Committee for Risk Assessment

RAC

Opinion

proposing harmonised classification and labelling
at EU level of

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

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

CLH-O-0000006964-62-01/F

Adopted

18 March 2021

18 March 2021

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

EC Number: **-**

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

The proposal was submitted by **Finland** and received by RAC on **12 February 2020.**

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

PROCESS FOR ADOPTION OF THE OPINION

Finland 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 **23 March 2020**. Concerned parties and Member State Competent Authorities (MSCA) were invited to submit comments and contributions by **22 May 2020**.

ADOPTION OF THE OPINION OF RAC

Rapporteur, appointed by RAC: **Nathalie Printemps**

Co-Rapporteur, appointed by RAC: **Anja Menard Srpčič**

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 **18 March 2021** 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	foramsulfuron (ISO); 2-{[(4,6-dimethoxypyrimidin-2-yl)carbamoyl]sulfamoyl}-4-formamido-N,N-dimethylbenzamide; 1-(4,6-dimethoxypyrimidin-2-yl)-3-(2-dimethylcarbamoyl-5-formamidophenylsulfonyl) urea	-	173159-57-4	Carc. 2 Aquatic Acute 1 Aquatic Chronic 1	H351 H400 H410	GHS08 GHS09 Wng	H351 H410		M=1000 M=100	
RAC opinion	tbd	foramsulfuron (ISO); 2-{[(4,6-dimethoxypyrimidin-2-yl)carbamoyl]sulfamoyl}-4-formamido-N,N-dimethylbenzamide; 1-(4,6-dimethoxypyrimidin-2-yl)-3-(2-dimethylcarbamoyl-5-formamidophenylsulfonyl) urea	-	173159-57-4	Carc. 2 Aquatic Acute 1 Aquatic Chronic 1	H351 H400 H410	GHS08 GHS09 Wng	H351 H410		M=1000 M=100	
Resulting Annex VI entry if agreed by COM	tbd	foramsulfuron (ISO); 2-{[(4,6-dimethoxypyrimidin-2-yl)carbamoyl]sulfamoyl}-4-formamido-N,N-dimethylbenzamide; 1-(4,6-dimethoxypyrimidin-2-yl)-3-(2-dimethylcarbamoyl-5-formamidophenylsulfonyl) urea	-	173159-57-4	Carc. 2 Aquatic Acute 1 Aquatic Chronic 1	H351 H400 H410	GHS08 GHS09 Wng	H351 H410		M=1000 M=100	

GROUNDS FOR ADOPTION OF THE OPINION

RAC general comment

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

RAC evaluation of physical hazards

Summary of the Dossier Submitter's proposal

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

Explosives

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

Flammable solids

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

Self-reactive substances

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

Pyrophosphoric solids

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

Self-heating substances

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

Substances which in contact with water emit flammable gases

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

Oxidising solids

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

Corrosive to metals

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

Comments received during consultation

One industry representative supported the DS's proposal.

Assessment and comparison with the classification criteria

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

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

HUMAN HEALTH HAZARD EVALUATION

RAC evaluation of acute toxicity

Summary of the Dossier Submitter's proposal

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

Comments received during consultation

One industry representative agreed with the DS's proposal.

Assessment and comparison with the classification criteria

Acute toxicity: oral

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

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

Acute toxicity: inhalation

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

Acute toxicity: dermal

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

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

Summary of the Dossier Submitter's proposal

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

Comments received during consultation

One industry representative agreed with the DS's proposal.

Assessment and comparison with the classification criteria

There was no relevant human data in the dossier. In the acute inhalation toxicity study, clinical signs suggesting respiratory tract irritation such as occasional increase or decrease respiration and red/brown staining around the eyes, snout or head were observed in several animals. These clinical signs were reversible by day 1 and no abnormalities were observed at necropsy. As the substance is a solid, the mechanical effect of solid particles may have contributed to the irritation

observed. The substance was without irritant effect in the eyes or the skin of rabbits. No gross pathological findings in the lung were observed at necropsy. Therefore, RAC agrees with the DS's proposal not to classify foramsulfuron STOT SE 3 for respiratory tract irritation.

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

RAC evaluation of skin corrosion/irritation

Summary of the Dossier Submitter's proposal

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

Comments received during consultation

One industry representative agreed with the DS's proposal.

Assessment and comparison with the classification criteria

Irritation/corrosivity was tested in an *in vivo* rabbit study, conducted according to OECD TG 404 (GLP-compliant). In this study, no dermal reactions were seen in 6 animals after 4-h exposure (foramsulfuron moistened with water) under semi-occlusive conditions. The slight erythema noted in 2 out of 10 animals in the dermal acute toxicity study in rats was fully reversible on day 2 of the study. RAC agrees with the DS that **foramsulfuron does not meet the CLP criteria for skin corrosion/irritation and no classification is warranted**.

RAC evaluation of serious eye damage/irritation

Summary of the Dossier Submitter's proposal

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

Comments received during consultation

One industry representative agreed with the DS's proposal.

Assessment and comparison with the classification criteria

An eye irritation study, conducted according to OECD TG 405 (GLP-compliant), was performed in 7 rabbits including a screen animal and a pilot animal. In a screened rabbit, foramsulfuron was instilled into one eye that was rinsed for 30 seconds with distilled water 30 seconds after instillation. As this did not cause any severe reaction, the treated eye of the pilot animal was not rinsed. The other five animals were treated as the pilot rabbit; i.e. the treated eyes were not rinsed. The mean scores for 24-72 h in the six rabbits (eyes unrinsed) were:

- 0 in all six rabbits for corneal opacity and iritis,

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

All the eye effects were resolved 48h post instillation.

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

RAC evaluation of skin sensitisation

Summary of the Dossier Submitter's proposal

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

Comments received during consultation

One industry representative agreed with the DS's proposal.

Assessment and comparison with the classification criteria

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

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

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

Summary of the Dossier Submitter's proposal

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

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

Comments received during consultation

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

Assessment and comparison with the classification criteria

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

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

RAC evaluation of germ cell mutagenicity

Summary of the Dossier Submitter's proposal

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

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

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

Comments received during consultation

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

Assessment and comparison with the classification criteria

In vitro data

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

Foramsulfuron was negative in an *in vitro* gene mutation assay in mammalian cells, conducted according to OECD TG 476.

With regard to the *in vitro* chromosomal aberration study in human lymphocytes, the study was similar to OECD TG 473 but no short-term exposure was performed without S9 mix. As noted by the DS, this is not considered to be a major limitation as a long-term treatment was performed. At the top dose of 2400 µg/l, some precipitation was noted at 21-h harvest. At this dose, an increase in aberrant cells excluding gaps was noted and repeated in three out of four assays (21h or 45h harvest times). RAC considers that cytotoxicity was not high at this dose; a reduction of about 50 percent of cell growth was not exceeded. The increase was slightly above the historical control data. Nevertheless, according to the DS, the historical control data may not be reliable due to missing information on the underlying studies. Overall, RAC considers the assay positive in the absence of S9 mix and negative in the presence of metabolic activation.

In vivo data

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

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

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

There was also limited evidence of systemic toxicity:

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

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

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

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

RAC evaluation of carcinogenicity

Summary of the Dossier Submitter's proposal

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

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

- Increased incidence of malignant astrocytoma in both sexes,

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

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

Comments received during consultation

One MSCA agreed with the DS's proposal.

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

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

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

Assessment and comparison with the classification criteria

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

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

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

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

Astrocytoma

An increased incidence of malignant astrocytoma (brain + spinal cord) was observed in both male and female rats. Brain and spinal cord astrocytomas at interim and terminal kills are reported in

the tables below. No other findings in brain were seen in the chronic study. RAC notes that pre-neoplastic findings for this type of tumours may not be seen.

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

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

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

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

Statistical significance and dose-response relationship

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

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

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

Comparison with historical control data (HCD)

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

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

HCD from the laboratory compiled the results of nine studies conducted between 1982 and 1998 with the same strain of rat, including the current study (2000, M-193439-01-1). As a 5-year period before the conduct of the study was considered as the most relevant time range, the DS considered the values obtained in four studies conducted before the current study (1995-1998), studies 6 to 9 in the table below, as valid. RAC agrees that studies 6-8 are relevant HCD studies, but excludes the current study from the HCD and considers two additional studies performed between 1990-1992 as relevant HCD studies because they almost fit within the five-year range before the conduct of the present study. Still, RAC notes that the HCD are limited as only 5 studies are considered relevant. Brain astrocytomas were not seen in these relevant HCD studies,

but they were only seen in one study of the laboratory conducted during years 1982-1984 (see the table below). Spinal cord astrocytomas were not reported.

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

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

Grey: data considered relevant for the present study

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

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

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

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

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

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

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

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

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

Age at tumour detection and survival

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

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

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

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

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

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

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

Thyroid follicular and c cell tumours

Thyroid follicular cell tumours

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

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

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

In males, an increase in thyroid follicular cell adenomas at the top dose was observed above the historical control data range. The increase was not statistically significant and no dose-response was noted. Although of lower relevance, the incidence was inside the HCD range considering data

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

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

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

C-cell tumours

As regards c-cell tumours, an increase in adenomas was noted in males above the HCD range at 100, 6000 and 12000 ppm. Nevertheless, no dose-response was noted and the increase was not statistically significant, as shown in the table below. However, the control values of the study were slightly above the historical control data range. In view of the high background incidence in this strain of rats and the absence of statistical significance, the increase in c-cell adenomas in male rats is considered of uncertain toxicological relevance. As to the increase in carcinoma at 600 and 20000 ppm, the absence of dose-response and preneoplastic finding also raised uncertainties on their toxicological relevance.

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

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

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

Malignant lymphoma

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

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

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

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

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

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

Mode of action and relevance to human

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

The toxicokinetic data on foramsulfuron indicates that foramsulfuron levels in male and female rat blood, plasma, brain and thyroid are low. Nevertheless, in the study KCA 5.1.1/06 (1999) with a 14-day exposure at a low dose (10 mg/kg bw/day), more than 3-fold increase in residue levels was found in thyroid and brain of males suggesting a potential exposure of these organs. In this study, male rats showed higher brain and thyroid levels of foramsulfuron than females and may therefore be more sensitive for a tumorigenic effect on astrocytes or thyroid cells. This was not clear in this carcinogenicity study. Nevertheless, as highlighted by the DS, RAC notes that toxicokinetic data were not available following repeated-dose exposure at high dose levels.

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

Structural similarity

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

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

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

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

Compounds	**Evidence of carcinogenic potential**
Bensulfuron, Ethamethsulfuron-methyl, halosulfuron, mesosulfuron-methyl, metsulfuron-methyl, rimsulfuron, triasulfuron	None
Chlorsulfuron	↑ Leydig cell tumours in rats

Prosulfuron	↑ Leydig cell tumours and mammary gland adenoma in rats
Trisulfuron-methyl	↑ Leydig cell adenoma in rats
Sulfosulfuron	↑ Transitional cell carcinoma and papilloma in female rats (low incidences) at the top dose. ↑ mesenchymal tumours in the urinary bladder of male mice at highest doses
Thifensulfuron-methyl	↑ Total tumour incidences (mainly due to mammary gland tumours) in female rats
Nicosulfuron	↑ liver adenoma in male mice

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

RAC agrees with industry that there is not one clear pattern of carcinogenicity for all sulfonylureas. Moreover, no increase in incidences of brain, thyroid or lymphatic system tumours were reported for other sulfonylureas based on the analysis by industry representatives.

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

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

Comparison with criteria

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

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

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

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

RAC evaluation of reproductive toxicity

Summary of the Dossier Submitter's proposal

Sexual function and fertility

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

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

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

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

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

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

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

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

Developmental toxicity

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

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

In the rabbit range-finding study, one high dose dam had 6 slightly small foetuses. Two foetuses of another high dose dam showed bent forepaws. As only few animals were exposed per group

(4 mated females/dose), the DS considered this finding of unclear toxicological significance. In the main rabbit developmental toxicity study, foramsulfuron was not toxic to development.

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

Overall, the DS proposed no classification for developmental toxicity.

Adverse effects on or via lactation

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

Comments received during consultation

One industry representative supported the DS's proposal.

Assessment and comparison with the classification criteria

Sexual function and fertility

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

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

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

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

Developmental toxicity

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

Adverse effects on or via lactation

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

RAC evaluation of aspiration toxicity

Summary of the Dossier Submitter's proposal

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

Comments received during consultation

One industry representative agreed with the DS's proposal.

Assessment and comparison with the classification criteria

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

ENVIRONMENTAL HAZARD EVALUATION

RAC evaluation of aquatic hazards (acute and chronic)

Summary of the Dossier Submitter's proposal

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

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

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

Degradation

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

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

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

No ready biodegradation test is available for foramsulfuron.

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

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

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

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

Bioaccumulation

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

Aquatic Toxicity

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

Acute toxicity

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

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

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

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

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

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

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

Chronic toxicity

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

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

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

Four chronic toxicity studies with four different algae species and six studies with different plant species were available using foramsulfuron. The blue-green alga *Anabaena flos-aquae* was the most sensitive species tested in algae chronic studies, with a nominal 96-h NOE_rC of < 2.6 mg/L. The most sensitive plant species tested was duck weed *Lemna gibba*. From the different studies performed with *Lemna gibba* the following most relevant values were derived, a nominal 7-d

NOEC of 0.36 µg/L (biomass and growth rate) and nominal 7-d E_rC_{10} of 0.125 µg/L (growth rate and frond number). There are other studies on the foramsulfuron (97.3 % purity) that derive toxicities within the same range. No significant toxicity for *Lemna gibba* was observed for any other degradant than for F130619. The toxicity of degradant F130619 (7d-NOE_rC of 0.179 µg/L) was within a similar order of magnitude as for foramsulfuron.

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

Comments received during consultation

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

Assessment and comparison with the classification criteria

Degradation

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

- Foramsulfuron undergoes hydrolysis which is pH dependant. Hydrolysis DT_{50} values are 3.7 day (pH 4), 10.1 day (pH 5), 128 day (pH 7) and 132 day (pH 9) at 25°C. Two main degradants were found, AE F092944 and AE F153745. Data on hydrolysis might be considered for classification purposes only when the longest half-life determined within the pH range 4-9 is less than 16 days (corresponding to a degradation of > 70 % within 28 days). Accordingly, foramsulfuron is hydrolytically stable. Furthermore, according to DS the minor hydrolysis product AE F130619 (<10 % AR) fulfils the criteria for classification as hazardous to the aquatic environment.
- There was no ready biodegradability study available.
- In the surface water simulation test no degradation was observed and mineralisation was negligible.
- The half-life in the total system in a water/sediment system study was 26.0 - 28.7 days (silty clay loam sediment) and 37.9 - 41.4 days (sand sediment). Low mineralization was observed (6.2 %). Two main degradants were formed, namely AE 0338795 and AE F153745.

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

Bioaccumulation

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

Aquatic toxicity

RAC is of the opinion that reliable acute and long-term toxicity data for foramsulfuron are available for fish, invertebrates, algae and aquatic plants and also agrees with using the nominal values, as these values were analytically verified. RAC agrees with the DS to use the endpoint

based on growth rate reduction for algae and aquatic plants as this is in line with the current CLP Guidance (Version 5.0, July 2017).

Acute toxicity

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

Chronic toxicity

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

RAC evaluation of hazards to the ozone layer

Summary of the Dossier Submitter's proposal

The degradation of the substance in the atmosphere was calculated by the software AOPWIN. Foramsulfuron is not expected to remain stable in the air (half-life of 0.07 days in maximum). Due to its low half-life in the atmosphere combined with a low vapour pressure (4.2×10^{-11} Pa at 20 °C) indicating non-volatility and resulting in a low value for the Henry's Law constant (5.8×10^{-12} Pa m^3/mole at 20 °C), foramsulfuron is considered not to be subject to transport via air or cause hazard to ozone layer.

Comments received during consultation

One Member State and one company-manufacturer provided public comments, and both agreed with the DS proposal not to classify the substance as hazardous to the ozone layer.

Assessment and comparison with the classification criteria

Atmospheric transport of foramsulfuron in is considered to be negligible due to its low vapor pressure and Henry´s Law constant, whilst its photodegradation in air is expected to be rapid. Therefore, exposure of ozone to foramsulfuron is expected to be negligible.

Thus, RAC agrees with the DS´s proposal that **no classification is warranted for hazards to the ozone layer.**

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).