising solids

Table 15: Summary table of studies on oxidising solids

Method	Results	Remarks	Reference
EEC A.17	The burning rate of the test item was lower than that of a barium nitrate reference, therefore test item not oxidising		R. L. Gravell and C. M. Hirata (2009)

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

Burning train tests conducted on cellulose/test substance mixtures showed a maximum burning rate that was less than the burning rate for the cellulose/barium nitrate reference, meaning that the test substance is not considered an oxidizer.

8.13.2 Comparison with the CLP criteria

A substance is classified as an oxidising solid when the burning time of a sample-to-cellulose mix-ture is less than or equal to the burning time of the appropriate reference sample – in this case barium nitrate. A mixture of ethametsulfuron-methyl and cellulose had a lower burning rate than barium nitrate. Therefore, the criteria for classification are not met.

8.13.3 Conclusion on classification and labelling for oxidising solids

Not classified – conclusive but not sufficient for classification.

8.14 Organic peroxides

Not relevant as the chemical structure of the active substance does not exhibit a peroxide moiety.

8.15 Corrosive to metals

Table 16: Summary table of studies on the hazard class corrosive to metals

Method	Results	Remarks	Reference
-	-	No data available	-

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

No data available.

8.15.2 Comparison with the CLP criteria

A substance is classified as corrosive to metals under CLP using the test method outlined in section 37.4 of the UN RTDG Manual of Tests and Criteria when the corrosion rate on either steel or aluminium surfaces exceeds 6.25 mm per year at a test temperature of 55°C. The test method notes that it is used to determine the corrosive properties of 'liquids and solids that may become liquids on transport'.

Although there is no data available for this endpoint, given the relatively high boiling point (~190°C) and relative insolubility in water, it is unlikely that the active substance will become liquid on transport. Therefore the hazard is not relevant to the active substance.

8.15.3 Conclusion on classification and labelling for corrosive to metals

Not relevant as the active substance is a solid and unlilkely to become liquid during transit.

RAC evaluation of physical hazards

Summary of the Dossier Submitter's proposal

The dossier submitter (DS) proposes the no classification of ethametsulfuron-methyl for physical hazards on the basis of the following data:

- An EEC A.14 test in which ethametsulfuron-methyl was not explosive when subjected to thermal or physical shock, nor with respect to friction;
- An EEC A.10 test in which ethametsulfuron-methyl melted but did not ignite;
- An ECC A.16 test for autoflammability showing no exothermic behaviour up to the melting temperature of approximately 190 °C;
- A test conducted following OECD 111 guideline showing that ethametsulfuron-methyl is stable in contact with water with hydrolysis occurring primarily in acidic environments (DT = 28 days at pH 4 and apparently stable at pH 7 and above);
- An EEC A.17 test showing as the burning rate of ethametsulfuron-methyl was lower than that of a barium nitrate reference.

Comments received during public consultation

One company-manufacturer supported the no classification of ethametsulfuron-methyl for physical hazards.

Assessment and comparison with the classification criteria

RAC notes that:

- Ethametsulfuron-methyl contains no groups associated with explosivity and therefore no classification is warranted;
- Assay A.10 is not a test supported under CLP and therefore no classification as

flammable solid is warranted **based on lack of data** ;

- Ethametsulfuron-methyl does not contain structural alerts (i.e. no groups associated with explosive or self-reactive properties) and therefore no classification as a self-reactive substance is supported;
- Experience in manufacturing and handling of ethametsulfuron-methyl shows that the substance or mixture does not ignite spontaneously and therefore no classification as a pyrophoric solid due is warranted;
- The CLH-report does not contain acceptable studies for assessing ethametsulfuron-methyl as a self-heating substance and therefore no classification is supported **based on lack of data**;
- Ethametsulfuron-methyl does not containing metals or metalloids and therefore, no classification as a substance, which in contact with water, emits flammable gases is warranted;
- Assay A.17 is not a test supported in CLP and therefore, no classification as an oxidizing solid is warranted **based on lack of data**;
- It is not likely that solid ethemetsulfuron-methyl becomes liquid during storage and transportation and therefore, no classification as corrosive to metals is warranted.

In conclusion, **RAC supports the proposal of the DS for no classification of ethametsulfuron-methyl with regards to physical hazards noting that some physical hazards were not supported by adequate data.**

9 TOXICOKINETICS (ABSORPTION, METABOLISM, DISTRIBUTION AND ELIMINATION)

9.1 Short summary and overall relevance of the provided toxicokinetic information on the proposed classification(s)

The toxicokinetics of ethametsulfuron-methyl have been well investigated in single and repeated dosing studies in rats. Additionally, a limited investigation of metabolism was conducted using whole liver preparations. There are no data to inform on the potential toxicokinetics of ethametsulfuron methyl in humans.

Ethametsulfuron-methyl was moderately well absorbed following oral administeration, as shown by 45-59% of the low dose and 40-53% of the high dose appearing in urine within 5 days.

The available studies indicated that, in rats, ethametsulfuron-methyl is relatively rapidly metabolised, principally via hepatic N-demethylation and O-dealkylation. Distribution was widespread, especially to the blood, liver and kidneys.

Excretion in faeces was approximately to the same extent as in urine. Excretion by both routes combined was extensive and reasonably fast, with >90% of the low dose excreted within 2 days and >80-90% of the high dose within 3 days. Very little of the dose (<0.2%) remained in the sampled tissues (= the main body tissues) at termination.

No clear differences in excretory patterns were noted between males and females. Although marked toxicity was seen at the top dose, excretory patterns were similar at the high and low dose. At the low dose, repeated

exposure resulted in slightly higher faecal excretion than after single exposure. There were no marked differences in excretory patterns between 14-C labelling positions at the high dose.

The extensive and rapid excretion in urine and faeces, and low residue levels in tissues at 5 days post dose, suggest that ethametsulfuron-methyl shows very little potential for accumulation.

10 EVALUATION OF HEALTH HAZARDS

The following summary is based upon the information provided in the Pesticide Draft Assessment Report (DAR) prepared for review under Regulation (EC) 1107/2009 (repealing Directive 91/414/EEC) and the information from the REACH registraiton dossiers available at the time of submission.

Unless indicated otherwise, all studies were conducted in accordance with the relevant OECD TGs and in a GLP environment.

Acute toxicity

The acute toxicity of ethametsulfuron-methyl has been well investigated in single exposure studies, conducted in rats via the oral and inhalation routes of exposure, and in rabbits via the dermal route. Additional, more limited studies, in rats and rabbits via the oral and dermal routes are also available.

10.1 Acute toxicity - oral route

Table 17: 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}	Remarks	Reference
Oral (rat) Similar to OECD TG 401 Limit Test	5 m and f rats (Sprague Dawley strain)	Ethametsulfuron-methyl, 96.8%	5000 mg/kg	>5000 mg/kg	No deaths, clinical signs of toxicity, or findings of specific target organ toxicity were noted at 5000 mg/kg, the only dose tested.	Anonymous (1991a)
Oral (rat) Similar to OECD TG 401 Limit Test	5 m and f rats (Sprague Dawley strain)	Ethametsulfuron-methyl, >98%	5000 mg/kg	>5000 mg/kg	No deaths, clinical signs of toxicity, or findings of specific target organ toxicity were noted at 5000 mg/kg, the only dose tested.	Anonymous (1987a)
Oral (rat) Similar to OECD TG 401	5 f rats (Sprague Dawley strain)	Ethametsulfuron-methyl, 96.8 % In acetone/corn oil or corn oil alone	1000 mg/kg	>1000 mg/kg	No deaths, clinical signs of toxicity, or findings of specific target organ toxicity were noted at doses of up to 1000 mg/kg, the highest dose tested.	Anonymous (1986c)
Oral (rat) Similar to OECD TG 401	Single m and f per dose (Crl:CD®(SD)BR strain)	Ethametsulfuron-methyl, 96.4%	3400, 5000, 7500 or 11000 mg/kg	>11000 mg/kg	No deaths, clinical signs of toxicity, or findings of specific target organ toxicity were noted at doses of up to 1100 mg/kg, the highest dose tested.	Anonymous (1985a)
Oral (rabbit) Similar to OECD	Single m (New Zealand White)	Ethametsulfuron-methyl, 96.4%	1500, 2200, 3400 or 5000	>5000 mg/kg	No deaths, clinical signs of toxicity, or findings of	Anonymous (1986a)

Method, guideline, deviations if any	Species, strain, sex, no/group	Test substance	Dose levels, duration of exposure	Value LD_{50}	Remarks	Reference
TG 401			mg/kg		specific target organ toxicity were noted at doses of up to 5000 mg/kg, the highest dose tested.	

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

Data are available from acute oral dosing studies in rats and rabbits. These studies indicate that ethametsulfuron-methyl is of low toxicity by the oral route, with LD_{50} values of > 5000 mg/kg.

10.1.2 Comparison with the CLP criteria

The oral LD_{50} of > 5000 mg/kg bw for rats is above the value for classification provided in the CLP Regulation (i.e. 2000 mg/kg bw). No classification is proposed.

10.1.3 Conclusion on classification and labelling for acute oral toxicity

Not classified – Conclusive but not sufficient for classification.

10.2 Acute toxicity - dermal route

Table 18: 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}	Remarks	Reference
Dermal. Similar to OECD TG 402 Limit Test	5 m and f rabbits (New Zealand White)	Ethametsulfuron-methyl, 96.8%	2000 mg/kg	> 2000 mg/kg	No deaths, clinical signs of toxicity, or findings of specific target organ toxicity were noted at 2000 mg/kg, the only dose tested.	Anonymous (1991b)
Dermal. Similar to OECD TG 402 Limit Test	5 m and f rats (Wistar)	Ethametsulfuron-methyl, >98%	2000 mg/kg	> 2000 mg/kg	No deaths, clinical signs of toxicity, or findings of specific target organ toxicity were noted at 2000 mg/kg, the only dose tested.	Anonymous (1987b)

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

The acute dermal toxicity of ethametsulfuron-methyl has been well investigated in rabbits and no deaths or clinical signs of toxicity were observed at a dose of 2000 mg/kg, the only dose tested.

In a further study, conducted in rats, using a limit dose of 2000 mg/kg, no deaths or clinical signs of toxicity were reported.

10.2.2 Comparison with the CLP criteria

The dermal LD50 of > 2000 mg/kg bw for rats is above the value for classification provided in the CLP Regulation (i.e. 2000 mg/kg bw). No classification for acute dermal toxicity is proposed.

10.2.3 Conclusion on classification and labelling for acute dermal toxicity

Not classified – Conclusive but not sufficient for classification

10.3 Acute toxicity - inhalation route

Table 19: Summary table of animal studies on acute inhalation toxicity

Method, guideline, deviations if any	Species, strain, sex, no/group	Test substance	Dose levels, duration of exposure	Value LC_{50}/LD_{50}	Remarks	Reference
Inhalation OECD TG 403 Limit Test It should be noted that the test material is granular in appearance and had to be milled to ensure a respirable test atmosphere, although the MMAD is above that recommended for inhalation exposure studies.	Rats (Crl:CD®(SD)BR strain, 10/sex)	Ethametsulfuron-methyl, 96.8%	5.1 and 5.7 mg/l, m and f respectively MMAD 7-9 µm	>5.7mg/l	No deaths, clinical signs of toxicity, or findings of specific target organ toxicity were noted at 5.7mg/l, the only concentration tested Immediately post exposure red ocular and nasal discharge was noted, which apparently resolved rapidly post-exposure.	Anonymous (1991c)

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

The four-hour LC_{50} of ethametsulfuron-methyl in rats was >5.7 mg/l.

10.3.2 Comparison with the CLP criteria

The 4 h inhalation LC_{50} of > 5 mg/l for rats is above the value for classification in the CLP Regulation (i.e. 5 mg/L for dusts and mists). No classification for acute inhalation toxicity is proposed.

10.3.3 Conclusion on classification and labelling for acute inhalation toxicity

Not classified – Conclusive but not sufficient for classification

RAC evaluation of acute toxicity

Summary of the Dossier Submitter's proposal

DS proposed no classification for acute oral toxicity since the available studies showed LD_{50} higher than 1000 mg/kg bw and 2000 mg/kg bw for oral and dermal routes, respectively and LC_{50} higher than 5.7 mg/l for inhalation route.

Comments received during public consultation

One company-manufacturer supported the no classification of ethametsulfuron-methyl for acute toxicity.

Assessment and comparison with the classification criteria

Tables 1, 2 and 3 summarise the main findings reported in the CLH report on acute oral, dermal and inhalation toxicity studies, respectively.

Table 1: *Summary of animal studies on acute oral toxicity with ethametsulfuron-methyl*

Study	Dose level	Results	Reference
Similar to OECD TG 401 5 males and females Sprague Dawley rats	Limit Test Ethametsulfuron-methyl (purity 96.8%) 5000 mg/kg bw	LD_{50} > 5000 mg/kg bw No deaths, clinical signs of toxicity, or findings of specific target organ toxicity were noted at 5000 mg/kg bw	Anonymous (1991a)
Similar to OECD TG 401 5 males and females Sprague Dawley rats	Limit Test Ethametsulfuron-methyl (purity higher than 98%) 5000 mg/kg bw	LD_{50} >5000 mg/kg bw No deaths, clinical signs of toxicity, or findings of specific target organ toxicity were noted at 5000 mg/kg bw	Anonymous (1987a)
Similar to OECD TG 401 5 females rats Sprague Dawley rats	Ethametsulfuron-methyl (purity = 96.8 %) in acetone/corn oil or corn oil alone 1000 mg/kg bw	LD_{50} >1000 mg/kg bw No deaths, clinical signs of toxicity, or findings of specific target organ toxicity were noted at doses of up to 1000 mg/kg bw	Anonymous (1986c)
Similar to OECD TG 401 Single male and female Crl:CD®(SD)BR rats per dose	Ethametsulfuron-methyl (purity = 96.4%) 3400, 5000, 7500 or 11000 mg/kg bw	LD_{50} >11000 mg/kg bw No deaths, clinical signs of toxicity, or findings of specific target organ toxicity were noted at doses of up to 1100 mg/kg bw	Anonymous (1985a)
Similar to OECD	Ethametsulfuron-methyl	LD_{50} >5000 mg/kg bw	Anonymous

TG 401 Single male New Zealand White rabbit per dose	(purity = 96.4%) 1500, 2200, 3400 or 5000 mg/kg bw	No deaths, clinical signs of toxicity, or findings of specific target organ toxicity were noted at doses of up to 5000 mg/kg bw	(1986a)

Table 2: *Summary of animal studies on acute dermal toxicity with ethametsulfuron-methyl*

Study	Dose level	Results	Reference
Similar to OECD TG 402 5 males and females New Zealand White rabbits	Limit Test Ethametsulfuron-methyl (purity = 96.8%) 2000 mg/kg bw	LD_{50} > 2000 mg/kg bw No deaths, clinical signs of toxicity, or findings of specific target organ toxicity were noted at 2000 mg/kg bw	Anonymous (1991b)
Similar to OECD TG 402 5 males and females Wistar rats	Limit Test Ethametsulfuron-methyl (purity >98%) 2000 mg/kg bw	LD_{50} > 2000 mg/kg bw No deaths, clinical signs of toxicity, or findings of specific target organ toxicity were noted at 2000 mg/kg bw	Anonymous (1987b)

Table 3: *Summary of animal study on acute inhalation toxicity with ethametsulfuron-methyl*

Study	Dose level	Results	Reference
OECD TG 403 10 Crl:CD®(SD)BR rats/sex	Limit Test It should be noted that the test material is granular in appearance and had to be milled to ensure a respirable test atmosphere, although the MMAD is above that recommended for inhalation exposure studies. Ethametsulfuron-methyl (purity = 96.8%) 5.7 mg/l, m and f respectively MMAD = 7-9 µm	LD_{50} >5.7mg/l No deaths, clinical signs of toxicity, or findings of specific target organ toxicity were noted at 5.7 mg/l Reversible red ocular and nasal discharge was noted immediately post exposure	Anonymous (1991c)

Comparison with the criteria

There are:

- Four different acute oral toxicity studies with rats (2 different strains) and one study with rabbits yielded LD_{50} higher than the maximum dose required for triggering classification (2000 mg/kg bw) (Table 1). Moreover, these data is supported by a fifth study in rats providing a LD_{50} higher than 1000 mg/kg bw

(Table 1).

- Two independent dermal studies provided evidences that the LD_{50} is higher than the maximum dose required for triggering classification by dermal route (2000 mg/kg bw) (Table 2).
- The reported LD_{50} (> 5.7 mg/l) (Table 3) was also higher than the limit for warranting classification by inhalation route (5 mg/l).

Based on the data provided and in line with the DS, RAC considers that **no classification of ethametsulfuron-methyl with regards to acute oral, dermal and inhalation toxicity is warranted..**

10.4 Skin corrosion/irritation

The skin irritation potential of ethametsulfuron-methyl has been investigated in two rabbit studies, the first using a non standard exposure periof of 24-hours and the second using a standard 4-hour exposure period.

Table 20: 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
Similar to OECD TG 404 The study utilized a 24-hour exposure, not the standard 4-hour exposure period.	Rabbits New Zealand White (n=6)	Ethametsulfuron-methyl, 96.8%	Vehicle; dimethylphthalate	Mean 24, 48, 72 hour individual animal intact scores: Oedema 0,0,0,0,0,0 Erythema 0,0,0,0,0,0	Anonymous (1991d)
Similar to OECD TG 404 The study utilized a 4-hour exposure	Rabbits New Zealand White (n=3, female)	Ethametsulfuron-methyl, 98%	Vehicle; water	Mean 24, 48, 72 hour individual animal intact scores: Oedema 0,0,0 Erythema 0,0,0	Anonymous (1987c)

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

The skin irritation potential of ethametsulfuron-methyl has been investigated in two studies in rabbits. No evidence of skin irritation was observed at any time point in either study.

Mean scores for oedema and erythema for all animals were 0.

10.4.2 Comparison with the CLP criteria

No corrosion of the skin occurred. The mean scores for erythema/eschar or oedema formation were < 2.3 in all animals. The criteria for classification are not met.

10.4.3 Conclusion on classification and labelling for skin corrosion/irritation

Not classified – Conclusive but not sufficient for classification.

RAC evaluation of skin corrosion/irritation

Summary of the Dossier Submitter's proposal

DS proposed no classification of ethametsulfuron-methyl on the basis of one rabbit study using a non-standard exposure period of 24-hours and another rabbit study using a 4-hours exposure period showing neither oedema nor erythema.

Comments received during public consultation

One company-manufacturer supported the no classification of ethametsulfuron-methyl for skin corrosion/irritation.

Assessment and comparison with the classification criteria

Table 4 summarises the main findings reported in the CLH report on skin corrosion/irritation studies.

Table 4: *Summary of the animal studies on skin corrosion/irritation with ethametsulfuron-methyl*

Study	Dose level	Results	Reference
Similar to OECD TG 404 The study utilized a 24-hour exposure New Zealand White rabbits (n=6)	Ethametsulfuron-methyl (purity 96.8%) Vehicle: dimethylphthalate	Mean 24, 48, 72 hour individual animal intact scores: Oedema: 0,0,0,0,0,0 Erythema: 0,0,0,0,0,0	Anonymous (1991d)
Similar to OECD TG 404 The study utilized a 4-hour exposure New Zealand White rabbits (3 females)	Ethametsulfuron-methyl (purity 98%) Vehicle: water	Mean 24, 48, 72 hour individual animal intact scores: Oedema: 0,0,0 Erythema: 0,0,0	Anonymous (1987c)

Comparison with the criteria

No evidence of irritation or corrosion were observed at any time in either study (mean scores for oedema and erythema for all animals were 0; Table 4). Therefore, the criteria for classification are not met and RAC supports the DS's proposal for **no classification of ethametsulfuron-methyl as a skin irritant.**

10.5 Serious eye damage/eye irritation

The eye irritation potential of ethametsulfuron-methyl has been investigated in a non standard rabbit study, and in two briefly reported studies also conducted in rabbits.

Table 21: Summary table of animal studies on serious eye damage/eye irritation

Method, guideline, deviations if any	Species, strain, sex, no/group	Test substance,	Results - Observations and time point of onset - Mean scores/animal - Reversibility	Reference
Similar to OECD TG 405	Rabbits; New Zealand White (n=9) **6 animals unrinsed eyes** **3 animals rinsed eyes**	Ethametsulfuron-methyl, 96.8%	Mean 24, 48, 72 hour individual animal scores *Unwashed:* **Redness:** 0.3 in all 6 animals **Chemosis:** 0.3 in all 6 animals **Cornea:** 0, 1, 1, 0.3, 1.3 and 1 (persisted until the observation on day 7 in 1 animal). **Iris:** 0 in all 6 animals *Washed:* **Redness:** 0.3, 0, 0 **Chemosis:** 0.3, 0, 0 **Cornea:** 1, 1, 0.3 **Iris:** 0 in all 3 animals	Anonymous (1991e)
Similar to OECD TG 405 Scoring system: draize	Rabbits; New Zealand White (single male and female)	Ethametsulfuron-methyl, 96.4%	Mean 24, 48, 72 hour mean scores using the Draize system **Conjunctival redness:** 2/20 – fully reversible (within 24 h) **Conjuctival chemosis: 2/20 –** fully reversible (within 24 h) **Cornea:** 0 . **Iris:** 0	Anonymous (1984a)
OECD TG 405 Scoring system: draize	Rabbits; New Zealand White (3 female)	Ethametsulfuron-methyl, >98%	Mean 24, 48, 72 hour mean scores using the Kay and Calandra scoring system **Conjuctiva – 1/3** **Cornea:** 0 .	Anonymous (1987d)

			Iris: 0	

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

The eye irritation potential of ethametsulfuron-methyl was investigated in a well-conducted, but non-standard, rabbit study. A single dose of ethametsulfuron-methyl was administered into the lower conjunctival sac of the right eye of 9 female young adult New Zealand White rabbits. The eyes remained unrinsed after treatment in 6 of the rabbits, and for 3 of the rabbits both eyes were rinsed approximately 10 seconds after the test material was administered (rinsing lasted approximately 1 minute with room temperature water). The conjunctiva, iris, and cornea of each treated eye were evaluated for evidence of irritation approximately 24, 48, and 72 hours following administration of the test substance. Further eye examinations were performed on 6 of the rabbits at 7 days, 2 rabbits at 10 days, and 1 rabbit at 13, 16, 20, and 21 days. In the unwashed group, conjunctival redness and chemosis (score of 1) was observed at the 24 hour observation, but had resolved by 48 hours in all 6 rabbits. No reactions were observed in the iris at any time point. Corneal opacity (scores of 1-2) was observed in 5 animals at 24 hours, reducing to 4 animals with a score of 1at 48 and 72 hours. This persisted in one animal until day 7, but had resolved by the next observation on day 10. In the washed group, conjunctival redness and chemosis were observed in 1 animal at 24 hours, but no reaction was seen at 48 or 72 hours. No effects were seen in the iris. Corneal opacity (score of 1) was observed in all animals at 24 hours and in 2 animals at the 48 and 72 hour observation points. This again persisited until day 7, but had resolved by the next observation on day 10. In a briefly reported study ethametsulfuron methyl was instilled into the eyes of a single male and female rabbit. The conjunctiva, iris, and cornea of each treated eye were evaluated for evidence of irritation approximately 24, 48, and 72 hours following administration of the test substance using the Draize scoring system. Slight eye irritation (conjunctival chemosis/redness) was reported immediately post-instillation, which resolved within 24-hours.

In a second briefly reported study ethametsulfuron methyl was instilled into the eyes of 3 female rabbits. The conjunctiva, iris, and cornea of each treated eye were evaluated for evidence of irritation approximately 24, 48, and 72 hours following administration of the test substance using the Kay and Calandra scoring system. Slight eye irritation (conjunctiva – chemosis and redness score 1/3) was reported immediately post-instillation, which resolved within 24-hours.

10.5.2 Comparison with the CLP criteria

The criteria for classification as a category 2 eye irritant are:

If, when applied to the eye of an animal, a substance produces:

– at least in 2 of 3 tested animals, a positive response of:

– corneal opacity ≥ 1 and/or

– iritis ≥ 1, and/or

– conjunctival redness ≥ 2 and/or

– conjunctival oedema (chemosis) ≥ 2

– calculated as the mean scores following grading at 24, 48 and 72 hours after installation of the test material, and which fully reverses within an observation period of 21 days.

Where 6 animals are used, the criteria are amended such that 4/6 tested animals exhbit a positive response as outlined above.

Corneal opacity with a score of ≥ 1 was observed in 4/6 animals in the unwashed group and 2/3 animals in the washed group. Therefore, the criteria for classification in category 2 are met for this study.

There is no explanation for the two negative results obtained in the more briefly reported rabbit studies, Overall, classification with category 2 is proposed.

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

Eye Irritation 2: H319 – 'Causes serious eye irritation'

RAC evaluation of serious eye damage/irritation

Summary of the Dossier Submitter's proposal

DS proposed classification of ethametsulfuron-methyl as eye irritant category 2 on the basis of one non-standard rabbit study reporting corneal opacity score of ≥ 1 in 4/6 animals in which the eye was not washed after instillation and 2/3 animals in which the eye was washed after instillation.

Comments received during public consultation

Two member state competent authorities and one company-manufacturer supported the classification of ethametsulfuron-methyl as eye irritant category 2 H319.

Assessment and comparison with the classification criteria

Table 5 summarises the main findings reported in the CLH report on serious eye/damage studies.

Table 5: *Summary of the animal studies on serious eye damage with ethametsulfuron-methyl*

Study	Dose level	Results	Reference
Similar to OECD TG 405 New Zealand White rabbits Scoring system: Draize	Ethametsulfuron-methyl (96.8% purity) 6 animals unrinsed eyes 3 animals rinsed eyes	Mean 24, 48, 72 hours individual animal scores <u>Unwashed</u> Redness: 0.3 in all 6 animals Chemosis: 0.3 in all 6 animals Cornea: 0, 1, 1, 0.3, 1.3 and 1 (persisted until the observation on day 7 in 1 animal and resolved by day 10) Iris: 0 in all 6 animals <u>Washed (1 min of rinsing approximately</u>	Anonymous (1991e)

		10 seconds after instillation) Redness: 0.3, 0, 0 Chemosis: 0.3, 0, 0 Cornea: 1, 1, 0.3 (persisted until the observation on day 7 in 1 animal and resolved by day 10) Iris: 0 in all 3 animals	
Similar to OECD TG 405 Zealand White rabbits Scoring system: Draize	Ethametsulfuron-methyl (purity 96.4%) Single male and female	Mean 24, 48, 72 hours Conjunctival redness: 2/20 – fully reversible (within 24 h) Conjunctival chemosis: 2/20 – fully reversible (within 24 h) Cornea: 0 Iris: 0	Anonymous (1984a)
OECD TG 405 New Zealand White rabbits	Ethametsulfuron-methyl (purity >98%) 3 females	Mean 24, 48, 72 hour mean scores using the Kay and Calandra scoring system Conjunctival: 1/3 (resolved within 24 hours) Cornea: 0 Iris: 0	Anonymous (1987d)

Comparison with the criteria

According to the CLP Criteria the classification as eye irritant category 2 is warranted if the substance causes in at least in 2 of 3 (or, according to the Guidance on the Application CLP Criteria, 4 of 6) tested animals a positive response of corneal opacity ≥1 calculated as the mean scores following grading at 24, 48 and 72 hours after installation of the test material, and which fully reverses within an observation period of 21 days. One of the studies summarised in Table 5 shows a reversible cornel opacity ≥ 1 in the eyes of 4 of 6 unwashed animals and in 2 of 3 washed animals.

RAC notes two other studies with rabbits (performed with lower number of animals that the one showing positive results) were showing only conjunctival effects not high enough for warranting classification. However, there is no reason to diminish the weight of the positive results and RAC supports the DS's proposal for **classification of ethametsulfuron-methyl as an eye irritant category 2 H319 (causes serious eye irritation)..**

10.6 Respiratory sensitisation

No data are available.

10.6.1 Conclusion on classification and labelling for respiratory sensitisation

Not classified, data lacking.

10.7 Skin sensitisation

Table 22: 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
OECD TG 429 LLNA	Mouse, 5f (CBA/JHsd strain)	Ethametsulfuron-methyl, 99.2%	0, 5, 25, 50 and 75% in dimethylsulfoxide	**Negative** **Control and test animals;** SI <3 **Positive control: 25%** hexylcinnamenaldehyde SI 4.47	Anonymous (2008a)
Buehler test Consistent with OECD TG 406	Guinea pig Dunkin Hartley 10 males/concentration	Ethametsulfuron-methyl, 96.4%	9 Induction applications Induction and Challenge: 5 and 50% Vehicle: dimethyl phthalate	**Negative** (no positive control group)	Anonymous (1991q)
Buehler test OECD TG 406	Guinea pig Dunkin Hartley 20 test and 10 control (female)	Ethametsulfuron-methyl, 96.4%	4 Induction applications Induction: 50% Challenge: 10, 25 and 50% Vehicle methyl cellulose	**Negative** **Responses at 24 and 48 hours** **10%: 0/20 and 1/20** **25%: 1/20 and 1/20** **50%: 1/10 and 1/20** (no positive control group)	Anonymous (1987e)

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

The skin sensitisation potential of ethametsulfuron-methyl has been well investigated in a LLNA.

In the LLNA, groups of 5 mice were tested with 0, 5, 25, 50 and 75% ethametsulfuron-methyl in dimethylformamide. The concurrent positive control substance was 25% hexylcinnamonaldehyde. All animals were treated daily for 3 consecutive days, after which the animals were sacrificed and the draining lymph nodes excised for further analysis. Stimulation indices (SI) for ethametsulfuron-methyl were below 3 for all test concentrations. The positive control produced a SI of 4.7. Overall, ethametsulfuron-methyl tested negative. It was not possible to determine an EC_{50} value.

The skin sensitisation potential of ethametsulfuron-methyl has been investigated in Guinea pigs using a 9-induction Buehler protocol. Ethametsulfuron-methyl was applied at concentrations of 5 and 50%. The study also included a negative control (treated with vehicle only), but no infromation on a positive control group was provided. The highest concentration employed was reported to have been identified using a range-

finding test, but these data are not available. No positive skin reactions were reported at any concentration or time point.

In a second Buehler study using a 4-induction protocol; ethametsulfuron-methyl was applied at concentrations of 10, 25 and 50% (20 test and 10 control Guinea pigs). The study also included a negative control (treated with vehcile only), but no information on a positive control group was provided. The highest concentration employed was reported to have been identified using a range-finding test, but these data are not available. A positive respose (grade 2 erythemna at 24 and 48 hours) was reported in 1 animal only challenged with 20 and 50%.

10.7.2 Comparison with the CLP criteria

The stimulation indices for ethametsulfuron-methyl were below 3 for all test concentrations in the LLNA. No evidence of skin sensitisation was reported in one Buehler Guinae pig test. In a second study, a response was noted in 5% (1/20) of the treated animals, but this is below the value of 15% for a non-adjuvant Guinea pig test to be considered positive. Therefore, the criteria for classification were not met for either the LLNA or Buehler studies

10.7.3 Conclusion on classification and labelling for skin sensitisation

Not classified – conclusive but not sufficient for classification.

RAC evaluation of skin sensitisation

Summary of the Dossier Submitter's proposal

The DS proposed no classification of ethametsulfuron-methyl on the basis of the negative results of three tests (one lymph node assay (LLNA) in mice and two Buehler assays in guinea pigs).

Comments received during public consultation

One company-manufacturer supported the no classification of ethametsulfuron-methyl for skin sensitisation.

Assessment and comparison with the classification criteria

Table 6 summarises the main findings reported in the CLH report on skin sensitisation studies.

Table 6: *Summary of the animal studies on skin sensitisation with ethametsulfuron-methy.*

Study	Dose level	Results	Reference
OECD TG 429 LLNA CBA/JHsd mouse	Ethametsulfuron-methyl (purity 99.2%) 0, 5, 25, 50 and 75% in dimethylsulfoxide during 3 consecutive days	Control and test animals: SI <3 Positive control: SI 4.47 **Conclusion: negative**	Anonymous (2008a)

5 females/group	Positive control: 25% hexylcinnamenaldehyde		
Buehler test Consistent with OECD TG 406 Dunkin Hartley guinea pig 10 males/group	Ethametsulfuron-methyl (purity 96.4%) 9 induction applications Induction and Challenge: 5 and 50% Vehicle: dimethyl phthalate No positive control	No skin reactions at any concentration or time point **Conclusion: negative**	Anonymous (1991q)
Buehler test OECD TG 406 Dunkin Hartley guinea pig Females: 20 test and 10 control	Ethametsulfuron-methyl (purity 96.4%) 4 induction applications Induction: 50% Challenge: 10, 25 and 50% Vehicle methyl cellulose No positive control	Responses at 24 and 48 hours: 10%: 0/20 and 1/20 25%: 1/20 and 1/20 50%: 1/10 and 1/20 **Conclusion: negative**	Anonymous (1987e)

Comparison with the criteria

According to the CLP criteria the classification of a substance as skin sensitizer is warranted if: i) the stimulation index in LLNA is higher than 3 with EC_3 higher than 2%; or; ii) there is more than 15 % of response with a topical induction dose higher than 20% in the Buehler test.

Table 6 shows that the stimulation index in LLNA was lower than 3 and no EC_3 could be derived and moreover, the response of guinea pig to 50% induction dose was lower than 15% in two independent tests. Therefore, RAC considers that the criteria have not been met and supports the DS's proposal for **no classification of ethametsulfuron-methyl as a skin sensitizer.**

10.8 Germ cell mutagenicity

Table 23: 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
Ames (OECD 471)	Ethametsulfuron-methyl, 96.4%	S. typhimurium TA97, TA98, TA100 and TA1535 First experiment 0-2.5 µg/plate –S9 and 0-10 µg/plate +S9	- S9: Negative + S9: Negative Although the test gave a negative result, it was not possible to achieve very high concentrations due to bacteriotoxicity. Positive controls were included and gave the	Gerber K.M. (1991a)

Method, guideline, deviations if any	Test substance,	Relevant information about the study including rationale for dose selection (as applicable)	Observations	Reference
		Second experiment 0-0.5 µg/plate –S9 and 0-1 µg/plate +S9	expected results.	
Ames (OECD 471)	Ethametsulfuron-methyl, >98%	S. typhimurium TA1535, TA1538, TA98, TA1535, and TA100 0- 5000 µg/plate + and–S9	- S9: Negative + S9: Negative Positive controls were only incubated for 3-hours and gave lower responses than normally expected	Anonymoue (1987f)
Mammalian cell gene mutation (CHO/HPRT) (OECD 476)	Ethametsulfuron-methyl, 96.8%	61-3400 ug/ml in both experiments, with and without S9	- S9: Negative + S9: Negative Positive controls were included and gave the expected results Lower survival was noted in trial 1 but it was always at least c.50%, ie: - during expression with S9 (survival 53-72%) - at selection without S9 (survival 48-68%).	Rickard, L.B. (1991)
In vitro UDS (OECD TG 482)	Ethametsulfuron-methyl, 98.8%	Rat hepatocytes 0, 0.2, 0.2, 2, 20, 40, 205 and 352µg/ml in both experiments	Negative Positive controls were included and gave the expected response. Only 100 cells per dose were scored. There was no evidence of cytotoxicity in either trial.	Bentley, K.S. (1991)

Table 24: 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
Bone Marrow chromosomal aberration - broadly consistent with OECD 475 50 (instead of 100) cells animal were scored for aberrations and the mitotic index was based on 500 (instead of 1000) cells per rat. These deviations are not	Ethametsulfuron-methyl, 96.8%	0, 500, 1500 and 5000 mg/kg via, gavage in corn oil Mice (CD-1 strain) 5/sex/group	Negative The positive controls responded as expected At 6h, mitotic index was reduced (statistically significant) in both sexes at 5000 mg/kg and in males at 1500 mg/kg . There was no effect on mitotic index at 24 or 48h. It is notable that the mitotic index of the corn oil controls was much higher at 6h (17.8 -18.6 mitoses per 500 cells) than at 24 or 48 h (7.4 -10.6 mitoses per 500 cells). No statistically or biologically significant changes in chromosomal aberrations were observed.	Anonymous (1991f)

Method, guideline, deviations if any	Test substance,	Relevant information about the study (as applicable)	Observations	Reference
considered to have compromised the reliability of the study.				
Bone Marrow chromosomal aberration - broadly consistent with OECD 475	Ethametsulfuron-methyl, >98%	0, and 5000 mg/kg via, gavage in methyl cellulose Mice (Swiss srain) 5/sex/group	Negative The positive controls responded as expected No statistically or biologically significant changes in chromosomal aberrations were observed.	Anonymous (1987g)
Bone Marrow micronucleus, OECD 474	Ethametsulfuron-methyl, 96.8%	0, 500, 1500 and 5000 mg/kg via, gavage in corn oil Mice (Cr1:CD-1®BR rain) 5/sex/group and 8/sex group for 72 hr time point	Negative The positive controls responded as expected No statistically or biologically significant increases in the incidence of micronucleated polychromatic erythrocytes, compared to vehicle controls were observed.	Anonymous (1991g)

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

The in vitro genotoxicity of ethametsulfuron-methyl has been well investigated in two Ames tests, a mammalian cell gene mutation test (TK) and an *in vitro* UDS test using rat hepatocytes. The appropriate positive controls were included and gave the expected results. Overall, it can be concluded that ethametsulfuron-methyl is not genotoxic in vitro.

The *in vivo* genotoxicity of ethametsulfuron-methyl has been investigated in two mouse bone marrow micronucleus tests and a mouse bone marrow cytogenetics test. The appropriate positive controls were included and gave the expected results. In all studies, the highest dose was based on a preliminary study, conducted to establish the maximum tolerated dose.
Ethametsulfuron-methyl tested negative all tests, in which animals were administered single gavage doses of up to 5000 mg/kg/day, well in excess of the modern limit dose of 2000 mg/kg. These studies were conducted before the OECD TG's were updated to include a requirement to take blood samples to provide evidence of bone marrow exposure. There are no toxicokinetic studies conducted in mice which might inform on bone marrow exposure. However, there are toxicokinetic data from rats, which indicate that ethametsulfuron/ethametsulfuron metabolites distribute to the blood. Assuming there are no significant toxicokinetic differences between rats and mice in relation to ethametsulfuron-methyl, it is reasonable to conclude that the bone marrow would have been exposed in these in vivo micronucleus and cytogenetics studies as it is a well perfused tissue.
Ethametsulfuron-methyl has been well investigated for genotoxicity in standard *in vitro* and *in vivo* studies and it can be concluded that ethametsulfuron-methyl is not genotoxic.

The available data indicate that ethametsulfuron-methyl is not mutagenic, either *in vitro* or *in vivo*.

10.8.2 Comparison with the CLP criteria

Ethametsulfuron-methyl tested negative in vitro and in vivo, and no classification for germ-cell mutagenicity is proposed.

10.8.3 Conclusion on classification and labelling for germ cell mutagenicity

Not classified – conclusive but not sufficient for classification.

RAC evaluation of germ cell mutagenicity

Summary of the Dossier Submitter's proposal

DS proposed no classification of ethametsulfuron-methyl for germ cell mutagenicity in the basis of the following results:

- Two negative Ames tests;
- One negative mammalian cell gene mutation test;
- One negative *in vitro* unscheduled DNA synthesis (UDS) test;
- Two negative *in vivo* bone marrow chromosomal aberration tests;
- One negative *in vivo* bone marrow micronucleus test.

Comments received during public consultation

One company manufacturer supported the proposal of no classification for germ cell mutagenicity.

A member state competent authority considered that no classification of the substance is needed on the basis of available studies but there is data lacking because several deviations from the test guideline for the bacterial reverse mutation test. Only four Salmonella typhimurium strains were used, a test with either *Salmonella typhimurium* TA102 or an appropriate E. coli strain was not conducted and accordingly, DNA damage induced by oxidative damage may not be detected. The DS replied that there is sufficient *in vitro* and *in vivo* information from well-conducted standard studies to conclude on the mutagenic potential of ethametsulfuron-methyl.

A second member state competent authority commented that neither the CLH report nor Annex I contain a presentation of the results and an independent assessment of this endpoint could not be made. DS replied to this comment that the results of the available mutagenicity studies were clearly negative and, as such, sufficient information was provided in the CLH report to enable RAC to conclude on germ cell mutagenicity.

Assessment and comparison with the classification criteria

Tables 8 and 9 summarise the main findings reported in the CLH report on *in vitro* and *in vivo* mutagenicity/genotoxicity studies with ethametsulfuron-methyl; respectively.

Table 8: *Summary table of mutagenicity/genotoxicity in vitro studies with ethametsulfuron-methyl*

Method	Tested concentrations	Results	Reference
Ames OECD 471 *Salmonella typhimurium* TA97, TA98, TA100 and TA1535	Ethametsulfuron-methyl (purity 96.4%) <u>First experiment</u> -S9 : 0-2.5 µg/plate +S9 : 0-10 µg/plate <u>Second experiment</u> -S9 : 0-0.5 µg/plate +S9 : 0-1 µg/plate	**- S9: Negative** **+ S9: Negative** Positive controls were included and gave the expected results Although the test gave a negative result, it was not possible to achieve very high concentrations due to cytotoxicity	Gerber K.M. (1991a)
Ames OECD 471 *Salmonella typhimurium* TA1535, TA1538, TA98, TA1535, and TA100	Ethametsulfuron-methyl (purity >98%) 0- 5000 µg/plate (both with and without S9)	**- S9: Negative** **+ S9: Negative** Positive controls were only incubated for 3-hours and gave lower responses than normally expected	Anonymous (1987f)
Mammalian cell gene mutation OECD 476 CHO/HPRT cells	Ethametsulfuron-methyl (purity 96.8%) 61-3400 µg/ml in both with and without S9	**- S9: Negative** **+ S9: Negative** Positive controls were included and gave the expected results Lower survival was noted in trial 1: 53-72% with S9 and 48-68% without S9	Rickard, L.B. (1991)
UDS OECD TG 482 Rat hepatocytes	Ethametsulfuron-methyl (purity 98.8%) 0, 0.2, 0.2, 2, 20, 40, 205 and 352 µg/ml in both experiments	**Negative** Positive controls were included and gave the expected response Only 100 cells per dose were scored. No evidence of cytotoxicity in either trial	Bentley, K.S. (1991)

Table 9: *Summary table of mutagenicity/genotoxicity in vivo studies with ethametsulfuron-methyl*

Method	Tested concentrations	Results	Reference
Bone Marrow chromosomal aberration Broadly consistent with OECD 475 CD-1 mice 5/sex/group	Ethametsulfuron-methyl (purity 96.8%) 0, 500, 1500 and 5000 mg/kg via gavage in corn oil	**Negative** The positive controls responded as expected At 6h, mitotic index was reduced (statistically significant) in both sexes at 5000 mg/kg and in males at 1500 mg/kg No effect on mitotic index at 24 or 48h <u>Mitotic index of the corn oil</u>	Anonymous (1991f)

		controls was much higher at 6h (17.8 -18.6 mitoses per 500 cells) than at 24 or 48 h (7.4 -10.6 mitoses per 500 cells) No statistically or biologically significant changes in chromosomal aberrations were observed. 50 (instead of 100) cells per animal were scored for aberrations and the mitotic index was based on 500 (instead of 1000) cells per animal (these deviations are not considered to have compromised the reliability of the study)	
Bone Marrow chromosomal aberration Broadly consistent with OECD 475 Swiss mice 5/sex/group	Ethametsulfuron-methyl (purity >98%) 0, and 5000 mg/kg via gavage in methyl cellulose	**Negative** The positive controls responded as expected No statistically or biologically significant changes in chromosomal aberrations were observed	Anonymous (1987g)
Bone Marrow micronucleus OECD 474 Cr1:CD-1®BR mice 5/sex/group and 8/sex group for 72 hr time point	Ethametsulfuron-methyl (purity 96.8%) 0, 500, 1500 and 5000 mg/kg via, gavage in corn oil	**Negative** The positive controls responded as expected No statistically or biologically significant increases in the incidence of micronucleated polychromatic erythrocytes, compared to vehicle controls were observed	Anonymous (1991g)

Comparison with CLP criteria

RAC notes that the bioavailability of ethametsulfuron-methyl in bone marrow is not demonstrated. However, RAC also notes that the highest dose used in the three *in vivo* assays (5000 mg/kg bw) is clearly above the limit dose and also notes that the toxicokinetic data in rats clearly demonstrated that ethametsulfuron-methyl and its metabolites are distributed to the blood. Assuming that toxicokinetics in rat might be comparable to toxicokinetic in mouse, these two considerations cause RAC to consider it reasonable that these three *in vivo* studies are valid for classification purposes.

According to the Guidance on the Application of the CLP Criteria the minimum classification (category 2) for germ cell mutagenicity is triggered only when positive evidence of genotoxicity was found from somatic cell mutagenicity tests *in vivo* in mammals or from other *in vivo* somatic cell genotoxicity tests, which are supported by positive results from in vitro mutagenicity assays. The available database provides an array of *in vitro* and *in vivo* negative results that do not allow concluding that the classification was warranted.

Therefore, RAC supports the DS's proposal for **no classification of ethametsulfuron-methyl with regards to germ cell mutagenicity..**

10.9 Carcinogenicity

Table 25: 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
OECD TG 453 Rat Sprague-Dawley Crl:CDBR strain, 72/sex/dose, (including interim sacrifice at 12 months of 10/sex/group)	Ethametsulfuron-methyl, 96.8% Dosed for 24 months, via the diet 0, 50, 500 and 5000 ppm ethametsulfuron-methyl Equivalent to 0, 2.1, 21, and 210; and 0, 2.6, 26 and 267 mg/kg/day in males and females respectively	**Neoplastic changes** No toxicologically significant increases in tumor incidence were observed.	Anonymous (1991h)
OECD TG 453 Mouse (80/sex/dose) Crl:CD®(SD)BR strain Interim sacrifice (12 months): 10/sex/group	Ethametsulfuron-methyl, 96.8% Dosed for 18 months, via the diet 0, 50, 500 and 5000 ppm ethametsulfuron-methyl Equivalent to 0, 3.5, 68, and 705; and 0, 4.6, 95 and 930 mg/kg/day in males and females respectively	**Neoplastic changes** No toxicologically significant increases in tumor incidence were observed	Anonymous (1991i)

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

The carcinogenic potential of ethametsulfuron-methyl has been well investigated in standard studies, in rats and mice. Discussion of the non-neoplastic findings can be found in the repeated dose section (section 10.12).

Rat

Sprague-Dawley rats (Crl:CDBR strain 72/sex/dose) were administered ethametsulfuron-methyl at doses of up to 210 and 267 mg/kg/day, in males and femals respectively,for up to 104 weeks (62/sex/dose) or up to 52 weeks (10/sex/dose) for the interim sacrifice. No treatment-related changes were observed in food consumption, body weight, body-weight gain or mortality rates.

The non neoplastic effects observed in this study are reported and evaluated in the repeated dose section (10.12). However, the most prominent adverse effects observed were mammary gland enlargement with chronic inflammation of enlarged mammary gland ducts in high dose females. The incidences of microscopic lesions in the mammary gland are shown in the table below.

	0 ppm	**50 ppm**	**500 ppm**	**5000 ppm**
No. examined	**60**	**48**	**57**	**62**
Adenoma	3	0	3	5
Adenocarcinoma	13	16	17	15
Fibroadenoma	24	16	27	26
Hyperplasia, diffuse	52	34	37	59
Dilatation, duct	1	1	3	2

Historical control data for female rats of the same strain at the test laboratory (study reports dated 1984-1990) compared with control values for the current study (data from Frame, 2006)
Adenoma: Range: 0-9% (current study control: 5%)
Adenocarcinoma: 4-23% (current study control: 22%)
Fibroadenoma: 20-33% (current study control: 40%)

Overall, it is concluded that there was no treatment-related increases in tumour incidence (including in the mammary gland as noted in the EFSA conclusion) in either sex, at interim or terminal sacrifice at doses of up to 210-267 mg/kg/day (males and females), the highest dose tested.

Mice

Crl:CD(SD)BR strain mice (70+10 sex/dose) were administered ethametsulfuron-methyl at doses of up to 705-930 mg/kg/day in males and females respectively, for up to 80 weeks. There were no treatment-related changes in food consumption, body weight, body-weight gain or mortality rates.

No toxicologically significant non neoplastic changes were observed in this study. The repeated dose effects are reported and evaluated in the repeated dose toxicity section (10.12).

No treatment-related increases in tumour incidence were observed in either sex, at interim or terminal sacrifice at doses of up to 705-930 mg/kg/day, the highest dose tested.

10.9.2 Comparison with the CLP criteria

The carcinogenic potential of ethametsulfuron-methyl has been investigated in standard studies in rats and mice, and no evidence of tumour induction was observed. Therefore, ethametsulfuron-methyl does not meet the criteria for classification for carcinogenicity.

10.9.3 Conclusion on classification and labelling for carcinogenicity

Not classified – conclusive but not sufficient for classification.

RAC evaluation of carcinogenicity

Summary of the Dossier Submitter's proposal

The carcinogenicity of ethametsulfuron-methyl was well investigated in standard studies in rats and mice. The DS proposed no classification of ethametsulfuron-methyl for the substance because:

- No treatment-related increases in tumour incidence were observed in either sex, at interim or terminal sacrifice at doses of up to 705-930 mg/kg bw/day, the highest

dose tested in mice;

- There was no treatment-related increases in tumour incidence in either sex, at interim or terminal sacrifice at doses of up to 210-267 mg/kg bw/day (males and females), the highest dose tested in rats.

Comments received during public consultation

Two member states competent authorities and one company manufacturer supported the proposal of no classification for carcinogenicity. Another member state competent authority questioned the dosing in the rat study. DS replied to this comment that, independently of the dosing, there were no evidences of a treatment related increase in tumour incidences and, therefore, the criteria for classification as a carcinogen are not met based on the available data.

Assessment and comparison with the classification criteria

Carcinogenicity study in mice

Crl:CD(SD)BR strain mice (70+10 sex/dose) were administered with ethametsulfuron-methyl at doses of up to 705-930 mg/kg bw/day in males and females respectively, for up to 80 weeks. There were no treatment-related changes in food consumption, body weight, body-weight gain or mortality rates. The non-neoplastic findings were summarised in Table 7 (study Anonymous 1991i) and included histopathological alterations in mesenteric lymph node, kidney, epididymides, prostate, urinary bladder and lachrymal glands and reductions in absolute and relative weight of spleen without evidences of organ malfunction.

No treatment-related increases in tumour incidence were observed in either sex, at interim or terminal sacrifice at doses of up to 705-930 mg/kg/day, the highest dose tested.

Carcinogenicity study in rats

Sprague-Dawley rats (Crl:CDBR strain 72/sex/dose) were administered ethametsulfuron-methyl at doses of up to 210 and 267 mg/kg/day, in males and females respectively, for up to 104 weeks (62/sex/dose) or up to 52 weeks (10/sex/dose) for the interim sacrifice. No treatment-related changes were observed in food consumption, body weight, body-weight gain or mortality rates. The non-neoplastic findings were summarised in Table 7 (study Anonymous 1991h) and included histopathological alterations in mammary gland ducts, lungs, bone marrow, naso-lachrymal duct, pituitary and ovaries.

The most prominent adverse effects observed were mammary gland enlargement with chronic inflammation of enlarged mammary gland ducts and the microscopic lesions summarised in Table 9.

Table 9: *Incidences of microscopic lesions in the mammary gland reported in the carcinogenicity study of ethametsulfuron-methyl in rats.* Historical control data (HCD) corresponds to female rats of the same strain in the performing facility 1984-1990.

	mg/kg bw/day				
	0	**2.6**	**26**	**267**	**HCD**
No. examined	60	48	57	62	-
Adenoma	3 (5%)	0 (0%)	3 (5%)	5 (8%)	0-9%
Adenocarcinoma	13 (22%)	16 (33%)	17 (30%)	15 (24%)	4-23%
Fibroadenoma	24 (40%)	16 (33%)	27 (47%)	26 (42%)	20-33%
Hyperplasia, diffuse	52 (87%)	34 (71%)	37 (65%)	59 (95%)	-
Dilatation, duct	1 (2%)	1 (2%)	3 (5%)	2 (3%)	-

RAC notes that the HCD provided in the CLH report belongs to the period of time of 6 years immediately before the beginning of the study and therefore do not meet the typical requirement of ±5 years of the date of the study; which reduces the reliability of this HCD. Overall, RAC notes that the incidences of adenoma, adenocarcinoma and fibroadenoma in treated rats were not statistically different from the incidences in controls and moreover, such incidences do not observe a dose-response. Finally, it is also remarkable that no relevant neoplastic incidences in mammary glands of mice treated with doses up to 3.5 times the highest dose used in rats were found.

RAC also notes a possible deviation from the guidelines because the maximum dose assayed in this study (267 mg/kg bw/day) does not seem to be close to the maximum tolerable dose since the 2-generation study reports that a dose of 1869 mg/kg bw/day causes only a reduction of around 10% in body weight of males and therefore the full potential of ethametsulfuron-methyl was not assessed in this study.

Overall RAC does not consider the effects observed in the mammary gland of rats as sufficient to support a classification and agrees the DS's proposal for **no classification of ethametsulfuron-methyl for carcinogenicity.**

10.10 Reproductive toxicity

10.10.1 Adverse effects on sexual function and fertility

Table 26: 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 study OECD 416	Ethametsulfuron-methyl, 96.8% 0, 250, 5000 and 20000 ppm equivalent to, 20,	**Parental toxicity** There were no adverse effects on body weight, body weight gain and food consumption in females. Body weight gain was decreased in males, by around	Anonymous (1991j)

Method, guideline, deviations if any, species, strain, sex, no/group	**Test substance, dose levels duration of exposure**	**Results**	**Reference**
Oral (diet) Rat Sprague-Dawley 23/sex/dose	395 and 1582 mg/kg /day in males and 0, 19, 449 and, 1817mg/kg /day in females of the F0 generation and 22, 439, and 1756 mg/kg day in males and 18, 448, and 1869 mg/kg /day in females of the F1 generation	10% compared to controls in both parental generations. ***20000 ppm*** *F0* ↑ relative (13%) testis weight. *F1a* ↑ relative (21%) testis weight ***5000 and 250 ppm*** No toxicologically significant changes **Reproductive effects** No toxicologically significant adverse effects on reproduction were observed **Offspring effects** The only adverse effect observed was a 16% increase in absolute and relative spleen weights in top dose F2b pups.	
One-generation reproductive toxicity preliminary study Oral (diet) Rat Sprague-Dawley 6/sex/dose)	Ethametsulfuron-methyl, 96.8% 0, 100, 1000 and 5000 ppm estimated to be equivalent to, 7.3, 71 and 365 mg/kg /day in males and 0, 9.5, 88 and, 453mg/kg /day in females	**Parental toxicity** No toxicologically significant changes were observed. **Reproductive effects** No adverse effects on fertility were observed. **Offspring effects** No toxicologically significant changes were observed.	Anonymous (1991k)

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

There are two studies available, conducted to investigate the potential of ethametsulfuron-methyl to adversely affect sexual function and fertility, both conducted in rats. One is a 2-generation study and the other a 1-generation screening study.

The effects of ethametsulfuron-methyl on sexual function and fertility have been investigated in a 2-generation study conducted in Sprague-Dawley rats (Crl:CDBR strain). Limited additional information is also available from a non-standard 1-generation preliminary study, conducted in the same strain of rats.

The potential for ethametsulfuron-methyl to adversely affect fertility has been well investigated in a standard 2-generation dietary study (OECD TG 416) in rats, at doses of up to 20,000 ppm (estimated to be equivalent to 0, 20, 395 and 1582 mg/kg /day in males and 0, 19, 449 and, 1817mg/kg /day in females of the F0 generation and 0, 22, 439, and 1756 mg/kg day in males and 0, 18, 448, and 1869 mg/kg /day in females of the F1 generationmg/kg/day). The top dose in this study was selected on the basis of a combined 90-day/one-generation study. Histopathological investigations were confined to control and high dose animals. No toxicologically significant changes in food consumption, body weight, or body weight gain were observed at any dose level tested in females. In males, a slight decrease in body weight gain (of 10% compared to controls) was observed in both parental generations. No other changes were observed in parental males. There was no substance-related effect on litter size, pup survival, pup growth or clinical signs during lactation, in either generation

In this study no toxicologically significant adverse effects on sexual function or fertility were observed at doses of up to 1817 mg/kg/day, the highest dose tested.

In the preliminary study, groups of 6 male and female rats (Crl:CD BR strain) were fed diet containing 0, 100, 1000 or 5000 ppm ethametsulfuron-methyl (estimated to be equivalent to 0, 7.3, 71 and 365 mg/kg /day in males and 0, 9.5, 88 and, 453mg/kg /day in females). After 6 weeks, the animals were mated to produce a single litter to weaning. After weaning, the pups and parents were killed. A limited histopathological examination was conducted on the parental animals.

No toxicologically significant changes in food consumption, body weight, or body weight gain were observed at any dose level tested. No treatment-related changes were observed in the general toxicology investigations (clinical chemistry, haematology, gross and histopathology) at doses of up to 365-453 mg/kg/day.

In this study no toxicologically significant adverse effects on reproductive performance were observed at doses of up to 365-453 mg/kg/day, the highest dose tested.

The potential for ethametsulfuron-methyl to adversely affect sexual function and fertility has been investigated in a standard 2-generation study in rats, and in a preliminary 1-generation study, also conducted in rats. No treatment-related adverse effects on fertility were observed in the 2-generation study at doses of up to 1582-1817 mg/kg/day, the highest dose tested. Similarly, no adverse effects on fertility were observed in the sighting study, at doses of up to 365-453 mg/kg/day, the highest dose tested.

10.10.3 Comparison with the CLP criteria

No adverse effects on fertility have been observed, no classification is proposed for sexual function and fertility.

10.10.4 Adverse effects on development

Table 27: 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	Ethametsulfuron-methyl, 96.8%	**Dams** No mortalities were observed.	Anonymous (1991l)

<table>
<tr><th>Method, guideline, deviations if any, species, strain, sex, no/group</th><th>Test substance, dose levels duration of exposure</th><th>Results</th><th>Reference</th></tr>
<tr><td>Oral (gavage)
OECD 414 (1981)
Rat
Sprague-Dawley 25/group</td><td>0, 60, 250, 1,000 or 4000 mg/kg /day on days 7-16 of gestation
Vehicle: methylcellulose</td><td>Adjusted body weight gain was statistically significantly decreased at the top dose (by 22% compared to controls) from day 7- 22, and food consumption by 13% over the dosing period.
Foetuses
Foetal weights were comparable between test and control groups.
There were no treatment-related increases in skeletal or visceral malformations or variations.</td><td></td></tr>
<tr><td>Oral (gavage)
OECD 414 (1983)
Rabbit
New Zealand White (22/group)</td><td>Ethametsulfuron-methyl, 96.8%
0, 250, 1000 or 4000 mg/kg /day on days 7-19 of gestation
Vehicle: methylcellulose</td><td><u>Maternal toxicity</u>
Mortalities: 2, 0, 1, 8 at 0, 250, 1000 and 4000 mg/kg/day
Body weight gain: Unadjusted bwg statistically significantly↓ compared to controls on days 7-20 by 24%, 22% and 52% at 250, 1000 and 4,000 mg/kg/day respectively
No other toxicologically significant changes in body weight or food consumption were reported
Abortion: 1, 1, 3, 7 at 0, 250, 1000 and 4000 mg/kg/day
<u>Foetal loss:</u>
The numbers of resorptions was statistically significantly increased and the number of live foetuses statistically significantly decreased, compared to controls, at the top dose.
<table>
<tr><th></th><th>0 (mg/kg bw/day)</th><th>250(mg/kg bw/day)</th><th>1000(mg/kg bw/day)</th><th>4000(mg/kg bw/day)</th></tr>
<tr><td>Pregnant dams</td><td>17</td><td>18</td><td>20</td><td>19</td></tr>
<tr><td>Total resoptions</td><td>1</td><td>0</td><td>1</td><td>2</td></tr>
<tr><td>No. of litters</td><td>13</td><td>17</td><td>16</td><td>6</td></tr>
<tr><td>No. of live foetuses</td><td>8.5</td><td>7.5</td><td>6.5</td><td>5.3**</td></tr>
<tr><td>Early resporptions/ litter</td><td>0.3 (4.8%)</td><td>1.5 (16.2%)</td><td>1.2 (17.8%)</td><td>1.7 ** (18.2%)</td></tr>
<tr><td>Late resoroptions/ litter</td><td>0.3 (3%)</td><td>0.2 (2.5%)</td><td>0.1 (0.6%)</td><td>0.2 (3.3%)</td></tr>
<tr><td>Total resorptions/litter</td><td>0.6 (7.8%)</td><td>1.7 (18.6%)</td><td>1.3 (18.6%)</td><td>1.8** (21.6%)</td></tr>
</table>
** Significantly different (p≤0.025) from the control group by Mann-Whitney U Test
Rabbit Historical Control Data</td><td>Anonymous (1991m)</td></tr>
</table>

<table>
<tr><th>Method, guideline, deviations if any, species, strain, sex, no/group</th><th>Test substance, dose levels duration of exposure</th><th>Results</th><th>Reference</th></tr>
<tr><td></td><td></td><td>
<table>
<tr><th></th><th></th><th>Oct 1984-July 1988</th><th>Feb 1983-May 1992</th></tr>
<tr><td>Number of resorptions</td><td>Total</td><td>Mean 0.5
Range 0.1-0.8</td><td>Mean 0.5
range 0.1-1.1</td></tr>
<tr><td></td><td>Early</td><td>Mean 0.3
Range 0-0.5</td><td>Mean 0.3
Range 0-1.1</td></tr>
<tr><td>Percentage of resorptions</td><td>Total</td><td>Mean 6.5
Range 0.5-10.6</td><td>Mean 7.1
Range 0.5-13.7</td></tr>
<tr><td></td><td>Early</td><td>Mean 4.4
Range 0-10.6</td><td>Mean 5.4
Range 0-12.8</td></tr>
<tr><td>Live fetuses</td><td>Total</td><td>Mean 6.6
Range 4.0-8.5</td><td>Mean 7.0
Range 4.0-8.5</td></tr>
</table>
<u>Fetuses</u>

There were no fetal deaths and fetal weights were comparable between treated and controls.

There were no skeletal or visceral malformations observed.

The incidence of skeletal and visceral variations was comparable between treated and control groups.
</td><td></td></tr>
<tr><td>Oral (gavage)
Non Standard
Rabbit
New Zealand White (10/group)</td><td>Ethametsulfuron-methyl, 96.8%
0, 25, 100, 250, or 1000 mg/kg /day on days 7-28 of gestation
Vehicle: methylcellulose</td><td>
<u>Dams</u>

A single dam sacrificed in extremis on day 17 at the top dose of 1000 mg/kg/day

No other intercurrent deaths in any group

Food consumption, body weight, body weight gain and gravid uteri weights were comparable between treated and control groups

Foetal Loss
<table>
<tr><th></th><th>0 (mg/kg bw/day)</th><th>25(mg/kg bw/day)</th><th>100(mg/kg bw/day)</th><th>250(mg/kg bw/day)</th><th>1000(mg/kg bw/day)</th></tr>
<tr><td>Pregnant dams</td><td>8</td><td>10</td><td>10</td><td>9</td><td>9</td></tr>
<tr><td>Total resoptions</td><td>3.4</td><td>1.4</td><td>4.1</td><td>3.9</td><td>5.9</td></tr>
<tr><td>No. of litters</td><td>8</td><td>10</td><td>10</td><td>9</td><td>9</td></tr>
<tr><td>No. of live foetuses</td><td>8</td><td>10</td><td>9</td><td>9</td><td>9</td></tr>
<tr><td>Early resporptions/litter</td><td>2.3</td><td>1.5</td><td>1.2</td><td>3.9</td><td>1.6</td></tr>
<tr><td>Late resoroptions/litter</td><td>1.1</td><td>0</td><td>2.8</td><td>0</td><td>4.3</td></tr>
<tr><td>Total resorptions/litter</td><td>3.4</td><td>1.4</td><td>4.1</td><td>3.9</td><td>5.9</td></tr>
</table>
Foetuses
Foetal weights were comparable between test and control groups.
There were no treatment-related increases in visceral malformations or variations
</td><td>Anonymous (2018a)</td></tr>
</table>

Method, guideline, deviations if any, species, strain, sex, no/group	Test substance, dose levels duration of exposure	Results	Reference
		in any treatment group. Historical control for late resorptions; 0-5.51%, from 187 studies covering August 2006-August 2017, from the same test facility	

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

The developmental toxicity of ethametsulfuron-methyl has been well investigated in standard studies in rats and rabbits. It is noted that the dosing schedule used in these studies is shorter that that recommended in the current test guideline. However the dosing schedule used was compliant with the OECD TG in use at the time, and is not considered to have had a significant impact on the outcome of these studies. The top doses employed were 4000 mg/kg/day, which markedly exceed the currently acceptable limit of 1000 mg/kg/day. In addition, a very recent non standard rabbit developmental toxicity study has been conducted to further investigate post implantation loss in this species.

Rats

Dams (Sprague-Dawley rats (Crl:CDBR strain) 25/dose) were administered ethametsulfuron-methyl in methylcellulose via gavage, at doses of 0, 60, 250, 1000 and 4000 mg/kg/day on days 7-16 of gestation. Dams were sacrificed on day 22 of gestation and foetuses examined for skeletal and visceral variations and malformations.

There were no treatment-related mortalities at any dose level. Adjusted maternal body weight gain was statistically significantly decreased (compared to controls, by 15% on days 1-22 and by 22% on days 7-22) at 4000 mg/kg/day only. Food consumption was statistically significantly decreased by 13% compared to controls during the dosing period at 4000 mg/kg/day only. No toxicologically significant maternal body weight changes were observed.

There were no toxicologically significant fetal weight changes observed at doses of up to 4000 mg/kg/day. No skeletal or visceral malformations or visceral variations were observed at doses of up to 4000 mg/kg/day, the highest dose tested.

A limited number of minor skeletal variations and retardations were observed, such as retarded ossification of the skull bones, partial ossification of the sternebrae and calloused/wavy ribs. None of the observed changes were statistically significantly increased compared to controls, or exceeded the expected background incidence. Overall, based on this study, ethametsulfuron-methyl is not a developmental toxicant in rats at doses of up to 4000 mg/kg/day, the highest dose tested.

Rabbits

Dams (New Zealand White rabbits/22/dose) were administered ethametsulfuron-methyl in methylcellulose via gavage, at doses of 0, 250, 1000 and 4000mg/kg/day on days 7-19 of gestation. Dams were sacrificed on day 29 of gestation and foetuses examined for skeletal and visceral variations and malformations. The dose levels used were identified from a preliminary study, which is not available for evaluation.

Compared to controls, unadjusted maternal body weight gain was statistically significantly decreased in all treatment groups (by 24, 22 and 52% at 250, 1000 and 4000 mg/kg/day respectively). There were no other toxicologically significant changes in food consumption, body weight or body weight gain.

Treatment-related deaths were confined to the top dose, with 8/22 dams dying during the study. The cause of death appeared to be gastro-intestinal blockage caused by the viscous nature of the dosing material. A dose-related increase in abortions was observed at doses of 1000 mg/kg/day and above (3 and 7 at 1000 and 4000 mg/kg/day). It was noted that 4 of the high-dose dams aborting litters also had a gastro-intestinal blockage. It is unclear whether the abortions at 1000 mg/kg/day were associated with any gastro-intestinal blockage.

The number and percentage of total (0.6 (7.8%), 1.7 (18.6%), 1.3 (18.6%) and 1.8 (21.6%) at 0, 250, 1000 and 4000 mg/kg/day) and early resorptions per litter (0.3 (4.8%), 1.5 (16.2%), 1.2 (17.8%) and 1.7 (18.2%) at 0, 250, 1000 and 4000 mg/kg/day) were increased at all dose levels, with the difference being statistically significant at the high dose. With almost all of the resorptions being early. The number and percentage of resorptions also exceeded the historical control range at all test doses. The numbers of live fetuses observed was also decreased (8.5, 7.5, 6.5 and 5.3 at 0, 250, 1000 and 4000 mg/kg/day). However, the observed changes are within the historical control range, including the statistically significant decrease at the top dose. The decrease in live fetuses is considered to reflect the increase in resorptions, and is not regarded as a separate treatment-related effect.

Increased early/total resorptions and decreased live foetuses were observed at all dose levels, achieving statistical significance at the maternally lethal dose of 4000 mg/kg/day, well in excess of the current limit dose of 1000 mg/kg/day. Increased early resorptions are a relatively unusual event in rabbits, as evidenced by the low historical control rate of 1:100 to 1:1000. Therefore the early resorptions of around 1 fetus/litter observed at 250 and 1000 mg/kg/day, in the absence of severe maternal toxicity, raise a concern.

The number and percentage of early resorptions per litter (0.3 (4.8%), 1.5 (16.2%), 1.2 (17.8%) and 1.7 (18.2%) at 0, 250, 1000 and 4000 mg/kg/day) were increased at all dose levels, but only achieving statistical significance at the maternally lethal dose of 4000 mg.kg.day. In numerical terms, this represents an increase in early resorptions (for all treatment groups) from around 1 early resorption in every 3 litters in controls to around 1.5/litter in treated dams, around a 3-fold increase. Although this change only achieved statistical significance at the top dose, a 3-fold increase in early resorptions is of concern. Late resorptions were only marginally increased at the maternally toxic top dose.

In a follow-up study, dams (New Zealand White rabbits/10/dose) were administered ethametsulfuron-methyl in methylcellulose via gavage, at doses of 0,25, 100, 250 and 1000 mg/kg/day on days 7-28 of gestation. Dams were sacrificed on day 29 of gestation; investigations were confined to implantation,resorption, foetal weight and detailed external and visceral examination. Specific skeletal investigations were not conducted. Although the number of dams is small compared to a standard study, numbers are considered sufficient to detect decreases in pre-implantation loss.

A single, high dose, dam was sacrificed on GD 17 due to severe stress following a gavage error. There were no more mortalities in any group. Food consumption, body weight, body weight gain and gravid uterine weights were comparable between treated and control groups. There were no adverse effects observed on early resorptions, pre/post implantation loss, corpora lutea, viable foetuses and sex ratio. A slight increase in late resorptions was obsereved at the top dose (4.3% per litter, compared to 0.4% in concurrent controls). Individual animal data indicates that this change was largely due to a single high dose dam with 3 late resorptions. The historical control incidence for late resorprions in the same test facility is 0-5.5%. Taking into consideration the absence of a dose-response and information on concurrent background incidence, the slight increase in late resorption is considered to be natural biological variation, not treatment-related. There were no visceral malformations or variations. Overall, on the basis of this study, ethametsulfuron-methyl is not a developmental toxicant.

10.10.6 Comparison with the CLP criteria

There are no human data available to inform on the potential of ethametsulfuron-methyl to cause developmental toxicity. Therefore classification in category 1A can be excluded.

Ethametsulfuron-methyl did not induce any structural or visceral malformations/variations in standard studies conducted in rats or rabbits. The absence of malformations or other severe treatment-related fetal changes in experimental animals suggests that classification in 1B can also be excluded.

Ethametsulfuron-methyl induced a small increase in early resorptions in the absence of marked maternal toxicity at doses of up to 1000 mg/kg/day in a standard rabbit developmental toxicity study. Similar changes were not observed in rats. In a second rabbit developmental toxicity study, specifically conducted to investigate pre/post implantation loss, the incidence of early resorptions was comparable between treated and control groups up to 1000 mg/kg/day, the highest dose tested. There were no other treatment-related effects on late resorptions, or visceral malformations/variations. The failure to confirm the increase in early resorptions in a second study in the same strain of rabbit, even at the limit dose of 1000 mg/kg/day reduces concern that the late resorptions observed in the first rabbit study are treatment-related.

Overall, it can be concluded that ethametsulfuron-methyl is not a developmental toxicant. No classification is proposed.

10.10.7 Adverse effects on or via lactation

No specific studies were conducted to investigate effects on or via lactation.

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

No adverse effects on pups (inlcuding mortality, bodyweight or bodyweight gain) were observed in a standard 2-generation reproductive toxicity study.

10.10.9 Comparison with the CLP criteria

There were no specific studies conducted to investigate effects on or via lactation. However, no adverse effects on pups (inlcuding mortality, bodyweight or bodyweight gain) were observed in a standard 2-generation reproductive toxicity study during lactation. Therefore, there are no concerns that ethametsulfuron-methyl can cause adverse effects on or via lactation. No classification is proposed.

10.10.10 Conclusion on classification and labelling for reproductive toxicity

Not classified – conclusive but not sufficient for classification

RAC evaluation of reproductive toxicity

Summary of the Dossier Submitter's proposal

The DS proposed no classification for sexual function and fertility on the basis of one one-generation reproductive toxicity preliminary study and one two-generation study (both in rats) showing no adverse effects on fertility and sexual function.

DS proposed no classification for developmental toxicity because the small increase in early resorptions in absence of marked maternal toxicity detected in one rabbit study could be confirmed neither in a second study even at the limit dose of 1000 mg/kg bw/day a nor in

rats at 4000 mg/kg bw/day.

Comments received during public consultation

Two member state competent authorities and one company-manufacturer supported the no classification of ethametsulfuron-methyl for both fertility and sexual function and development.

Three member state competent authorities raised issues about the potential of ethametsulfuron-methyl as developmental toxicant and suggested classification within category 2 because, in addition to the issues discussed in the CLH report, they also noted that:

- heart and heart vessels malformations were seen in two foetuses in two different litters at a dose level of 250 mg/kg bw/day;
- no meaningful evaluation of resorption rate or malformations was feasible in the highest dose group receiving 4000 mg/kg bw/day;
- EFSA also proposed classification Repr 2;
- the follow up study dated on 2018 was not guideline-compliant because only a small number of animals were used and a rate of resorptions rather high (in particular when compared to the previous study) in nearly all groups including the concurrent control.

On these issues, the DS replied that:

- the cardiovascular changes should be considered chance findings and should not be used to support classification for developmental toxicity because the reported effects (cardiac and great vessel malformations) were observed in 2 foetuses from two separate litters at the lowest dose of 250 mg/kg/day only in the 1991 study and not in other treatment groups or in the follow up study dated on 2018 in rabbits or in the rat study at 4000 mg/kg bw/day;
- the follow up study was separated from the first one by 17-years and it might justify the differences in the resorption rates in the controls;
- the follow up study provides a robust HCD and the increase in late resorptions was within this HCD;
- although the supplementary study is limited, compared to the statistical power of a standard guideline developmental toxicity study, the DS considered it provides reliable and relevant information on the potential of ethametsulfuron-methyl to increase the early resorption rate in rabbits.

Overall, taking a weight of evidence approach, in the DS's view the results of the second study reduce concern that the findings are treatment related.

Assessment and comparison with the classification criteria

Tables 10 and 11 summarise the main findings reported in the CLH report on sexual function and fertility and developmental toxicity with ethametsulfuron-methyl, respectively.

Table 10: *Summary table for animal studies on adverse effects on sexual function and fertility with ethametsulfuron-methyl*

Method	Results	Reference
One-generation reproductive toxicity preliminary study Oral (diet) Sprague-Dawley rats 6/sex/dose Ethametsulfuron-methyl (purity 96.8%) 0, 100, 1000 and 5000 ppm estimated males: 7.3, 71 and 365 mg/kg bw/day females: 0, 9.5, 88 and, 453 mg/kg bw /day	<u>Parental toxicity</u> No toxicologically significant changes were observed <u>Reproductive effects</u> No adverse effects on fertility were observed <u>Offspring effects</u> No toxicologically significant changes were observed	Anonymous (1991k)
Two-generation study OECD 416 Oral (diet) Sprague-Dawley rats 23/sex/dose Ethametsulfuron-methyl (purity 96.8%) 0, 250, 5000 and 20000 ppm equivalent Males F0: 0, 20, 395 and 1582 mg/kg bw/day Females F0: 0, 19, 449 and 1817 mg/kg bw/day Males F1: 22, 439, and 1756 mg/kg bw/day Females F1: 18, 448, and 1869 mg/kg bw/day	<u>Parental toxicity</u> No adverse effects on body weight, body weight gain and food consumption in females. Body weight gain was decreased in males, by around 10% compared to controls in both parental generations. <u>20000 ppm</u> F0: ↑ relative (13%) testis weight. F1a: ↑ relative (21%) testis weight <u>5000 and 250 ppm</u> No toxicologically significant changes <u>Reproductive effects</u> No toxicologically significant adverse effects on reproduction were observed <u>Offspring effects</u> The only adverse effect observed was a 16% increase in absolute and relative spleen weights in top dose F2b pups.	Anonymous (1991j)

Table 11: *Summary table for animal studies on developmental toxicity with ethametsulfuron-methyl*

Method	Results	Reference
OECD 414 Oral (gavage) Sprague-Dawley rats	<u>Dams</u> No mortalities were observed <u>Adjusted body weight gain was statistically significantly</u>	Anonymous (1991l)

25/group

Ethametsulfuron-methyl (purity 96.8%)

0, 60, 250, 1,000 or 4000 mg/kg bw /day on days 7-16 of gestation

Vehicle: methylcellulose

decreased at the top dose (by 22% compared to controls) from day 7- 22, and food consumption by 13% over the dosing period

<u>Foetuses</u>

Foetal weights were comparable between test and control groups

There were no treatment-related increases in skeletal or visceral malformations or variations

OECD 414

Oral (gavage)

New Zealand White rabbits

22/group

Ethametsulfuron-methyl (purity 96.8%)

0, 250, 1000 or 4000 mg/kg bw/day on days 7-19 of gestation

Vehicle: methylcellulose

<u>Maternal toxicity</u>

Mortalities: 2, 0, 1 and 8 at 0, 250, 1000 and 4000 mg/kg bw/day

Body weight gain: Unadjusted body weight gain statistically significantly ↓ compared to controls on days 7-20 by 24%, 22% and 52% at 250, 1000 and 4,000 mg/kg bw/day respectively

No other toxicologically significant changes in body weight or food consumption were reported

<u>Abortion</u>

1, 1, 3, 7 at 0, 250, 1000 and 4000 mg/kg bw/day

<u>Foetal loss</u>

	mg/kg bw/day			
	0	**250**	**1000**	**4000**
Pregnant dams	17	18	20	19
Total resorptions	1	0	1	2
No. of litters	13	17	16	6
No. of live foetuses	8.5	7.5	6.5	5.3**
Early resorptions/litter	0.3 (4.8%)	1.5 (16.2%)	1.2 (17.8%)	1.7** (18.2%)
Late resorptions/litter	0.3 (3%)	0.2 (2.5%)	0.1 (0.6%)	0.2 (3.3%)
Total resorptions/litter	0.6 (7.8%)	1.7 (18.6%)	1.3 (18.6%)	1.8** (21.6%)
** Significantly different ($p<0.025$) from the control group by Mann-Whitney U Test				

Rabbit Historical Control Data		
Number of resorptions	Total	Mean: 0.5 Range: 0.1-0.8
	Early	Mean: 0.3 Range: 0-0.5
Percentage of resorptions	Total	Mean: 6.5 Range: 0.5-10.6
	Early	Mean: 4.4 Range: 0-10.6
Live foetuses	Total	Mean: 6.6 Range: 4.0-8.5

Anonymous (1991m)

Foetuses

There were no foetal deaths and foetal weights were comparable between treated and controls.

There were no skeletal or visceral malformations observed.

The incidence of skeletal and visceral variations was comparable between treated and control groups.

Non-standard developmental toxicity study

Oral (gavage)

New Zealand White rabbits

10/group

Ethametsulfuron-methyl (purity: 96.8%)

0, 25, 100, 250, or 1000 mg/kg bw/day on days 7-28 of gestation

Vehicle: methylcellulose

Anonymous (2018a)

Dams

A single dam sacrificed in extremis on day 17 at the top dose of 1000 mg/kg bw/day. No other deaths in any group

Food consumption, body weight, body weight gain and gravid uteri weights were comparable between treated and control groups

Foetal Loss

	mg/kg bw/day				
	0	**25**	**100**	**250**	**1000**
Pregnant dams	8	10	10	9	9
Total resorptions	3.4	1.4	4.1	3.9	5.9
No. of litters	8	10	10	9	9
No. of live foetuses	8	10	9	9	9
% Early resorptions/litter	2.3	1.5	1.2	3.9	1.6
% Late resorptions/litter	1.1	0	2.8	0	4.3
% Total resorptions/litter	3.4	1.45	4.1	3.9	5.9
Historical control for late resorptions: 0-5.51%, from 187 studies covering August 2006-August 2017, from the same test facility					

Foetuses

Foetal weights comparable between test and control groups

No treatment-related increases in visceral malformations or variations in any treatment group

Comparison with the criteria

RAC notes that a preliminary one-generation study and a 2-generation study on reproductive toxicity showed no effects on fertility and sexual performance of rats at doses up to 1582 mg ethametsulfuron-methyl/kg bw/day causing reduction in male parental body weight gain by around 10% (Table 10). Therefore, no adverse effects were observed and the no classification is warranted.

Thirty six percent of maternal mortality was reported in the main developmental toxicity study with rabbits dosed with 4000 mg/kg bw/day (Table 11). Therefore, the developmental effects at that dose level cannot be considered by RAC for supporting a potential classification.

The number of early and total resorptions/litter at doses of 250 and 1000 mg/kg bw/day were higher than 1 and, although not statistically different from control, both records were clearly higher than the figures reported in the HCD; which increases the concern. Nevertheless, RAC notes that the HCD provided in the CLH report and DAR do not contain information in the usual range of ±5 years of the study's date, which reduces the reliability if this HCD.

Two member state competent authorities raised during the public consultation a potential issue with heart and heart vessel malformations reported in rabbits. This issue was not included in the CLH-report but could be assessed by RAC through DAR of the substance. RAC supports the DS considerations about the lack of robustness of these effects for warranting a classification considering that: i) the only malformations were cardiac and great vessel malformations, observed in 2 foetuses from two separate litters at the lowest dose of 250 ppm, but not at 5000 ppm in absence of maternal toxicity in the 1991 study; ii) no variations anticipating the cardiac malformations were reported; and, iii) no cardiac or great vessel malformations were observed in the supplemental study dated in 2018 at 1000 mg/kg bw/day.

A second developmental toxicity study in rabbits no effects on early resorptions, pre/post implantation loss, corpora lutea, viable foetuses and sex ratio were noted with doses up to 1000 mg/kg bw/day.

In summary, RAC do not consider relevant for classification purposes the effects on live foetuses or early and total resorption in rabbits because these effects:

- were found at doses causing maternal mortality clearly above 10%;
- do not observe dose-response;
- could not be reproduced in a second study in rabbits at a limit dose of 1000 mg/kg bw/day.

There were no specific studies conducted to investigate effects via lactation. However, no adverse effects on pups (including mortality, bodyweight or bodyweight gain) were observed in a standard 2-generation reproductive toxicity study during lactation. Therefore, there are no concerns that ethametsulfuron-methyl can cause adverse effects on or via lactation.

Overall, RAC, concurs with DS and proposes the **no classification of ethametsulfuron-methyl for reproductive toxicity and lactation.**

10.11 Specific target organ toxicity-single exposure

Refer to sections 10.1-10.3 for a summary of the relevant data. No other relevant studies are available.

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

No deaths, clinical signs of toxicity, or other findings of specific target organ toxicity were noted in any of the acute toxicity studies for any relevant route of exposure. Refer to sections 10.1, 10.2, and 10.3.

10.11.2 Comparison with the CLP criteria

Substances that have produced significant toxicity in humans or that, on the basis of evidence from studies in experimental animals, can be presumed to have the potential to produce significant toxicity in humans following single exposure are classified in STOT-SE 1 or 2. Classification is supported by evidence associating single exposure to the substance with a consistent and identifiable toxic effect.

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

Since there was no clear evidence of specific toxic effects on a target organ or tissue, no signs of respiratory tract irritation or narcotic effects, no classification for specific target organ toxicity (single exposure) is proposed.

10.11.3 Conclusion on classification and labelling for STOT SE

Not classified – conclusive but not sufficient for classification.

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

Summary of the Dossier Submitter's proposal

The DS proposed no classification of the substance for STOT SE since no death, clinical signs of toxicity, or other findings of specific organ toxicity were noted in any of the acute toxicity studies for any relevant route of exposure.

Comments received during public consultation

One company-manufacturer supported the no classification of ethametsulfuron-methyl for STOT SE.

Assessment and comparison with the classification criteria

RAC notes absence of effect from studies in experimental animals after a single exposure and therefore, the classification of the substance as STOT SE categories 1 or 2 is not warranted. RAC also notes in such studies the absence of narcotic effects or respiratory

tract irritation and therefore, classification as STOT SE category 3 is not supported. In conclusion, RAC supports the DS's proposal for **no classification of ethametsulfuron-methyl for specific target organ toxicity (single exposure).**

10.12 Specific target organ toxicity-repeated exposure

Table 28: 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**
14day study Rat (Sprague-Dawley (Crl:CDBR strain, 6m/dose) Gavage in corn oil	Ethametsulfuron-methyl, 96.4% 0 or 2200 mg/kg/day	There were no deaths or treatment-related clinical signs of toxicity observed in any dose group. **Kidney** Kidney weights were reported to have been increased Intracytoplasmic protein droplets in epithelial cells and occasional necrotic epithelial cells observed in proximal tubules 2/6. No other adverse effects were observed.	Anonymous (1986b)
28-day study Rat (Sprague-Dawleystrain, 6 sex /dose) Gavage in methyl cellulose	Ethametsulfuron-methyl, >98 % 0, 100, 300 and 1000 mg/kg/day	There were no deaths or treatment-related clinical signs of toxicity observed in any dose group. No adverse effects were reported at any dose level	Anonymous (1987h)
90-day study OECD TG 408 Rat (Sprague-Dawley (Crl:CDBR strain, 10/sex/dose)	Ethametsulfuron-methyl, 96% Dietary concentration: 0, 100, 1000 and 5000 ppm Achieved intake: Males;0, 7.3, 71, and 365 mg/kg/day Females;0, 9.1, 85 and 453 mg/kg/day Guidance value e.g., 100 mg/kg bw/day	There were no toxicologically significant changes observed at any dose level.	Anonymous (1991k)

2-year study OECD TG 453 Rat (Sprague-Dawley (Crl:CDBR strain, 72/sex/dose)	Ethametsulfuron-methyl, 96.8% Dosed for 24 months, via the diet Interim sacrifice 10/sex/dose after 12-months Dietary concentration: 0, 50, 500 and 5000 ppm Achieved intake: Males; 0, 2.1, 21, and 210 mg/kg/day Females; 0, 2.6, 26 and 267 mg/kg/day Guidance value 12 mg/kg/day	There were no differences between treated animals and controls in mortality rates, food consumption, body weight or body weight gain at any dose level. **<u>Non-neoplastic changes</u>** No toxicologically significant changes in, hematology, clinical chemistry, urinalysis or organ weights. **Histopathology** Mammary gland: female only Dilation of ducts with chronic inflammation Interim sacrifice: 0/12, 1/2, 1/3 and 3/10 at 0, 50, 500 and 5000 ppm Terminal sacrifice: 0/60, 2/48, 2/47 and 7/62* at 0, 50, 500 and 5000 ppm Combined incidence: 0/72, 3/50, 3/60 and 10/72 at 0, 50, 500 and 5000 ppm Lung: Acute/sub-acute inflammation Males: 4/56, 11/61, 6/61 and 16/61* at 0, 50, 500 and 5000 ppm Bone marrow erythroid hyperplasia Males 0/56, 0/32, 1/38 and 8/60* at 0, 50, 500 and 5000 ppm Naso-lachrymal duct, chronic-active inflammation: Males 5/56, 4/31, 5/38 and 10/60* at 0, 50, 500 and 5000 ppm Pituitary cyst Females 0/60, 1/53, 2/59 and 6/62* at 0, 50, 500 and 5000 ppm Ovarian atrophy Females 53/60, 44/46, 34/35 and 61/61* at 0, 50, 500 and 5000 ppm	Anonymous (1991h)
90-day study OECD TG 408 Mice (CD-1 (Crl:CDBR strain, 10 sex/dose)	Ethametsulfuron-methyl, 96% Dietary concentration: 0,50, 500, 2500 and 5000 ppm Achieved intake: Males; 0, 7, 73, 346, and 686 mg/kg/day Females; 0 9.8, 63, 491 and 916 mg/kg/day Guidance Value 100 mg/kg/day	There were no toxicologically significant changes observed at any dose level; including food consumption, body weights, haematology, clinical chemistry, gross or histopathology.	Anonymous (1991n)

Lifetime study OECD TG 453 Mouse (CD-1 strain) (80/sex/dose) Interim sacrifice (12 months): 10/sex/group	Ethametsulfuron-methyl, 96% Dosed for 18 months at 0, 25, 500 and 5000 ppm Achieved intake: Males; 0, 3.5, 68, and 765 mg/kg/day Females; 0 4.6, 95 and 930 mg/kg/day Guidance value 16.6 mg/kg/day	There were no differences between treated animals and controls in mortality rates, food consumption, body weight or body weight gain at any dose level. **Non Neoplastic changes** There were no differences between treated animals and controls in mortality rates, food consumption, body weight or body weight gain at any dose level. **Clinical Chemistry** No toxicologically significant changes in clinical chemistry, hematology or urinalysis were observed **Organ weights** Spleen Males: absolute weight; ↑ by 25, 41 and 39% at 0, 25, 500 and 5000 ppm relative weight , ↑ by 26, 46 and 44% at 0, 25, 500 and 5000 ppm **Histopathology** (terminal sacrifice) Mesenteric lymph node angiectasis: Males; 0/76, 1/43, 3/46 and 10/74* at 0, 25, 500 and 5000 ppm Kidney periarteritis Males; 1/80, 3/80, 1/80 and 7/80* at 0, 25, 500 and 5000 ppm Epididymides; unilateral oligospermia 1/80, 1/37, 2/49 and 10/74* at 0, 25, 500 and 5000 ppm Prostate: prostitis/ coagulating gland- atrophy/fibrosis/adenitis 0/80, 2/41, 1/50 and 5/80* at 0, 25, 500 and 5000 ppm Mandibular lymph node, lymphoid hyperplasia: Females; 6/77, 5/22, 2/24, and 14/74* at 0, 25, 500 and 5000 ppm Mandibular lymph node,plasmacytosis: Females; 8/77, 6/22, 4/24, and 16/74* at 0, 25, 500 and 5000 ppm Urinary bladder; lymphocytic infiltrate submucosal hyperplasia Females; 21/77, 8/19, 3/21, and 34/79* at 0, 25, 500 and 5000 ppm Exorbital lachrymal glands; lymphocytic infiltrate hyperplasia Females; 30/77, 9/20, 6/20, and 50/79* at 0, 25, 500 and 5000 ppm	Anonymous (1991i)
90-days week oral diet. Broadly consistent with OECD TG 409 Beagle dogs 4/sex/dose	Ethametsulfuron-methyl, 95.6% Doses of 0, 100, 3500 and 10000 ppm equivalent to 0, 3.6, 136 and 390 mg/kg bw/day; and 0, 3.9, 139 and 382 mg/kg bw/day in males and females respectively Guidance value 100 mg/kg/day	No toxicologically significant changes were reported in any haematology, clinical chemistry, gross and histopathological investigation conducted as part of this study.	Anonymous (1991o)

1-year oral diet. Broadly consistent with OECD TG Beagle dogs 6/sex/dose	Ethametsulfuron-methyl, 95.6% Doses of , 0, 250, 3000, or 15000 ppm, equivalent to0, 7.6, 87 and 478 mg/kg bw/day and 0, 6.9, 87 and 483 mg/kg bw/day in males and females respectively Guidance value 24 mg/kg/day	There were no deaths or treatment-related clinical signs of toxicity observed at any dose level. **<u>478-483 mg/kg/day</u>** ***Males :*** 33% ↓ body weight gain Liver weight statistically significantly increased (absolute 11%, relative 25%) Testis weigh statistically significantly increased (absolute 10%, relative 25%) **Females** Thyroid and parathyroid statistically significant decrease in absolute and relative weights (by around 20%) **<u>87 mg/kg/day</u>** **<u>Females</u>** Thyroid and parathyroid statistically significant decrease in relative weight only (by 19%) No other treatment-related changes were observed at any dose level	Anonymous (1991p)

± Values are reported as increased (↑) or decreased (↓) compared to controls

* Denotes statistical significance

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

Rats

In a briefly reported 28-day study, groups of rats (Sprague Dawley 6 sex/dose) were administered ethametsulfuron-methyl via gavage at concentrations of 0, 100, 300 and 1000 mg/kg/day. There were no deaths, treatment-related clinical signs of toxicity, or other toxicologically significant changes reported at doses up to 1000 mg/kg/day, well in excess of the classification guidance value for STOT RE 2 of 300 mg/kg/day.

In a 90-day study groups of rats (Alderley Park Wistar derived 20 sex/dose) were administered ethametsulfuron-methyl in the diet at concentrations of 0, 100, 1000 and 5000 ppm (equivalent to 0, 7.3, 71, and 365 and 0, 9.1, 85 and 453 mg/kg day for males and females respectively). There were no deaths, treatment-related clinical signs of toxicity, or other toxicologically significant changes observed at doses 365/453 mg/kg/day, well in excess of the classification guidance value for STOT RE 2 of 100 mg/kg/day.

In a lifetime study; groups of rats, (Sprague-Dawley strain 12 interim +50/main study - sex/dose) were administered ethametsulfuron-methyl in the diet for 2-years at concentrations of 0, 100, 1000 and 5000 ppm (equivalent to mg/kg day 0, 2.1, 21, and 210 and 0, 2.6, 26 and 267 mg/kg/day for males and females respectively). There were no deaths or treatment-related clinical signs of toxicity. No toxicologically significant changes were observed below the classification guidance value.

However, at the highest dose tested (210/267 mg/kg/day in males/females), increased incidences of chronic inflammation of the mammary gland, pituitary cysts, and ovarian atrophy were observed in females, and acute/sub-acute lung inflammation, bone marrow erythroid hyperplasia and chronic-active inflammation of the nasal lachrymal duct in males. These changes occurred at dose levels well in excess of the classification guidance value for STOT RE 2 of 12 mg/kg/day.

Mice

In a 90-day study groups of mice (CD-1 strain 20 sex/dose) were administered ethametsulfuron-methyl in the diet at concentrations of 0, 50, 500, 2500 and 5000 ppm (equivalent to 0, 7, 73, 346, and 686 and 0 9.8, 63,

491 and 916 mg/kg day for males and females respectively) via the diet. There were no deaths, treatment-related clinical signs of toxicity, or other toxicologically significant changes observed at doses of 365/453 mg/kg/day, well in excess of the classification guidance value for STOT RE 2 of 100 mg/kg/day.

In a lifetime study; CD-1 strain mice were administered ethametsulfuron-methyl at concentrations of 0, 25, 500, and 5000 ppm (equivalent to 0, 3.5, 68 and 705 and 0, 4.6, 95 and 930 mg/kg day for males and females respectively) via the diet for 104 weeks. Absolute (by 25, 41 and 39% at 0, 25, 500 and 5000 ppm) and relative spleen (by 26, 46 and 44% at 0, 25, 500 and 5000 ppm) weights were increased in males. However, without evidence of related findings such as relevant histopathological changes, elevated spleen weights alone are not considered sufficient to support classification.

At the highest dose (686/916 mg/kg/day in males/females), kidney periarteritis mesenteric lymph node angiectasis, epididymal oligospermia prostatitis/coagualating gland atrophy/fibrosis were observed in males, and mandibular lymph node hyperplasia/plasmacytosis, urinary bladder lymphocytic infiltration/hyperplasia and lymphocytic infiltration of the exorbital lachyrymal gland. These changes occurred at dose levels well in excess of the classification guidance value for STOT RE 2 of 16.7 mg/kg/day.

Dogs

Beagle dogs (4 sex/ dose) were administered ethametsulfuron-methyl at doses of 0, 100, 3500 and 10000 ppm equivalent to 0, 3.6, 136 and 390 mg/kg bw/day and 0, 3.9, 139 and 382 mg/kg bw/day in males and females respectively for 90-days. The age of the dogs on commencement of the study was 20-23 weeks. The range of in-life and study termination investigations was comparable with those expected for a standard OECD TG 409 study.

Isolated instances of decreases in body weight gain were noted in top dose animals, but these are not regarded as toxicologically significant. The terminal body weight of high dose males was found to be statistically significantly decreased, by 6% only.

No treatment-related effects were noted in any parameter investigated in this study.

Beagle dogs (6 sex/ dose) were administered ethametsulfuron-methyl at doses of 0, 250, 3000, or 15000 ppm, equivalent to 0, 7.6, 87 and 478 mg/kg bw/day and 0, 6.9, 87 and 483 mg/kg bw/day in males and females respectively diet for1-year. The age of the dogs on commencement of the study was 20-23 weeks. The range of in-life and study termination investigations was comparable with those expected for a standard OECD TG 409 study.

With the exception of some organ weight changes (liver and testes in males and thyroid/parathyroid in females) without histopathological correlates, no other treatment-related changes were observed in this study.

Summary

The repeated dose toxicity of ethametsulfuron-methyl has been well investigated in standard 90-day and lifetime dietary studies in rats and mice, and in 90-day and 1 year studies in dogs.

Ethametsulfuron-methyl appears to be without significant repeated dose toxicity when administered for 90-days to rats (up to 210/267 mg/kg/day in males and females respectively), mice (up to 365/453 mg/kg/day in males and females respectively) and dogs (up to 390/382 mg/kg/day in males and females respectively). Ethametsulfuron-methyl was similarly non-toxic in a 1-year dog study (478/473 mg/kg/day in males and females respectively).

In the lifetime studies, the only treatment-related change observed at or below the repeated dose classification guidance value was a statistically significant increase in absolute and relative spleen weights in male mice at a dose of 3.5 mg/kg/day and above. There were no supporting histopathological changes, or clinical chemistry/haematology findings to suggest the spleen function was perturbed.

In the rat lifetime study, at the highest dose tested (210/267 mg/kg/day in males/females), increased incidences of chronic inflammation of the mammary gland, pituitary cysts, and ovarian atrophy were

observed in females, and acute/sub-acute lung inflammation, bone marrow erythroid hyperplasia and chronic-active inflammation of the nasal lachrymal duct in males.

In contrast, in the mouse (686/916 mg/kg/day in males/females), kidney periarteritis mesenteric lymph node angiectasis, epididymal oligospermia prostatitis/coagualating gland atrophy/fibrosis were observed in males, and mandibular lymph node hyperplasia/plasmacytosis, urinary bladder lymphocytic infiltration/hyperplasia and lymphocytic infiltration of the exorbital lachyrymal gland.

Overall, the oral repeated dose toxicity of ethametsulfuron-methyl has been well investigated and it appears to be without significant toxicity. No studies are available via the inhalation and dermal routes of exposure.

10.12.2 Comparison with the CLP criteria

The only treatment-related change observed at or below any repeated dose classification guidance value was a statistically significant increase in absolute and relative spleen weights in male mice at a dose of 3.5 mg/kg/day and above in a lifetime oral dosing study. There were no supporting histopathological changes, or clinical chemistry/haematology findings to suggest the spleen function was perturbed. Therefore, although dose-related, the lack of evidence of perturbed spleen function in mice, and absence of similar changes in standard studies in rats or dogs reduces the overall level of concern. No classification for STOT-RE is proposed.

10.12.3 Conclusion on classification and labelling for STOT RE

Not classified – conclusive but not sufficient for classification.

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

Summary of the Dossier Submitter's proposal

The DS proposed no classification of ethametsulfuron-methyl because the repeated dose toxicity of the substance has been well investigated in standard tests of 90-days, 1 and 2-years in rats, mice and dogs. It was found that the only treatment-related change observed at or below doses warranting classification was an increase in absolute and relative spleen weights in mice (but not in rats or dogs) without evidences of malfunctioning of the organ; which was not considered enough for supporting a classification.

Comments received during public consultation

One member state competent authority and one company-manufacturer supported the no classification of ethametsulfuron-methyl for STOT RE.

Assessment and comparison with the classification criteria

Table 7 summarises the main findings reported in the CLH report on repeated dose toxicity studies.

Table 7: *Summary table for repeated dose toxicity studies in animals with ethametsulfuron-methyl*

Method	Results	Reference
14 day study Sprague-Dawley rats (Crl:CDBR strain) 6 male/dose Gavage in corn oil Ethametsulfuron-methyl (purity 96.4%) 0 or 2200 mg/kg bw/day Limit dose for warranting classification: 600 mg/kg bw/day	No deaths or treatment-related clinical signs of toxicity observed in any dose group. Kidney weights were reported to have been increased Intracytoplasmic protein droplets in epithelial cells and occasional necrotic epithelial cells observed in proximal tubules 2/6.	Anonymous (1986b)
28-day study Rat (Sprague-Dawley) 6 sex /dose Gavage in methyl cellulose Ethametsulfuron-methyl (purity >98 %) 0, 100, 300 and 1000 mg/kg bw/day Limit dose for warranting classification: 300 mg/kg bw/day	No deaths or treatment-related clinical signs of toxicity observed in any dose group. No adverse effects were reported at any dose level	Anonymous (1987h)
90-day study OECD TG 408 Sprague-Dawley rats (Crl:CDBR) 10/sex/dose Ethametsulfuron-methyl (purity 96%) Dietary concentration: 0, 100, 1000 and 5000 ppm Males: 0, 7.3, 71, and 365 mg/kg bw/day	No toxicologically significant changes observed at any dose level	Anonymous (1991k)

Females: 0, 9.1, 85 and 453 mg/kg bw/day Limit dose for warranting classification: 100 mg/kg bw/day		
2-year study OECD TG 453 Sprague-Dawley rats (Crl:CDBR) 72/sex/dose Ethametsulfuron-methyl (purity 96.8%) Dosed for 24 months, via the diet Interim sacrifice 10/sex/dose after 12-months Dietary concentration: 0, 50, 500 and 5000 ppm Males: 0, 2.1, 21, and 210 mg/kg bw/day Females: 0, 2.6, 26 and 267 mg/kg bw/day Limit dose for warranting classification: 12 mg/kg bw/day	There were no differences between treated animals and controls in mortality rates, food consumption, body weight or body weight gain at any dose level. No toxicologically significant changes in haematology, clinical chemistry, urinalysis or organ weights. Combined incidence (interim + terminal) in dilation of mammary gland ducts with chronic inflammation: 0/72, 3/50, 3/60 and 10/72 at 0, 50, 500 and 5000 ppm. "The incidence (7/62) was statistically significant only at terminal sacrifice of animals dosed with 5000 ppm" Acute/sub-acute inflammation in male lung: 4/56, 11/61, 6/61 and 16/61(statistically significant) at 0, 50, 500 and 5000 ppm Bone marrow erythroid hyperplasia in males: 0/56, 0/32, 1/38 and 8/60 (statistically significant) at 0, 50, 500 and 5000 ppm Chronic-active inflammation in males naso-lachrymal duct: 5/56, 4/31, 5/38 and 10/60 (statistically significant) at 0, 50, 500 and 5000 ppm Pituitary cyst in females: 0/60, 1/53, 2/59 and 6/62 (statistically significant) at 0, 50, 500 and 5000 ppm Ovarian atrophy: 53/60, 44/46, 34/35 and 61/61 (statistically significant) at 0, 50, 500 and 5000 ppm	Anonymous (1991h)
90-day study OECD TG 408 CD-1 mice (Crl:CDBR) 10 sex/dose Ethametsulfuron-methyl (purity 96%) Dietary concentration: 0,50, 500, 2500 and 5000 ppm Males; 0, 7, 73, 346, and 686 mg/kg bw/day Females; 0 9.8, 63, 491 and 916 mg/kg bw/day	No toxicologically significant changes observed at any dose level; including food consumption, body weights, haematology, clinical chemistry, gross or histopathology.	Anonymous (1991n)

Limit dose for warranting classification: 100 mg/kg bw/day		
1.5-year study OECD TG 453 Mouse (CD-1 strain) 80/sex/dose Interim sacrifice (12 months): 10/sex/group Ethametsulfuron-methyl (purity 96%) Dosed for 18 months at 0, 25, 500 and 5000 ppm Males; 0, 3.5, 68, and 765 mg/kg bw/day Females; 0 4.6, 95 and 930 mg/kg bw/day Limit dose for warranting classification: 16.6 mg/kg bw/day	No differences between treated animals and controls in mortality rates, food consumption, body weight or body weight gain at any dose level. No toxicologically significant changes in clinical chemistry, haematology or urinalysis Absolute spleen weight in males: ↑ by 25, 41 and 39% at 25, 500 and 5000 ppm Relative spleen weight in males: ↑ by 26, 46 and 44% at 25, 500 and 5000 ppm Mesenteric lymph node angiectasis (males): 0/76, 1/43, 3/46 and 10/74 (statistically significant) at 0, 25, 500 and 5000 ppm Kidney periarteritis in males: 1/80, 3/80, 1/80 and 7/80 (statistically significant) at 0, 25, 500 and 5000 ppm Unilateral oligospermia in epididymides: 1/80, 1/37, 2/49 and 10/74 (statistically significant) at 0, 25, 500 and 5000 ppm Prostitis/coagulating gland- atrophy/fibrosis/adenitis: 0/80, 2/41, 1/50 and 5/80 (statistically significant) at 0, 25, 500 and 5000 ppm Mandibular lymphoid hyperplasia in females: 6/77, 5/22, 2/24, and 14/74 (statistically significant) at 0, 25, 500 and 5000 ppm Mandibular plasmacytosis in females: 8/77, 6/22, 4/24, and 16/74 (statistically significant) at 0, 25, 500 and 5000 ppm Lymphocytic infiltrate submucosal hyperplasia in female urinary bladder: 21/77, 8/19, 3/21, and 34/79 (statistically significant) at 0, 25, 500 and 5000 ppm Lymphocytic infiltrate hyperplasia in lachrymal glands: 30/77, 9/20, 6/20, and 50/79 (statistically significant) at 0, 25, 500 and 5000 ppm	Anonymous (1991i)
90-days week oral diet Broadly consistent with OECD TG 409 Beagle dogs 4/sex/dose Ethametsulfuron-methyl (purity 95.6%)	No toxicologically significant changes were reported in any haematology, clinical chemistry, gross and histopathological investigation conducted as part of this study	Anonymous (1991o)

Doses of 0, 100, 3500 and 10000 ppm Males: 0, 3.6, 136 and 390 mg/kg bw/day Females: 0, 3.9, 139 and 382 mg/kg bw/day Limit dose for warranting classification: 100 mg/kg bw/day		
1-year oral diet Broadly consistent with OECD TG Beagle dogs 6/sex/dose Ethametsulfuron-methyl (purity: 95.6%) Doses of 0, 250, 3000, or 15000 ppm Males: 0, 7.6, 87 and 478 mg/kg bw/day Females: 0, 6.9, 87 and 483 mg/kg bw/day Limit dose for warranting classification: 24 mg/kg bw/day	There were no deaths or treatment-related clinical signs of toxicity observed at any dose level. <u>478-483 mg/kg bw/day</u> Males 33% ↓ body weight gain Liver weight statistically significantly increased (absolute 11%, relative 25%) Testis weigh statistically significantly increased (absolute 10%, relative 25%) Females Thyroid and parathyroid statistically significant decrease in absolute and relative weights (by around 20%) <u>87 mg/kg bw/day</u> Females Thyroid and parathyroid statistically significant decrease in relative weight only (by 19%)	Anonymous (1991p)

Comparison with the criteria

Table 7 presents the following list of probably treatment-related adverse effects:

- Nephrotoxicity in the 14-days toxicity study in rats;
- Histopathological alterations in mammary gland ducts, lungs, bone marrow, naso-lachrymal duct, pituitary and ovaries in the 2-years study in rats;
- Histopathological alterations in mesenteric lymph node, kidney, epididymides, prostate, urinary bladder and lachrymal glands in the 1.5-years study in mice;
- Reductions in body weight gain, liver, thyroid and parathyroid weights in the 1-year study in dogs.
- Increase in testis weights in the 1-year study in dogs.

However, RAC notes that all these adverse effects appear at doses well above the respective limits of concentration for triggering classification within category 2 and therefore cannot

support a classification.

Table 7 also shows that ethametsulfuron-methyl was able to significantly reduce both the absolute and relative spleen weight by around 25% in the 1.5-years toxicity study in mouse at dose (3.5 mg/kg bw/day) that might warrant a classification within category 2. However, RAC notes that these reductions in spleen absolute and relative weight were not supported by histopathological alterations or clinical chemistry/haematological findings that might provide evidences of organ malfunction. This absence of evidences of perturbations in organ performance were also present at doses well above of limit for classification (765 mg/kg bw/day). In consequence, RAC does not consider the alterations in absolute and relative spleen weight sufficient to support a classification and agrees with the DS's proposal for **no classification of ethametsulfuron-methyl as STOT RE**

10.13 Aspiration hazard

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

Not applicable.

10.13.2 Comparison with the CLP criteria

Not applicable.

10.13.3 Conclusion on classification and labelling for aspiration hazard

Not applicable.

11 EVALUATION OF ENVIRONMENTAL HAZARDS

Ethametsulfuron-methyl (often referred to in test reports as DPX A7781) is a herbicide intended for use as a broad-leaved weed control in winter oilseed rape crops.

Available environmental fate and hazard studies have been considered under Regulation (EC) No 1107/2009 and summarised in the Draft Assessment Report (DAR) 2012.

Most of the environmental data presented in this CLH report is also presented in the REACH registration dossier for ethametsulfuron-methyl, available on ECHA's dissemination site[1]. In addition the REACH registration dossier includes some supporting information. Where relevant to hazard classification, further details are presented in this CLH report.

The key information pertinent to determining a classification is presented below.

The water solubility of ethametsulfuron-methyl in pure water has been experimentally determined (OECD 105, shake flask method) to be 16.8 mg/l at 20 °C. A pH dependence increase in water solubility was observed with the following solubilities determined at 20 °C:

- pH 5: 0.56 mg/l
- pH 7: 223 mg/l
- pH 9: 1858 mg/l

All radiolabelled studies used ^{14}C-ethametsulfuron-methyl with a purity of ≥95.5% as shown in Figure 1.

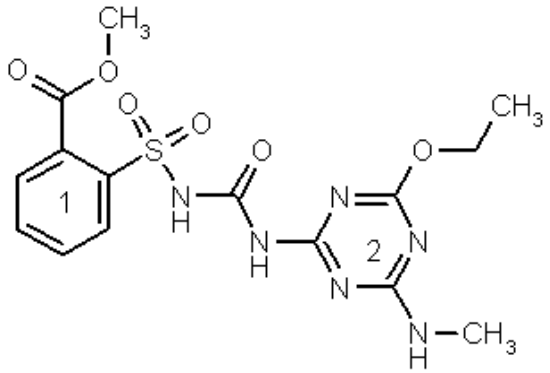


Figure 1: Structure of ethametsulfuron-methyl indicating positions of the 14C labels.

[1] Denotes [^{14}C-phenyl] ethametsulfuron-methyl

[2] Denotes [^{14}C-triazine] ethametsulfuron-methyl

Ethametsulfuron-methyl has a quoted dissociation constant of 4.2 (Anand, 2010). Therefore it is anticipated to dissociate and be ionised at environmentally relevant pH. Ecotoxicity studies were run at pH 5 or above reflecting environmental conditions where nearly all ethametsulfuron would be in its ionised form

Where available, information on degradation products is included in Annex II. These are considered less toxic than the parent substance and not considered further for classification.

A summary of reliable valid information on the aquatic fate of ethametsulfuron-methyl is presented in Table 29 below.

[1] https://echa.europa.eu/registration-dossier/-/registered-dossier/20802; accessed 1st Nov 2018

11.1 Rapid degradability of organic substances

Data on the fate of ethametsulfuron-methyl in soil is available in the REACH registration dossier. As reliable aquatic fate data are available (presented below), the soil fate data has not been considered further in this CLH report.

Table 29: Summary of relevant information on rapid degradability

Method	Results	Remarks	Reference
Aquatic hydrolysis OECD 111, GLP, purity 97.1%	pH 4: DT_{50} = 28 d at 20 °C pH 7: DT_{50} = 4618 d at 20 °C pH 9: DT_{50} = 8638 d at 20 °C pH 4: DT_{50} = 53 d at 12 °C pH 7: DT_{50} = 8758 d at 12 °C pH 9: DT_{50} = 16382 d at 12 °C	Valid	Reibach, 2010
Aquatic photolysis OECD 316, GLP, purity 97.1%	Stable at pH 7 over 21 experimental days	Valid	Li, 2010
Ready biodegradation OECD Guideline 301B, GLP, purity 98.9%	30.7% mineralisation day 28 Not readily biodegradable	Valid	Indrani, 2009
Freshwater aerobic mineralisation in surface water (simulation biodegradation), OECD Guideline 309, GLP, radiolabel purity 96.7-97%	DT_{50} = 67.5 days at 12 °C based on geometric mean of test systems and primary degradation Maximum 1.3% AR mineralisation as CO_2 by day 100	Valid	Sarff, 2010 Mackay & Khanijo, 2011

11.1.1 Ready biodegradability

Study 1 (Indrani, 2009)

A ready biodegradation study following OECD Test Guideline 301B (CO_2 Evolution) is available using ethametsulfuron-methyl (purity 98.9%). The conducting laboratory is located in a non-OECD member state although the report was stated to be conducted to GLP. During review under Directive 91/414/EEC certificates from German and Dutch GLP monitoring authorities were presented which cover the study duration.

The test substance was added to test vessels at a concentration of 33.33 mg/l of mineral medium (equivalent to 14.62 mg Carbon/l) which were inoculated with inoculum from a secondary effluent treatment plant receiving predominantly domestic sewage. Test vessels were incubated for 28 days at a nominal temperature range of 20 to 23 °C. The reference control was considered valid.

At day 14, 18.62% degradation was observed and at day 28, 30.7% degradation was observed. On this basis, ethametsulfuron-methyl is not considered readily biodegradable.

Supporting Study (Unnamed, 1987 presented in the REACH registration dossier)

A second ready biodegradation study following OECD Test Guideline 301B (CO2 Evolution) is available using ethametsulfuron-methyl with a quoted purity of >98%. The online summary states the study was conducted to GLP although further details of the test facility are not available.

The activated sludge is described as ‘freshly sampled from municipal sewage treatment plant’. The study employed two test concentration: 106 and 21.8 mg/l test item.

The following mineralisation was observed:

- 31.2% (at 10.6 mg/l concentration)
- 10.7% (at 21.8 mg/l concentration)

This study supports the conclusion that ethametsulfuron-methyl is not considered readily biodegradable.

11.1.2 BOD_5/COD

No data.

11.1.3 Hydrolysis

Study 1 (Reibach, 2010)
Following OECD Test Guideline 111 and using radio-labelled ^{14}C-ethametsulfuron (^{14}C-triazine and ^{14}C-phenyl), solutions at pH 4, 7 and 9 were incubated at varying temperatures for up to 30 days. Table 30 presents test pH and temperature conditions.

Table 30: **pH, temperature and sampling regimes used in ethametsulfuron-methyl aqueous hydrolysis study**

pH	Temperature (° C)	Sampling times (days after treatment)
4	10	0, 1, 3, 4, 7, 15, 21, 30
	25	0, 1, 3, 4, 7, 15, 21, 30
	35	0, 1 hour, 2 hours, 4 hours, 6 hours, 1, 2, 3, 6
4, 7, 9	50	0, 1, 2, 5
7, 9	60	0, 1, 2, 3, 4, 7, 10, 14
	70	0, 1, 2, 3, 4, 7

Analysis was undertaken using High Performance Liquid Chromatography (HPLC) with UV detection. A clear pH dependence on degradation was observed with increased hydrolysis under acidic conditions. Single First Order (SFO) DT_{50} values at 20 °C were calculated by extrapolation using ModelMaker 4.0 as follows:
pH 4 = 28 days
pH 7 = 4618 days
pH 9 = 8638 days

For classification, these values have been converted to 12 °C using the Arrhenius Equation to reflect a more environmentally relevant temperature:
pH 4 = 53 days
pH 7 = 8758 days
pH 9 = 16382 days

The study identified the following degradants:
- IN-D7556
- IN-00581
- IN-D5803
- IN-D5119

The degradants IN-D7556 and IN-00581 were observed under acidic conditions and at 10 °C. While IN-D5803 and IN-D5119 were observed only under warmer conditions (50 °C and above). One further degradant IN-N7468, was only observed a very low concentrations under alkaline conditions at 60 °C and above.

Overall, ethametsulfuron-methyl is considered hydrolytically stable at an environmentally relevant pH and temperature with a half-life greater than 16 days.

Additional information:

Three additional hydrolysis studies are presented in the REACH registration dossier. These are reported as Reliability 2 (reliable with restrictions) and were not conducted to GLP. In addition, some study details are not available. As reliable hydrolysis data are available, these additional studies are not considered further in this CLH report.

11.1.4 Other convincing scientific evidence

No data.

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

No data.

11.1.4.2 Inherent and enhanced ready biodegradability tests

No data.

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

Study 1 (Sarff, 2010 and Mackay & Khanijo, 2011)

A freshwater aquatic biodegradation simulation study is available following OECD Guideline 308 and GLP. The study used ^{14}C-phenyl and ^{14}C-triazine labelled ethametsulfuron-methyl (radiochemical purity 96.7-97%) and two natural aquatic systems: Calwich Abbey Lake, England and Swiss Lake, England. Table 31 presents the characteristics of each aquatic system.

Table 31: Physiochemical parameters of the ethametsulfuron-methyl water/sediment systems

Sediment Parameter	**Calwich Abbey Lake**				**Swiss Lake**			
Geographic Location	Calwich Abbey Lake, Calwich, Ashbourne, Derbyshire, England				Swiss Lake, Chatsworth, Derbyshire, England			
Texture Class	Silt Loam				Sand			
% Sand	28				89			
% Silt	65				10			
% Clay	7				1			
pH (1:1 soil:water ratio)	7.3				6.6			
% Organic Matter (Walkley Black)	8.0				1.8			
% Organic Carbon (Organic Matter/1.72)	4.7				1.0			
Soil Biomass Initial (µg/g dry wt.) Final	142.5 133.6				159.5 51.9			
CEC (meq/100 g)	10.5				3.9			
Water Parameter	**Calwich Abbey Lake**				**Swiss Lake**			
Temperature (°C)	20°C				20°C			
pH	7.5				6.8			
Hardness mg equivalent $CaCO_3$/L (ppm)	167				22			
Conductivity (mmhos/cm)	0.43				0.09			
Oxygen concentration (mg/L) at initiation:	5.60 and 5.45 (duplicate systems)				5.80 and 6.03 (duplicate systems)			
Total Dissolved Solids (ppm)	194				10			
Redox potential (mV)	Initial		Final		Initial		Final	
	Phenyl	Triazine	Phenyl	Triazine	Phenyl	Triazine	Phenyl	Triazine
	111.7	105.7	124.6	106.8	115.2	121.9	241.9	217.2

Test systems were prepared with filtered water (0.2 mm) and sediment (2.0 mm) at a ratio of 4:1 water:sediment (w:w). The test item was applied to the water layer at a rate of 0.167 µg a.s./g water. For analysis, water and sediment layers were separated by centrifugation with subsequent decanting of the water layer. The radioactivity in the water layer was quantified by Liquid Scintillation Counting (LSC) and then analysed by HPLC with UV and radiochemical detection.

During review under Regulation 1107/2009, it was noted that levels of ethametsulfuron-methyl in sediment at day 0 (and during the first 2 weeks of the study) were relatively high at approx. 7-10% AR. Given the substance has a relatively low Kfoc (25.7-367.9 ml/g, arithmetic mean 119.4 ml/g) this was considered unusual. In addition, it was noted that the redox potential, particularly in the sediment, was very variable with generally positive redox potential indicating anaerobic sediment conditions may not have been achieved over the whole study.

Given these issues, there was a concern that study conditions may have been inappropriate and there may have been an element of mixing between the water and sediment phases leading to the relatively high levels of apparent partitioning at day 0 and relatively high/variable redox potentials. In response the study owners suggested that 5-10% of the total volume of water was retained with the sediment after centrifuging and thereafter treated as sediment which may have contained some of the test item. Overall, the study limitations were not considered sufficient to invalidate the study and it is considered valid for the purpose of hazard classification.

The study ran for 100 days. Low levels of mineralisation observed in the phenyl label systems: max. 1.3% Applied Radioactivity (AR) in Calwich Abbey and 0.7% AR in Swiss Lake. No mineralisation was observed in the triazine labelled systems.

Whole systems DT_{50} values (representing primary degradation) at 20 °C were calculated using SFO kinetics as follows:

- Calwich Abbey (combined label data): 22.8 days
- Swiss Lake: 49 to 63.4 days with a geometric mean of 55.7 days
- Combined geometric mean: 35.6 days

For the purpose of classification these values have been converted 12 °C to reflect a more environmentally relevant temperature.

- Calwich Abbey (combined label data): 43 days
- Swiss Lake: 93 to 120 days with a geometric mean of 106 days
- Combined geometric mean: 67.5 days

The following degradants were observed during the study:

- IN-A8768: water max. 41% AR and sediment max. 38% AR
- IN-00581: water max. 13% AR and sediment max. 7% AR
- IN-D7556: water max. 9.5% AR and sediment max. 7% AR

For the principle degradants whole DT_{50} at 20 °C values were calculated following SFO based on the geometric mean of all labels. For the purpose of classification these have been converted 12 °C to reflect a more environmentally relevant temperature.

- IN-A8768: 270 days at 20 °C, 512 days at 12 °C
- IN-00581: 214 days, 406 days at 12 °C
- IN-D7556: 2000 days, 3794 days at 12 °C

11.1.4.4 Photochemical degradation

Study 1 (Li, 2010)

An aqueous photolysis study is available using ^{14}C-phenyl ethametsulfuron-methyl following OECD Test Guideline 316. Test solutions were incubated at pH 7 under continuous light and dark conditions for 21 days. Artificial sunlight was provided by a xenon lamp with removal of light below 290nm wavelength. Light conditions are considered representative of approximately 30 days midsummer sunlight at 40°N assuming a 12 hour light, 12 hour dark cycle. Radioactivity was determined by LSC with analysis by HPLC-UV. No photodegradation was observed in samples under these light conditions and ethametsulfuron-methyl is considered photolytically stable.

11.2 Environmental transformation of metals or inorganic metals compounds

Not relevant.

11.3 Environmental fate and other relevant information

Ethametsulfuron-methyl is considered hydrolytically stable at environmentally relevant pH and temperature.

Ethametsulfuron-methyl is considered photolytically stable.

In a ready biodegradation study, a maximum of 30.7% mineralsiation was observed by day 28. On this basis ethametsulfuron is not considered readily biodegradable.

In a water/sediment simulation study ethametsulfuron-methyl underwent primary degradation with very low levels of ultimate degradation (maximum of 1.3% AR as CO_2 after 100 days). Whole system DT_{50} values at 12 ºC based on primary degradation were 43 to 106 days with a geometric mean of 67.5 days for the two systems.

Relevant aquatic degradants include IN-A8768, IN-00581 and IN-D7556 which are themselves considered to have DT_{50} values at 12 ºC greater than 16 days.

Overall, ethametsulfuron-methyl is not considered to be rapidly degradable for the purpose of classification.

11.4 Bioaccumulation

Table 32: Summary of relevant information on bioaccumulation

Method	Results	Remarks	Reference
Partition coefficient, OECD 107, purity 99.2%	LogPow at pH 4 = 2.01 LogPow at pH 7 = -0.28 LogPow at pH 9 = -1.83 LogPow distilled water = 0.53 (all at 20 ºC)	Laboratory inspected by GLP	Pushpalataha, 2010

11.4.1 Estimated bioaccumulation

No data

11.4.2 Measured partition coefficient and bioaccumulation test data

Study 1 – Pushpalataha (2010)

The octanol:water partition coefficient of ethametsulfuron-methyl was determined following OECD Test Guideline 107 (shake flask method). The study was conducted to GLP principles in an Indian laboratory inspected by a GLP authority from the OECD MAD group and it was considered acceptable under Regulation 1107/2009. A pH dependence was observed with the following partition coefficients determined at 20 ºC:

- Distilled water: $LogP_{OW}$ = 0.53
- pH 4.0: LogPow= 2.01
- pH 7.0: LogPow = -0.28
- pH 9.0: LogPow= -1.83

11.4.3 Summary of bioaccumulation

Ethametsulfuron-methyl has a low LogPow below the CLP threshold of 4. Overall, it is considered to have a low bioaccumulation potential.

11.5 Acute aquatic hazard

A summary of available valid information on the aquatic toxicity of ethametsulfuron-methyl is presented in Table 33. Where available, a summary of valid information for degradants is also included in Annex II. These are considered less toxic than the parent substance and not considered further for classification.

Table 33: Summary of relevant information on acute aquatic toxicity

Method	Species	Test material	Results (mg/l)	Reference
Acute toxicity to fish, OECD 203, GLP Reliability 1*	Rainbow Trout (*Oncorhynchus mykiss*)	Ethametsulfuron-methyl (99.2%)	96-h LC_{50} >126 mg a.s./l (mm)	Anonymous (2009a)
Acute toxicity to fish OECD 203, GLP Reliability 1*	Bluegill sunfish (*Lepomis macrochirus*)	Ethametsulfuron-methyl (99.2%)	96-h LC_{50} >123 mg a.s./l (mm)	Anonymous (2009b)
Daphnia sp Acute Immobilisation OECD 202, GLP Reliability 1*	*Daphnia magna*	Ethametsulfuron-methyl (99.2%)	48-h $EC_{50\ (immobilisation)}$ >108 mg a.s./l (mm)	Minderhout, Kendall and Krueger (2009)
Freshwater Algal Growth Inhibition OECD 201, GLP Reliability 1*	*Pseudokirchneriella subcapitata***	Ethametsulfuron-methyl (99.2%)	72-h E_rC_{50} 0.421 mg a.s./l (mm)	Porch, Kendall and Krueger, 2009a
Freshwater Algal Growth Inhibition OECD 201, GLP Reliability 1*	*Anabaena flos-aquae*	Ethametsulfuron-methyl (99.2%)	96-h E_rC_{50} 0.83 mg a.s./l (n)	Dengler, 2009
Lemna sp. Growth Inhibition Test OECD 221, GLP Reliablilty 1	*Lemna gibba*	Ethametsulfuron-methyl (100%)	7-d $E_rC_{50\ frond\ number}$ 0.000808 mg a.s./l (mm)	Porch, Kendall and Krueger, 2009b

mm refers to mean measured concentrations
n refers to nominal concentrations
*taken from the REACH registration dossier, https://echa.europa.eu/registration-dossier/-/registered-dossier/20802; accessed 1st Nov 2018

***formerly Selenastrum capricornutum*

11.5.1 Acute (short-term) toxicity to fish

Two valid static, acute toxicity to fish studies using ethametsulfuron-methyl following GLP and OECD Test Guideline 203 are discussed below.

Study 1 - Anonymous (2009a)

Using Rainbow Trout (*Oncorhynchus mykiss*) a single test concentration of 120 mg a.s./l nominal was employed. Study conditions were acceptable and validity criteria were met. Analytical concentrations by HPLC UV were 105% of nominal. No mortality or sublethal effects were observed. The study 96-h LC_{50} was >126 mg a.s./l based on mean measured concentrations.

Study 2 - Anonymous (2009b)

Using Bluegill Sunfish (*Lepomis macrochirus*) a single test concentration of 120 mg a.s./l nominal was employed. Study conditions were acceptable and validity criteria were met. Analytical concentrations by HPLC UV were 103% of nominal. No mortality or sublethal effects were observed. The study 96-h LC_{50} was >123 mg a.s./l based on mean measured concentrations.

Additional information:

The REACH registration dossier includes four additional acute toxicity to fish studies. These data support the above acute toxicity to fish data with LC_{50} endpoints >1 mg/l for acute hazard classification.

Three of the studies did not include analytical verification of aged exposure concentrations and/or details of the test guideline. Therefore further details of these studies are not included in this CLH report.

Details of the remaining study considered Reliability 1 in the database are presented below:

Study 1 (Unnamed, 1991 - presented in the REACH registration dossier)

The static study was run to GLP following US EPA test guideline OPP 72-1 using Bluegill Sunfish (*Lepomis macrochirus*). The summary indicates analytical verification was undertaken although it is unclear if this refers to fresh or aged exposure solutions. The 96-h LC_{50} was >600 mg/l based on quoted mean measured concentrations.

11.5.2 Acute (short-term) toxicity to aquatic invertebrates

Study 1 - Minderhout, Kendall and Krueger (2009a)

A static acute toxicity to *Daphnia magna* study is available following GLP and OECD Test Guideline 202. Study conditions were acceptable and validity criteria were met. The exposure range was nominally 7.5, 15, 30, 60 and 120 mg a.s./l. Analytical measurement by HPLC-UV were 90-100% of nominal with mean measured concentrations 7.5, 14, 28, 56 and 108 mg a.s./l. Based on mean measured concentrations, the 48-h EC_{50} was >108 mg a.s./l.

Additional information:

The REACH registration dossier includes four additional acute toxicity to invertebrate studies. These data support the above acute toxicity to invertebrate EC_{50} >1 mg/l for acute hazard classification.

Three of the studies did not include analytical verification of aged exposure concentrations and/or details of the test guideline. Therefore further details of these studies are not included in this CLH report.

Details of the remaining study considered Reliability 1 in the database are presented below:

Study 1 (Unnamed, 1988 - presented in the REACH registration dossier)

The static study was run to GLP following US EPA test guideline E 72-1 using *Daphnia magna*. The 48-h $EC_{50\ (immobilisation)}$ was >550 mg/l based on quoted mean measured concentrations.

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

Two toxicity to algae studies and seven toxicity to aquatic plant studies are available using ethametsulfuron-methyl.

Study 1 – Porch, Kendall and Krueger, 2009a

A 72-hour static algal growth inhibition test using the freshwater algae *Pseudokirchneriella subcapitata* (formerly *Selenastrum capricornutum*) is available following GLP and OECD Test Guideline 201. Study conditions were acceptable and validity criteria were met. The nominal exposure range was 0.031, 0.063, 0.13, 0.25, 0.5 and 1.0 mg a.s./l. Analytical measurement by HPLC-UV were 79-93% of nominal with mean measured concentrations 0.025, 0.051, 0.10, 0.20, 0.40 and 0.87 mg a.s./l. In three lowest treatments, cells were observed to be normal. At higher treatments, cells appeared enlarged compared to control cells.

Growth was significantly reduced in all but the lowest treatment with a maximum of 74% growth inhibition for the highest treatment. The 72-h E_rC_{50} was calculated to be 0.421 mg a.s./l based on mean measured concentrations.

Study 2 – Dengler, 2009

A 96-hour static algal growth inhibition test using the blue-green algae *Anabaena flos-aquae* is available following GLP and OECD Test Guideline 201. Study conditions were acceptable and validity criteria were met. The nominal exposure range was 0.009, 0.03, 0.095, 0.31, 0.98, 3.13 and 10 mg a.s./l. Analytical measurement by HPLC-UV were 90-99% of nominal with mean measured concentrations 0.00831, 0.0268, 0.0932, 0.297, 0.903, 2.97 and 9.36 mg a.s./l. The 96-h E_rC_{50} was calculated to be 0.83 mg a.s./l based on nominal concentrations.

Study 3 – Porch, Kendall and Krueger, 2009b

A semi-static 7-day toxicity to *Lemna gibba* study is available following GLP and OECD Test Guideline 221 (2006). The nominal exposure range included 6 concentrations (4 replicates of each): 0.063, 0.13, 0.25, 0.50, 1.0 and 2.0 µg/l with blank controls (4 replicates) and an abiotic control without *Lemna* (1 replicate). Each replicate (except the abiotic control) contained four plants, each with three fronds, giving 12 fronds in total.

Test conditions during exposure were a temperature of 24±2 °C, pH of 7.9 – 9.0 and constant light regime with a mean light intensity of 4644 lux.

Test medium was prepared using 20X AAP medium and the relevant volume of stock solution. Each 250-ml glass test chamber contained 100 ml of solution.

Samples were taken on Day 0, 3 (test solution renewal) and 7 of the test to determine actual exposure concentrations using by Liquid chromatography–mass spectrometry (LC/MS). The The LOQ was 0.0500 µg/L and the LOD was 0.00429 µg/l. Geometric mean measured concentrations were 86-108% of nominal with mean measured concentrations 0.0540, 0.129, 0.249, 0.510, 1.02 and 2.16 µg a.s./l. Blank controls contained no detectable concentrations of ethametsulfuron methyl.

Frond counts were taken on Day 0, 3 and 5. Frond count, biomass and their corresponding growth rates were determined after 7 days. The plants used to determine biomass were dried at 60 °C for at least 48 hours before weighing. At test termination, healthy frond counts increased in the blank control by at least a factor of 7 in the 7-day exposure period, with a doubling time of 1.9 days. This means test guideline validity criteria were met.

The study endpoints were frond number, frond yield, biomass, and growth rate with growth rate endpoints (E_rC_{50} and NOE_rC based on frond number) determined using Dunnett's test $p<0.05$.

The growth rate endpoint based on geometric mean measured concentrations was:
7-d $E_rC_{50\ \text{frond number}}$ 0.808 µg/l equivalent to 0.000808 mg/l.

Overall, the study is considered valid and reliable for hazard classification.

Additional information:

A further *Lemna* study (Arnie, Kendall and Porch, 2012a) is available but this study employed variable exposure durations of 12, 24, 48 and 96 hours and is not considered suitable for the purpose of hazard classification. The REACH registration dossier includes an additional algal growth inhibition study. However, the study did not include analytical verification of aged exposure concentrations. Therefore further details of these studies are not included in this CLH report.

In addition to the above standard classification species, 7 studies using 6 non-standard aquatic macrophyte studies were submitted under Regulation 1107/2009 (summarised in the DAR and EFSA Peer review). Table 34 presents the available results with study information. It is noted that studies were not conducted using specific validated test guidelines and endpoints are not consistent with other CLH ecotoxicity endpoints as they were not based on growth rate and EC_{10}/NOEC endpoints were not included. Based on the analytical data with limited losses in the water phase, it is considered that the presence of sediment in test systems had limited impact. During the DAR process the following limitations were noted:

- Generally low levels of growth were observed in the controls meaning determination of significant effects is less clear.
- Limited dose-response relationships were observed with only 2 species (*Vallisneria americana* [Hoberg, 2010a study] and *Myriophyllum spicatum*). The slope of which were generally flat making it difficult to determine reliable endpoints.
- High levels of variability (>50%) were determined for *Vallisneria americana*, *Elodea canadenis* and *Ceratophyllum demersum* meaning confidence in the results is limited.
- Toxicity reference substance controls are not available meaning the sensitivities of test systems are unknown.
- *Vallisneria americana* is not a common European species although other tested species are fairly prevalent in European watercourses.
- Due to effects, NOECs could not be confidently determined.

Table 34: Summary of information on non-standard aquatic plant species aquatic toxicity

Method	Species	Test material	Results	Notes	Reference
Growth Inhibition (no guideline), GLP	*Vallisneria americana*	Ethametsulfuron-methyl (98.9%)	10-d $EC_{50\ shoot\ weight}$ (biomass) 5 mg a.s./l (mm) 10-d $EC_{50\ shoot\ length}$ (biomass) <0.77 mg a.s./l (mm) No NOEC available	Static Sediment phase included pH 7.9-9.8	Hoberg, 2010a
Growth Inhibition (no guideline), GLP	*Vallisneria americana*	Ethametsulfuron-methyl (98.9%)	14-d $EC_{50\ shoot\ weight}$ (biomass) 45 mg a.s./l (mm) No NOEC available	Static Sediment phase included pH 7.9-8.6	Kirkwood, 2012a
Growth Inhibition (no guideline), GLP	*Myriophyllum spicatum*	Ethametsulfuron-methyl (98.7%)	10-d $EC_{50\ shoot\ length}$ (biomass) ~0.23 mg a.s./l (mm) No NOEC available	Static Sediment phase included pH 8.2-10	Hoberg, 2010b
Growth Inhibition (no guideline), GLP	*Elodea canadenis*	Ethametsulfuron-methyl (98.7%)	14-d $EC_{50\ shoot\ length\ /\ weight}$ (biomass) >25 mg a.s./l (mm) No NOEC available	Static Sediment phase included pH 8.1-9.6 Morphological	Hoberg, 2010c

				abnormalities, chlorosis and necrosis observed from 0.83 mg a.s./l (mm) although a clear dose-response relationship not evident	
Growth Inhibition (no guideline), GLP	*Canomba caroliniana*	Ethametsulfuron-methyl (98.7%)	14-d $EC_{50\ shoot\ length\ /\ weight}$ (biomass) >28 mg a.s./l (mm) No NOEC available	Static Sediment phase included pH 8.1-9.5 Additional physical effects observed from 0.083 mg a.s./l	Hoberg, 2010d
Growth Inhibition (no guideline), GLP	*Ceratophyllum demersum*	Ethametsulfuron-methyl (98.7%)	10-d $EC_{50\ shoot\ weight}$ (biomass) 4.4 mg a.s./l (mm) No NOEC available	Static pH 7.9-9.9	Hoberg, 2010e
Growth Inhibition (no guideline), GLP	*Stuckenia pectinata*	Ethametsulfuron-methyl (98.7%)	14-d $EC_{50\ shoot\ weight}$ (biomass) 0.0015 mg a.s./l (mm) No NOEC available	Static Sediment phase included pH 8-10	Kirkwood, 2012b

For risk assessment under Regulation 1107/2009 a species sensitivity distribution (SSD) was considered for acute toxicity to aquatic plants. The DAR authors did not feel this was appropriate given the limitations for acute endpoints and the apparent lack of a log normal distribution for the data.

In addition, a geometric mean of 0.0102 mg/l based on the *Lemna gibba* E_bC_{50} (as other endpoint are based on biomass) and LOECs (as a proxy for the EC_{50}) from 5[2] other plant species was calculated. This mean was considered appropriate for application in some risk assessment scenarios given that other conservative assumptions were employed.

For the purpose of classification, the CLH report authors consider that the acute toxicity classification should be based on the Lemna gibba growth rate endpoint given the uncertainties discussed above regarding the available acute endpoints for other aquatic plant species. This is also considered appropriate given Lemna appear to be significantly more sensitive. Acute (short-term) toxicity to other aquatic organisms

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

No data.

11.6 Long-term aquatic hazard

Table 35: Summary of relevant information on chronic aquatic toxicity

Method	Species	Test material	Results	Reference
Fish Early-Life Stage toxicity, OECD 210, GLP Reliability 1*	Rainbow Trout (*Oncorhynchus mykiss*)	Ethametsulfuron-methyl (99.2%)	87-d NOEC 5.4 mg a.s./l (mm) based on time to hatch, hatching success, survival and growth	Anonymous (2010a)

[2] *Vallisneria americana*, *Myriophyllum spicatum*, *Elodea Canadensis*, *Cabomba caroliniana* and *Ceratophyllum spicatum*

			(length and dry weight)	
Daphnia magna Reproduction OECD 211, GLP Reliability 1*	*Daphnia magna*	Ethametsulfuron-methyl (100%)	21-d NOEC 4.7 mg a.s./l (mm) based on survival	Minderhout, Kendall and Krueger (2010)
Freshwater Algal Growth Inhibition OECD Guideline 201, GLP Reliability 1*	*Pseudokirchneriella subcapitata**	Ethametsulfuron-methyl (99.2%)	72-h NOE_rC 0.025 mg a.s./l (mm)	Porch, kendall and Krueger, 2009a
Freshwater Algal Growth Inhibition OECD Guideline 201, GLP Reliability 1*	*Anabaena flos-aquae*	Ethametsulfuron-methyl (99.2%)	96-h NOE_rC 0.03 mg a.s./l (n) analytically verified	Dengler, 2009
Lemna sp. Growth Inhibition Test OECD 221, GLP Reliablilty 1	*Lemna gibba*	Ethametsulfuron-methyl (100%)	7-d $NOE_rC_{\text{frond number}}$ 0.000129 mg a.s./l (mm) 7-d $NOE_rC_{\text{dry weight}}$ 0.000129 mg a.s./l (mm)	Porch, Kendall and Krueger, 2009b
Growth Inhibition, GLP	*Vallisneria americana*	Ethametsulfuron-methyl (98.9%)	10-d $NOEC_{\text{shoot length}}$ <0.077 mg a.s./l (mm)	Hoberg, 2010

Notes:
mm refers to mean measured concentrations
* taken from the REACH registration dossier, https://echa.europa.eu/registration-dossier/-/registered-dossier/20802; accessed 1st Nov 2018
n refers to nominal concentrations

11.6.1 Chronic toxicity to fish

Study 1 - Anonymous (2010a)

An 87-day flow-through chronic toxicity to fish study using ethametsulfuron-methyl following GLP and OECD Test Guideline 210 is available. The study used Rainbow Trout (*Oncorhynchus mykiss*) and the following endpoints: time to hatch, hatching success, survival and growth (length and dry weight). General observations were also recorded.

Study conditions were acceptable and validity criteria were met. The nominal exposure range was 0.38, 0.75, 1.5, 3.0 and 6.0 mg a.s./l. Exposure solutions were prepared with the aid of the solvent dimethylformamide (DMF) at 0.1 ml/l and a solvent control was included.

Analytical verification was by HPLC-UV with measured values 87-93% of nominal with mean measured concentrations 0.33, 0.7, 1.3, 2.8 and 5.4 mg a.s./l. Significant effects were determined by the Dunnett's test. There were no statistically significant differences between any treatments and controls for hatching success, time to swim-up or survival. A statistically significant difference in mean total length and mean weight was observed at the 1.3 mg a.s./l treatment. As significant differences were not observed at higher treatments, the effects were not considered treatment related. On this basis the 87-d NOEC for all parameters was considered to be 5.4 mg a.s./l based on the highest treatment and mean measured concentrations.

11.6.2 Chronic toxicity to aquatic invertebrates

Study 1 - Minderhout, Kendall and Krueger (2010)

A semi-static chronic toxicity to *Daphnia magna* study is available following GLP and OECD Test Guideline 211. The nominal exposure range was 0.63, 1.3, 2.5, 5.0 and 10.0 mg a.s./l. Analytical measurement by HPLC-UV were 98.7-99.7% of nominal with mean measured concentrations 0.59, 1.2, 2.4, 4.7 and 9.6 mg a.s./l. Study conditions were acceptable and the study is considered valid.

Daphnids in treatments that survived to study termination were observed to be normal although one adult in the 4.7 mg/l treatment was pale. Significant effects were determined by the Dunnett's test. There were no statistically significant differences between any treatments and controls for reproduction or mean length. A statistically significant difference was observed for survival at the highest treatment resulting in a 21-d NOEC of 4.7 mg a.s./l for survival.

A statistically significant difference was observed for mean dry weight at 4.7 mg a.s./l but not observed in the one higher treatment. On this basis the observation was not considered treatment related. For the purpose of classification, it is noted that any NOEC derived from this observation would be in the same 1-10 mg/l range as the 21-d NOEC for reproduction.

Additional information:

The REACH registration dossier includes an additional chronic toxicity to invertebrate study considered Reliability 1 in the database which supports the above chronic toxicity to invertebrate NOEC >1 mg/l for chronic hazard classification.

Study 1 (Unnamed, 1988 - presented in the REACH registration dossier)

The static study was run to GLP and followed US EPA test guideline OPP 72-4 and OECD 202. The study ran for 21 days with the following endpoints: survival, length and reproduction. The summary indicates analytical verification was undertaken although it is unclear if this refers to fresh or aged exposure solutions. The 21-d NOEC was 30 mg/l based on quoted measured concentrations.

11.6.3 Chronic toxicity to algae or other aquatic plants

Two toxicity to algae studies and seven toxicity to aquatic plant studies are available using ethametsulfuron-methyl. Study details are presented in section 11.5.3 above with chronic endpoints detailed below.

Study 1 – Porch, Kendall and Krueger, 2009a

Growth was significantly reduced in all but the lowest treatment with a maximum of 74% growth inhibition for the highest treatment. The 72-h NOE_rC for *Pseudokirchneriella subcapitata* was determined to be 0.025 mg a.s./l based on mean measured concentrations.

Study 2 – Dengler, 2009

The 96-h NOE_rC for *Anabaena flos-aquae* was determined to be 0.03 mg a.s./l based on verified nominal concentrations.

Study 3 – Porch, Kendall and Krueger, 2009b

Refer to section 11.5.3 above for full study details. Overall, the study endpoints are considered valid and reliable for hazard classification.

The 7-d $NOE_rC_{frond\ number}$ for *Lemna gibba* was determined to be 0.000129 mg/l based on geometric mean measured concentrations.

Additional information:

As discussed above in section 11.5.3, additional aquatic plant species data are available in the DAR and presented above. There are no valid true chronic endpoints.

11.6.4 Chronic toxicity to other aquatic organisms

No data.

11.7 Comparison with the CLP criteria

11.7.1 Acute aquatic hazard

Ethametsulfuron-methyl acute toxicity data are available for fish, invertebrates, algae and aquatic plants.

Algae and aquatic plants are the most acutely sensitive trophic level with EC_{50} values below 1 mg/l. Algal E_rC_{50} endpoints for two species are in the range 0.1-1 mg/l. However, *Lemna* are the most sensitive species with a 7-day E_rC_{50} of 0.000808 mg a.s./l.

Degradation products are less acutely toxic than the parent substance (see Annex II) and are not considered further for classification.

Based on this data, ethametsulfuron-methyl should be classified for the environment as Aquatic Acute 1. Based on the *Lemna* endpoint an acute M-factor of 1000 based on 0.0001 mg/l < EC_{50} ≤ 0.001 mg/l is appropriate.

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

Ethametsulfuron-methyl has a low LogPow less than 4. An experimental aquatic BCF is not available.

Ethametsulfuron-methyl is not readily biodegradable and photolytically stable.

Under experimental conditions, hydrolysis was observed under acidic conditions. However, ethametsulfuron-methyl is considered hydrolytically stable at an environmentally relevant pH and temperature with a half-life greater than 16 days.

In a water/sediment simulation study ethametsulfuron-methyl underwent primary degradation with very low levels of ultimate degradation (maximum of 1.3% AR as CO_2 after 100 days). Whole system DT_{50} values at 12 °C based on primary degradation were 43 to 106 days with a geometric mean of 67.5 days for the two systems.

Relevant aquatic degradants include IN-A8768, IN-00581 and IN-D7556 which are considered to have DT_{50} values at 12 °C greater than 16 days. As above, these are considered less chronically toxic than the parent substance (see Annex II) and are not considered further for classification

Overall, ethametsulfuron-methyl is not considered to be rapidly degradable for the purpose of classification.

Ethametsulfuron-methyl has a low log K_{ow} less than 4. An experimental aquatic BCF is not available. Overall it is considered to have a low potential to bioconcentrate.

Chronic toxicity to fish and invertebrate data are available with NOECs in the range 1-10 mg/l. Algae and aquatic plants are the most chronically sensitive trophic level with NOEC values below 1 mg/l. Algal chronic NOEC endpoints for two species are in the range 0.01-0.1 mg/l. However, *Lemna* is the most sensitive species with a 7-day NOE_rC of 0.000129 mg a.s./l.

Based on this data and given ethametsulfuron-methyl is not rapidly degradable, it should be classified for the environment as Aquatic Chronic 1. Based on the *Lemna* endpoint a chronic M-factor of 100 based on 0.0001 mg/l < NOEC ≤ 0.001 mg/l is appropriate.

11.8 CONCLUSION ON CLASSIFICATION AND LABELLING FOR ENVIRONMENTAL HAZARDS

Ethametsulfuron-methyl should be classified for the environment as Aquatic Acute 1 with an acute M-factor of 1000 based on *Lemna* E_rC_{50} data in the range 0.0001 mg/l < EC_{50} ≤ 0.001 mg/l.

Ethametsulfuron-methyl is not rapidly degradable and should be classified for the environment as Aquatic Chronic 1 with a chronic M-factor of 100 based on *Lemna* NOEC data in the range 0.0001 mg/l < NOEC ≤ 0.001 mg/l.

RAC evaluation of aquatic hazards (acute and chronic)

Summary of the Dossier Submitter's proposal

The Dossier Submitter (DS) presented the key information relevant for classification purposes. The studies have previously been considered under Regulation (EC) No 1107/2009 and summarised in the Draft Assessment Report (DAR) 2012 and in the REACH registration dossier available on ECHA's website.

The DS presented available and relevant data for degradation, bioaccumulation, and all the three trophic levels for acute and chronic aquatic ecotoxicity. Based on this dataset, the DS proposed to classify Ethametsulfuron-methyl as **Aquatic Acute 1 (H400) (M = 1000) and Aquatic Chronic 1 (H410) (M = 100)**.

The water solubility of ethametsulfuron-methyl in pure water at 20°C has been experimentally determined (OECD TG 105, shake flask method) to be 16.8 mg/L, 0.56 mg/L at pH 5; 223 mg/L at pH 7 and 1858 mg/L at pH 9. The solubility of ethametsulfuron-methyl is pH-dependent.

With a dissociation constant of 4.2, it is likely the substance will be largely dissociated and ionised within an environmentally relevant pH range (Anand, 2010).

Ethametsulfuron-methyl is surface active with a surface tension value of 68.8 mN/m (90% saturated solution) at 20°C (Sannappa, 2009).

Degradation

A summary of reliable valid studies considering the aquatic fate of ethametsulfuron-methyl and presented by the DS are listed in the table below.

***Table**: Summary of key studies on degradability*

Method	Results	Remarks	Referenc
Aquatic hydrolysis OECD TG 111, GLP, purity 97.1%	pH 4: DT_{50} = 28 d at 20°C pH 7: DT_{50} = 4618 d at 20°C pH 9: DT_{50} = 8638 d at 20°C	Valid	Reibach, 2010

	pH 4: DT_{50} = 53 d at 12°C pH 7: DT_{50} = 8758 d at 12°C pH 9: DT_{50} = 16382 d 12°C		
Aquatic photolysis OECD TG 316, GLP, purity 97.1%	Stable at pH 7 over 21 experimental days	Valid	Li, 2010
Ready biodegradation OECD TG 301B, GLP, purity 98.9%	30.7% mineralisation day 28 Not readily biodegradable	Valid	Indrani, 2009
Aerobic sediment/water study (simulation biodegradation), OECD TG 308, GLP, radiolabel purity 96.7-97%	DT_{50} = 67.5 days at 12°C based on geometric mean of test systems and primary degradation Maximum 1.3% AR mineralisation as CO_2 by day 100	Valid	Sarff, 2010 Mackay & Khanijo, 2011

Following OECD TG 111 and using radio-labelled ^{14}C-ethametsulfuron-methyl (^{14}C-triazine and ^{14}C-phenyl), solutions at pH 4, 7 and 9 were incubated at varying temperatures for up to 30 days. Analysis was undertaken using High Performance Liquid Chromatography (HPLC) with UV detection. A clear pH dependence on degradation was observed with increased hydrolysis under acidic conditions. For classification, these values have been converted to 12°C using the Arrhenius Equation to reflect a more environmentally relevant temperature. Four degradants were identified in this study. Three additional hydrolysis studies are presented in the REACH registration dossier. These studies were not conducted to GLP, some details were lacking, and as reliable hydrolysis data are available, these additional studies are not considered further by the DS. Ethametsulfuron-methyl is considered by the DS as hydrolytically stable at an environmentally relevant pHs and temperature. On this basis, ethametsulfuron-methyl is considered hydrolytically stable at an environmentally relevant temperature with a half-life greater than 16 days.

Based on an aqueous photolysis study using ^{14}C-phenyl ethametsulfuron-methyl following OECD TG 316 performed in light conditions representative of approximately 30 days midsummer sunlight at 40°N assuming a 12 hour light, 12 hour dark cycle, the DS considered ethametsulfuron-methyl as photolytically stable.

Two experimental studies performed according to OECD TG 301B (CO_2 evolution) and GLP are presented by the DS. In the first test, considered as the key study by the DS, 30.7% mineralisation was achieved after 28 days (Indrani, 2009). In the second test, the test substance was degraded between 10 and 30% depending on the ethametsulfuron-methyl concentration used. Due to the lack of details on the test facility, this study presented in the REACH registration dossier was considered as a supporting study by the DS.

Both studies supported the conclusion that ethametsulfuron-methyl is not considered readily biodegradable.

In a water/sediment simulation study (OECD TG 308) using radio-labelled ^{14}C-ethametsulfuron-methyl and two natural aquatic systems, primary degradation was

assessed for 100 days. The whole system DT_{50} values at 12°C ranged from 43 to 120 days for primary degradation of ethametsulfuron-methyl, and from 270 days to 3794 days for the principle degradants.

Owing to the low rate of mineralisation in the OECD TG 301B and the half-life in a water/sediment system greater than 16 days, the DS concluded that ethametsulfuron-methyl is not rapidly degradable for the purpose of classification.

Bioaccumulation

An experimental aquatic BCF was not available. The DS reported that an octanol:water partition coefficient was determined following the shake flask method (OECD TG 107) at pH4, 7 and 9 at 20°C. The quoted Log Pow values are 2.01, -0.28 and -1.83 at pH 4, 7 and 9 respectively. Based on this experimental data and Log Pow values below the CLP threshold of 4, ethametsulfuron-methyl is considered to have a low bioaccumulation potential.

Aquatic toxicity

Acute aquatic hazard

***Table**: Summary of relevant information on acute aquatic toxicity*

Method	Species	Test material	Results (mg/L)	Reference
Acute toxicity to fish, OECD TG 203, GLP Reliability 1*	Rainbow Trout (*Oncorhynchus mykiss*)	Ethametsulfuron-methyl (99.2%)	96h LC_{50} >126 mg a.s./L (mm)	Anonymous (2009a)
Acute toxicity to fish OECD TG 203, GLP Reliability 1*	Bluegill sunfish (*Lepomis macrochirus*)	Ethametsulfuron-methyl (99.2%)	96h LC_{50} >123 mg a.s./L (mm)	Anonymous (2009b)
Acute Immobilisation OECD TG 202, GLP Reliability 1*	*Daphnia magna*	Ethametsulfuron-methyl (99.2%)	48h EC_{50} (immobilisation) >108 mg a.s./L (mm)	Minderhout, Kendall and Krueger (2009)
Freshwater Algal Growth Inhibition OECD TG 201, GLP Reliability 1*	*Pseudokirchneri ella subcapitata*	Ethametsulfuron-methyl (99.2%)	72h E_rC_{50} 0.421 mg a.s./L (mm)	Porch, Kendall and Krueger, 2009a
Freshwater Algal Growth Inhibition OECD TG 201, GLP Reliability 1*	*Anabaena flosaquae*	Ethametsulfuron-methyl (99.2%)	96h E_rC_{50} 0.83 mg a.s./L (n)	Dengler, 2009

***Lemna* sp. Growth Inhibition Test OECD TG 221, GLP Reliabililty 1**	***Lemna gibba***	**Ethametsulfuron-methyl (100%)**	**7d ErC50 frond number 0.000808 mg a.s./L (mm)**	**Porch, Kendall and Krueger, 2009b**

mm refers to mean measured concentrations
n refers to nominal concentrations

*taken from the REACH registration dossier, https://echa.europa.eu/registration-dossier/-/registered-dossier/20802; accessed 1st Nov 2018

The DS reported two acute toxicity studies with fish and mentioned four further acute toxicity with fish studies using ethametsulfuron-methyl presented in the REACH registration dossier. As three of them did not include analytical verification and/or details of the test guideline, further details of these studies are not included in the CLH report. The fourth study was performed in static condition under GLP following US EPA test guideline OPP 72-1 using Bluegill Sunfish (*Lepomis macrochirus*). Analytical verification is unclear and the 96-h LC_{50} was >600 mg/L based on quoted mean measured concentrations.

Two valid static, acute toxicity studies with fish using ethametsulfuron-methyl following GLP and OECD TG 203 using a single test concentration of 120 mg a.s./L were valid and met the validity criteria. No mortality or sub-lethal effects were observed with Rainbow Trout (*Oncorhynchus mykiss*) or Bluegill Sunfish (*Lepomis macrochirus*) and the 96-h LC_{50} was >126 mg a.s./L and >123 mg a.s./L, respectively.

A static acute toxicity to *Daphnia magna* study is available following OECD TG 202 and GLP. Study conditions were acceptable and the validity criteria were met. The exposure range was nominally 7.5, 15, 30, 60 and 120 mg a.s./L. Analytical measurement by HPLC-UV were 90-100% of nominal with mean measured concentrations 7.5, 14, 28, 56 and 108 mg a.s./L. Based on mean measured concentrations, the 48h EC_{50} was >108 mg a.s./L. The REACH registration dossier includes four additional acute toxicity studies with invertebrates. These data support the above invertebrate EC_{50} >1 mg/L for acute hazard classification. The DS reported a lack of analytical verification of aged exposure concentrations and/or details of the test guideline for three of the studies.

There were two available tests presented for algae and seven for aquatic plants. Two static algal growth inhibition tests using the green algae *Pseudokirchneriella subcapitata* (72h exposure) and the blue-green algae *Anabaena flos-aquae* (96h exposure) are available following GLP and OECD TG 201. Study conditions were acceptable and validity criteria were met. The nominal exposure range was 0.031, 0.063, 0.13, 0.25, 0.5 and 1.0 mg a.s./L and 0.009, 0.03, 0.095, 0.31, 0.98, 3.13 and 10 mg a.s./L, respectively. Analytical measurement by HPLC-UV were 79-93% and 90-99% of nominal concentrations. The *Pseudokirchneriella subcapitata* 72h E_rC_{50} was calculated to be 0.421 mg a.s./L based on mean measured concentrations. The *Anabaena flos-aquae* 96h E_rC_{50} was calculated to be 0.83 mg a.s./L based on nominal concentrations.

A semi-static 7-day toxicity study with *Lemna gibba* following GLP and OECD TG 221 is presented by the DS. The nominal exposure range included 6 concentrations: 0.063, 0.13,

0.25, 0.50, 1.0 and 2.0 µg/L. Samples were taken on Day 0, 3 and 7 of the test to determine actual exposure concentrations using by Liquid chromatography–mass spectrometry (LC/MS). Geometric mean measured concentrations were 86-108% of nominal with mean measured concentrations 0.054, 0.129, 0.249, 0.510, 1.02 and 2.16 µg a.s./L. At test termination, as healthy frond counts increased in the blank control by at least a factor of 7 in the 7-day exposure period, with a doubling time of 1.9 days, the validity criteria were met. The growth rate endpoint based on geometric mean measured concentrations was: 7d E_rC_{50} frond number was 0.000808 mg/L.

The DS noted that additional data are presented in the REACH registration dossier. Another *Lemna* study (Arnie, Kendall and Porch, 2012a) and an additional algal growth inhibition study are available but due to the non-standard exposure durations of this study and the lack of analytical verifications, the DS considered them as not suitable for the purpose of hazard classification. In addition to the above standard classification species, 7 studies using 6 non-standard aquatic macrophyte studies were submitted under Regulation 1107/2009 (summarised in the DAR and EFSA Peer review). The DS presented a table with the available results with study information. These studies were not conducted using specific validated test guidelines and the presence of sediment in test systems is considered to have a limited impact. During the EFSA peer review process the following limitations were noted:

- Generally low levels of growth were observed in the controls meaning determination of significant effects is less clear.
- Limited dose-response relationships were observed with only 2 species (*Vallisneria americana* and *Myriophyllum spicatum*). The slopes of which were generally flat making it difficult to determine reliable endpoints.
- High levels of variability (>50%) were determined for *Vallisneria americana*, *Elodea canadenis* and *Ceratophyllum demersum* meaning confidence in the results is limited.
- Toxicity reference substance controls are not available meaning the sensitivities of test systems are unknown.
- *Vallisneria americana* is not a common European species although other tested species are fairly prevalent in European watercourses.

The DS concluded that the acute toxicity classification should be based on the *Lemna gibba*, as they constituted the most sensitive species.

Table: *Summary of information on non-standard aquatic plant species aquatic toxicity*

Method	Species	Test material	Results	Notes	Reference
Growth Inhibition (no guideline), GLP	*Vallisneria americana*	Ethametsulfuronmethyl (98.9%)	10d EC50 shoot weight (biomass) 5 mg a.s./L (mm) 10d EC50 shoot length (biomass) <0.77 mg a.s./L (mm) No NOEC available	Static Sediment phase included pH 7.9-9.8	Hoberg, 2010a

Growth Inhibition (no guideline), GLP	*Vallisneria americana*	Ethametsulfuronmethyl (98.9%)	14d EC50 shoot weight (biomass) 45 mg a.s./L (mm) No NOEC available	Static Sediment phase included pH 7.9-8.6	Kirkwood, 2012a
Growth Inhibition (no guideline), GLP	*Myriophyllum spicatum*	Ethametsulfuronmethyl (98.7%)	10d EC50 shoot length (biomass) ~0.23 mg a.s./L (mm) No NOEC available	Static Sediment phase included pH 8.2-10	Hoberg, 2010b
Growth Inhibition (no guideline), GLP	*Elodea canadenis*	Ethametsulfuronmethyl (98.7%)	14d EC50 shoot length / weight (biomass) >25 mg a.s./L (mm) No NOEC available	Static Sediment phase included pH 8.1-9.6 Morphological abnormalities, chlorosis and necrosis observed from 0.83 mg a.s./L (mm) although a clear dose-response relationship not evident	Hoberg, 2010c
Growth Inhibition (no guideline), GLP	*Cabomba caroliniana*	Ethametsulfuronmethyl (98.7%)	14d EC50 shoot length / weight (biomass) >28 mg a.s./L (mm) No NOEC available	Static Sediment phase included pH 8.1-9.5 Additional physical effects observed from 0.083 mg a.s./L	Hoberg, 2010d
Growth Inhibition (no guideline), GLP	*Ceratophyllum demersum*	Ethametsulfuronmethyl (98.7%)	10d $EC50_{\text{shoot weight}}$ (biomass) 4.4 mg a.s./L (mm) No NOEC available	Static pH 7.9-9.9	Hoberg, 2010e
Growth Inhibition (no guideline), GLP	*Stuckenia pectinata*	Ethametsulfuronmethyl (98.7%)	14d EC50 shoot weight (biomass) 0.0015 mg a.s./L (mm) No NOEC available	Static Sediment phase included pH 8-10	Kirkwood, 2012b

Myriophyllum spicatum is now a standard species (even though the test protocol is a non-standard one)

Long-term aquatic hazard

Valid studies relevant for the classification of ethametsulfuron-methyl are presented in the table below.

***Table**: Summary of relevant information on chronic aquatic toxicity*

Method	Species	Test material	Results	Reference
Fish Early-Life Stage toxicity, OECD TG 210, GLP Reliability 1*	Rainbow Trout (*Oncorhynchus mykiss*)	Ethametsulfuronmethyl (99.2%)	87d NOEC 5.4 mg a.s./L (mm) based on time to hatch, hatching success, survival and growth (length and dry weight)	Anonymous (2010
Reproduction OECD TG 211, GLP Reliability 1*	*Daphnia magna*	Ethametsulfuronmethyl (100%)	21d NOEC 4.7 mg a.s./L (mm) based on survival	Minderhout, Kend and Krueger (2010)
Freshwater Algal Growth Inhibition OECD TG 201, GLP Reliability 1*	*Pseudokirchneriella subcapitata**	Ethametsulfuronmethyl (99.2%)	72h NOE_rC 0.025 mg a.s./L (mm)	Porch, Kendall and Krueger, 2009a
Freshwater Algal Growth Inhibition OECD TG 201, GLP Reliability 1*	*Anabaena flos-aquae*	Ethametsulfuronmethyl (99.2%)	96h NOE_rC 0.03 mg a.s./L (n) analytically verified	Dengler, 2009
Growth Inhibition Test OECD TG 221, GLP Reliablilty 1	***Lemna gibba***	**Ethametsulfuron methyl (100%)**	**7d NOErC frond number 0.000129 mg a.s./L (mm)** **7d NOErC dry weight 0.000129 mg a.s./L (mm)**	**Porch, Kendall a Krueger, 2009b**
Growth Inhibition, GLP	*Vallisneria americana*	Ethametsulfuronmethyl (98.9%)	10d $NOEC_{shoot}$ length <0.077 mg a.s./L (mm)	Hoberg, 2010

Notes: mm refers to mean measured concentrations

** taken from the REACH registration dossier, https://echa.europa.eu/registration-dossier/-/registered-dossier/20802; accessed 1st Nov. 2018*

n refers to nominal concentrations

An 87-day flow-through chronic toxicity to fish study using ethametsulfuron-methyl following GLP and OECD TG 210 is available. The study used Rainbow Trout (*Oncorhynchus mykiss*) and the following endpoints: time to hatch, hatching success, survival and growth (length and dry weight). General observations were also recorded. Study conditions were acceptable and validity criteria were met. The nominal exposure range was 0.38, 0.75, 1.5, 3.0 and 6.0 mg a.s./L (with mean measured concentrations 0.33, 0.7, 1.3, 2.8 and 5.4 mg a.s./L). Exposure solutions were prepared with the aid of the solvent

dimethylformamide (DMF) at 0.1 ml/L and a solvent control was included. The 87-d NOEC for all parameters was considered to be 5.4 mg a.s./L based on the highest treatment and mean measured concentrations.

There is a semi-static chronic toxicity study with *Daphnia magna* following GLP and OECD TG 211. The nominal exposure range was 0.63, 1.3, 2.5, 5.0 and 10.0 mg a.s./L (mean measured concentrations 0.59, 1.2, 2.4, 4.7 and 9.6 mg a.s./L). The study is considered acceptable and valid. A statistically significant difference was observed for survival at the highest treatment resulting in a 21d NOEC of 4.7 mg a.s./L for survival. The DS emphasized that the REACH registration dossier includes an additional invertebrate chronic toxicity study performed under GLP and followed US EPA test guideline OPP 72-4 and OECD TG 202, considered as Reliability 1. The study ran for 21 days with the following endpoints: survival, length and reproduction. The 21d NOEC was 30 mg/L based on quoted measured concentrations.

The DS reported that two toxicity to algae studies and seven toxicity to aquatic plant studies were available using ethametsulfuron-methyl. The 72h NOErC for *Pseudokirchneriella subcapitata* was determined to be 0.025 mg a.s./L based on mean measured concentrations. The 96h NOErC for *Anabaena flos-aquae* was determined to be 0.03 mg a.s./L based on verified nominal concentrations. The 7d $NOErC_{frond}$ number for *Lemna gibba* was determined to be 0.000129 mg/L based on geometric mean measured concentrations. Like for acute toxicity, the DS described additional aquatic plant species data available in the DAR with no valid chronic endpoints.

Comments received during public consultation

Three Member States and one IND supported the classification proposed by the DS (Aquatic Acute 1 with an M-Factor of 1000 and Aquatic Chronic 1 with an M-Factor of 100) and to base the classification on the selected effect concentrations obtained for duckweeds.

Assessment and comparison with the classification criteria

Degradation

In a valid and reliable OECD TG 301B study, ethametsulfuron-methyl was considered as not readily biodegradable. Ethametsulfuron-methyl is considered hydrolytically stable at an environmentally relevant pH and temperature with a half-life greater than 16 days.

In a water/sediment simulation study ethametsulfuron-methyl underwent primary degradation with very low levels of ultimate degradation (maximum of 1.3% AR as CO_2 after 100 days). Whole system DT_{50} values at 12°C based on primary degradation were 43 to 106 days with a geometric mean of 67.5 days for the two systems.

All relevant aquatic degradants were considered less chronically toxic than the parent substance and were, thus, not considered further for classification purposes.

Overall, RAC agrees with the DS that ethametsulfuron-methyl should be considered as not rapidly degradable.

Bioaccumulation

Ethametsulfuron-methyl has a low Log Pow less than 4. As an experimental aquatic BCF is not available, RAC agrees with the DS that ethametsulfuron-methyl has a low potential for bioaccumulation.

Aquatic toxicity

Ethametsulfuron-methyl acute toxicity data are available for fish, invertebrates, algae and aquatic plants. Algae and aquatic plants are the most acutely sensitive trophic level with EC_{50} values below 1 mg/L. *Lemna* are the most sensitive species with a 7day ErC_{50} of 0.000808 mg a.s./L. RAC agrees that based on available and relevant data, ethametsulfuron-methyl should be classified for the environment as Aquatic Acute 1. Based on the duckweed endpoint between 0.0001 mg/L < EC_{50} ≤ 0.001 mg/L, an acute M-factor of 1000 is warranted.

For chronic toxicity, fish and invertebrate data are available with NOECs in the range 1-10 mg/L. Algae and aquatic plants are the most sensitive trophic level with NOEC values below 0.1 mg/L. *Lemna* is the most sensitive species with a 7-day NOErC of 0.000129 mg a.s./L.

Based on this data and given ethametsulfuron-methyl is not rapidly degradable, RAC considers that it should be classified for the environment as Aquatic Chronic 1. With a 0.0001 mg/L < NOEC ≤ 0.001 mg/L, a chronic M-factor of 100 is appropriate.

In conclusion, RAC agrees with the DS that ethametsulfuron-methyl should be classified as:

Aquatic Acute 1; H400, M = 1000

Aquatic Chronic 1; H410, M= 100.

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

No specific data available.

Ethemetsulfuron-methyl is a solid, with a corresponding extremely low vapour pressure. The boiling point exceeds 300 °C. Hence, it is unlikely that this substance would be available in the stratosphere.

Ethametsulfuron-methyl does not contain any halogen functionality.

12.1.2 Comparison with the CLP criteria

A substance is considered hazardous to the ozone layer 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.

Although no specific data have been provided for this hazard, considering the chemical structure and other available information on the physcio-chemcial properties, ethametsulfuron-methyl is not expected to be hazardous to stratospheric ozone.

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

Ethemetsulfuron-methyl is a solid, with a corresponding, extremely low vapour pressure. The boiling point exceeds 300 °C. Hence, it is unlikely that this substance would be available in the stratosphere. Ethametsulfuron-methyl does not contain any halogen functionality.

A substance is considered hazardous to the ozone layer 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.

Although no specific data have been provided for this hazard, considering the chemical structure and other available information on the physcio-chemcial properties, ethametsulfuron-methyl is not expected to be hazardous to stratospheric ozone.

Comments received during public consultation

One comment was received that "*Although no specific data have been provided for this hazard, considering the chemical structure and other available information on the physicochemical properties, ethametsulfuron-methyl is not expected to be hazardous to stratospheric ozone*".

Assessment and comparison with the classification criteria

RAC proposes no classification for hazards to the ozone layer.

13 ADDITIONAL LABELLING

Additional labelling is not required.

14 REFERENCES

A number of references have been removed for reasons of confidentiality. In the text, these are referred to as "Anonymous (YEARx)". Full details of these references can be found in the confidential annex for to this report (Annex III).

Further information relating to supporting supporting studies is also available in the REACH registration dossier, https://echa.europa.eu/registration-dossier/-/registered-dossier/20802; accessed 1st Nov 2018

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Dengler, D.	2009	Ethametsulfuron-methyl (DPX A7881) technical: Influence on growth and growth rate of the blue green alga Anabaena flos aquae (Cyanophyta). Eurofins GAB GmbH. Unpublished.	DuPont
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Porch, J.R., Kendall, T.Z., and Krueger, H.O.	2009	Ethametsulfuron-methyl (DPX A7881) technical: A 7 day static renewal toxicity test with duckweed (Lemna gibba G3). Wildlife International Ltd (USA). Unpublished.	DuPont
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Jagadish, B	2010	Ethametsulfuron methyl (DPX-A7881-074): Laboratory study of water solubility Sub Company : Owner Company : DU PONT (UK) LIMITED Report No : DuPont-27244 RV1 Date : 29/01/2010 GLP Status : yes	DuPont
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		Report No : DuPont-27242 Date : 01/02/2010 GLP Status : yes	
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Hoberg, J.R.	2010c	Ethametsulfuron-methyl (DPX A7881) technical effects on growth of the aquatic macrophyte Elodea Canadensis. Springborn Smithers Laboratories. Unpublished.	DuPont
Hoberg, J.R.	2010d	Ethametsulfuron-methyl (DPX A7881) technical effects on growth of the aquatic macrophyte Myriophyllum spicatum. Springborn Smithers Laboratories. Unpublished.	DuPont
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Arnie, J.R., Kendall, T.Z.,	2012a	Ethametsulfuron-methyl (DPX-A7881) technical: A 7-day, variable exposure duration toxicity test with duckweed (Lemna gibba G3). Wildlife International Ltd., Easton, Maryland, USA. Report No.:	DuPont

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15 ANNEXES

ANNEX I – Not provided. Both the EFSA Conlcusion and disseminated registration dossier are available in the public domain.

ANNEX II – Aquatic toxicity data for ethametsulfuron-methyl degradants

ANNEX III – Confidential References

ANNEX II – Aquatic toxicity data for ethametsulfuron-methyl degradants

Summary of relevant information on aquatic toxicity for ethametsulfuron methyl degradants

Degradant / Guideline / GLP	Species	Endpoint	Exposure		Results		Reference
			Design	Duration	Endpoint	Toxicity (mg/l)	
IN-A8768							
Daphnia magna Reproduction OECD Guideline 211 GLP, purity 95.5%	*Daphnia magna*	Mortality	Semi-static	21 days	NOEC	25 (mm)	Savers, 2010
Lemna sp. Growth Inhibition Test OECD 221, GLP, GLP, purity 96.9%	*Lemna gibba*	Cell multiplication inhibition	Static	7 days	E_rC_{50} frond number NOE_rC	13.59 (n) 1.58 (n) Analytical verification	Kuhl & Eicher, 2009a
IN-A9795							
Lemna sp. Growth Inhibition Test OECD 221, GLP, GLP, purity 98.3%	*Lemna gibba*	Cell multiplication inhibition	Static	7 days	E_rC_{50} frond number NOE_rC	>100 (n) 3.2 (n) Analytical verification	Kuhl & Eicher, 2010a
IN-N7468							
Lemna sp. Growth Inhibition Test OECD 221, GLP, GLP, purity 96.9%	*Lemna gibba*	Cell multiplication inhibition	Static	7 days	E_rC_{50} frond number NOE_rC	0.0128 (n) 0.00305 (n) Analytical verification	Kuhl & Eicher, 2010b
IN-N7469							
Lemna sp. Growth Inhibition Test OECD 221, GLP, GLP, purity 93%	*Lemna gibba*	Cell multiplication inhibition	Static	7 days	E_rC_{50} frond number NOE_rC	8.51 (n) 1.58 (n) Analytical verification	Kuhl & Eicher, 2009b
IN-D5119							
Lemna sp. Growth Inhibition Test OECD 221, GLP, GLP, purity 99.5%	*Lemna gibba*	Cell multiplication inhibition	Static	14 days	E_rC_{50} frond number NOE_rC	6.17 (n) ≤0.66 Effects at all concentrations Analytical verification	Sloman, 2000a
IN-D5803							

Lemna sp. Growth Inhibition Test OECD 221, GLP, GLP, purity 99.9%	*Lemna gibba*	Cell multiplication inhibition	Static	14 days	$E_rC_{50\ frond\ number}$ NOE_rC	>1.36 mg/l (mm) 0.16 (mm) mm based on geometric mean of initial concentration and LOQ at day 14 due to losses	Ward, Boeri and Wyskiel, 2004
IN-B9161							
Lemna sp. Growth Inhibition Test OECD 221, GLP, GLP, purity 95%	*Lemna gibba*	Cell multiplication inhibition	Static	7 days	$E_rC_{50\ frond\ number}$ NOE_rC	>25 (n) highest test concentration 25 (n) Analytical verification	Kuhl & Eicher, 2009c
IN-D7556							
Lemna sp. Growth Inhibition Test OECD 221, GLP, GLP, purity 99.6%	*Lemna gibba*	Cell multiplication inhibition	Static	7 days	$E_rC_{50\ frond\ number}$ NOE_rC	>100 (n) 10 (n) Analytical verification	Kuhl & Eicher, 2009d
IN-00581							
Lemna sp. Growth Inhibition Test OECD 221, GLP, GLP, purity 99.9%	*Lemna gibba*	Cell multiplication inhibition	Static	14 days	$E_rC_{50\ frond\ number}$ NOE_rC	5.48 (n) ≤0.625 (n) Effects at all concentrations Analytical verification	Sloman, 2000b
IN-RXR81							
Lemna sp. Growth Inhibition Test OECD 221, GLP, GLP, purity 99.3%	*Lemna gibba*	Cell multiplication inhibition	Semi-static	7 days	$E_rC_{50\ frond\ number}$ NOE_rC	>11 (mm) 2.6 (mm)	Arnie, Kendall and Krueger, 2000
IN-RYM15							
Lemna sp. Growth Inhibition Test OECD 221, GLP, GLP, purity 87.4%	*Lemna gibba*	Cell multiplication inhibition	Semi-static	7 days	$E_rC_{50\ frond\ number}$ $NOE_rC_{dry\ weight}$	>135 (mm) ≤8.7 (mm) Effects at all concentrations	Arnie, Kendall and Porch (2012b)

Notes:
'mm' refers to mean measured concentration
'n' refers to nominal concentration