Committee for Risk Assessment

RAC

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

Adopted

20 September 2019

20 September 2019

CLH-O-0000006714-71-01/F

OPINION OF THE COMMITTEE FOR RISK ASSESSMENT ON A DOSSIER PROPOSING HARMONISED CLASSIFICATION AND LABELLING AT EU LEVEL

In accordance with Article 37 (4) of Regulation (EC) No 1272/2008, the Classification, Labelling and Packaging (CLP) Regulation, the Committee for Risk Assessment (RAC) has adopted an opinion on the proposal for harmonised classification and labelling (CLH) of:

Chemical name: **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**

The proposal was submitted by the **United Kingdom** and received by RAC on **20 November 2018.**

In this opinion, all classification and labelling elements are given in accordance with the CLP Regulation.

PROCESS FOR ADOPTION OF THE OPINION

The United Kingdom has submitted a CLH dossier containing a proposal together with the justification and background information documented in a CLH report. The CLH report was made publicly available in accordance with the requirements of the CLP Regulation at ***http://echa.europa.eu/harmonised-classification-and-labelling-consultation/*** on **17 December 2018**. Concerned parties and Member State Competent Authorities (MSCA) were invited to submit comments and contributions by **1 March 2019**.

ADOPTION OF THE OPINION OF RAC

Rapporteur, appointed by RAC: **Miguel A. Sogorb**

Co-Rapporteur, appointed by RAC: **Laure Geoffroy**

The opinion takes into account the comments provided by MSCAs and concerned parties in accordance with Article 37(4) of the CLP Regulation and the comments received are compiled in Annex 2.

The RAC opinion on the proposed harmonised classification and labelling was adopted on **20 September 2019** by **consensus**.

Classification and labelling in accordance with the CLP Regulation (Regulation (EC) 1272/2008)

	Index No	Chemical name	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 current Annex VI entry										
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 = 1000 M = 100	
RAC opinion	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	
Resulting Annex VI entry if agreed by 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	

GROUNDS FOR ADOPTION OF THE OPINION

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.

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.**

HUMAN HEALTH HAZARD EVALUATION

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	Ethametsulfuron-methyl (purity = 96.4%)	LD_{50} >11000 mg/kg bw No deaths, clinical signs	Anonymous (1985a)

Single male and female Crl:CD®(SD)BR rats per dose	3400, 5000, 7500 or 11000 mg/kg bw	of toxicity, or findings of specific target organ toxicity were noted at doses of up to 1100 mg/kg bw	
Similar to OECD TG 401 Single male New Zealand White rabbit per dose	Ethametsulfuron-methyl (purity = 96.4%) 1500, 2200, 3400 or 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 doses of up to 5000 mg/kg bw	Anonymous (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.**

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).**

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.**

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 10 seconds after instillation)</u> 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	Anonymous (1991e)
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).**

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 5 females/group	Ethametsulfuron-methyl (purity 99.2%) 0, 5, 25, 50 and 75% in dimethylsulfoxide during 3 consecutive days Positive control: 25% hexylcinnamenaldehyde	Control and test animals: SI <3 Positive control: SI 4.47 **Conclusion: negative**	Anonymous (2008a)
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.**

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 %)	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)

0, 100, 300 and 1000 mg/kg bw/day Limit dose for warranting classification: 300 mg/kg bw/day		
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 Females: 0, 9.1, 85 and 453 mg/kg bw/day Limit dose for warranting classification: 100 mg/kg bw/day	No toxicologically significant changes observed at any dose level	Anonymous (1991k)
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	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)

classification: 12 mg/kg bw/day		
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 Limit dose for warranting classification: 100 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)
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	Anonymous (1991i)

	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	
90-days week oral diet Broadly consistent with OECD TG 409 Beagle dogs 4/sex/dose Ethametsulfuron-methyl (purity 95.6%) 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	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 (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.**

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	Anonymous (1991f)

		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. 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.**

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.**

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	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)

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 25/group Ethametsulfuron-methyl (purity 96.8%) 0, 60, 250, 1,000 or 4000 mg/kg bw /day on days 7-16 of gestation <u>Vehicle: methylcellulose</u>	<u>Dams</u> No mortalities were observed 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 <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	Anonymous (1991l)
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>	Anonymous (1991m)

	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

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.**

ENVIRONMENTAL HAZARD EVALUATION

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	Reference
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 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	Valid	Reibach, 2010
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*)	Ethametsulfuronm ethyl (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 (2010a)
Reproduction OECD TG 211, GLP Reliability 1*	*Daphnia magna*	Ethametsulfuronm ethyl (100%)	21d NOEC 4.7 mg a.s./L (mm) based on survival	Minderhout, Kendall and Krueger (2010)
Freshwater Algal Growth Inhibition OECD TG 201, GLP Reliability 1*	*Pseudokirchneriella subcapitata**	Ethametsulfuronm ethyl (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*	Ethametsulfuronm ethyl (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 and Krueger, 2009b**
Growth Inhibition, GLP	*Vallisneria americana*	Ethametsulfuronm ethyl (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.

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.

ANNEXES:

Annex 1 The Background Document (BD) gives the detailed scientific grounds for the opinion. The BD is based on the CLH report prepared by the Dossier Submitter; the evaluation performed by RAC is contained in 'RAC boxes'.

Annex 2 Comments received on the CLH report, response to comments provided by the Dossier Submitter and RAC (excluding confidential information).