COMMENTS AND RESPONSE TO COMMENTS ON CLH: PROPOSAL AND JUSTIFICATION

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Substance name: ethametsulfuron-methyl (ISO); methyl 2-({[4-ethoxy-6-(methylamino)-1,3,5-triazin-2-yl]carbamoyl}sulfamoyl)benzoate
CAS number: 97780-06-8
EC number: -
Dossier submitter: United Kingdom

CARCINOGENICITY

Date	Country	Organisation	Type of Organisation	Comment number
01.03.2019	Spain		MemberState	1
Comment received				
The Spanish CA agrees with the dossier submitter that there was no treatment-related increase in tumour incidence (including in the mammary gland observed in rat) and therefore, ethametsulfuron-methyl does not meet the criteria for classification for carcinogenicity.				

Date	Country	Organisation	Type of Organisation	Comment number
25.02.2019	United States	FMC Corporation	Company-Manufacturer	2
Comment received				
The carcinogenic potential of ethametsulfuron-methyl has been investigated in standard studies in rats and mice. No evidence of tumour induction was observed in any tissue for either species or gender. The applicant agrees with the RMS that ethametsulfuron-methyl does not meet the classification criteria for carcinogenicity.				

Date	Country	Organisation	Type of Organisation	Comment number
20.02.2019	Germany		MemberState	3
Comment received				
We agree to the DS proposal.				

Date	Country	Organisation	Type of Organisation	Comment number
27.02.2019	Sweden		MemberState	4
Comment received				
The section on carcinogenicity in the CLH report is very brief. Considering that there were no differences with respect to mortality, food consumption, body weight or body weight gain between treated animals and controls in the rat study, it may be discussed if dose levels selected were too low for a carcinogenicity study.				

MUTAGENICITY

Date	Country	Organisation	Type of Organisation	Comment number
25.02.2019	United States	FMC Corporation	Company-Manufacturer	5
Comment received				
The genotoxicity potential of ethametsulfuron-methyl has been investigated in standard in vitro and in vivo studies. Negative responses were observed in vitro in bacterial and mammalian cell culture systems, and in vivo in mice. No evidence of genotoxicity was observed. The applicant agrees with the RMS that ethametsulfuron-methyl does not meet the classification criteria for germ-cell mutagenicity.				

Date	Country	Organisation	Type of Organisation	Comment number
20.02.2019	Germany		MemberState	6
Comment received				
Inconclusive. No classification of the substance is needed on the basis of available studies but there is data lacking. Justification Regarding the data provided by the DS DAR and CLH report, several deviations from the test guideline for the bacterial reverse mutation test were confirmed. In the submitted Ames test, only four Salmonella Typhimurium strains were used and a test with either Salmonella Typhimurium TA102 or an appropriate E. coli strain was not conducted. Accordingly, the endpoint for ROS induced genotoxicity was not assessed. Although the test results were negative for all other genotoxicity studies conducted, the database is still considered as insufficient for a classification on genotoxicity.				

Date	Country	Organisation	Type of Organisation	Comment number
27.02.2019	Sweden		MemberState	7
Comment received				
Neither the CLH report nor annex I contain a presentation of results (frequencies etc) in the in vitro and in vivo tests. Consequently, the reviewer must rely on the DS and an independent assessment of this endpoint cannot be made.				

TOXICITY TO REPRODUCTION

Date	Country	Organisation	Type of Organisation	Comment number
01.03.2019	Spain		MemberState	8
Comment received				
Fertility No adverse effects on fertility have been observed. Therefore no classification is warranted for sexual function and fertility. Development Ethametsulfuron-methyl did not induce any structural or visceral malformations/variations in standard studies conducted in rats or rabbits. A small increase in early resorptions was observed in the absence of marked maternal toxicity at doses of up to 1000 mg/kg/day in a standard rabbit developmental toxicity study. However, in a second rabbit developmental toxicity study, specifically conducted to investigate pre/post implantation loss, the incidence of early resorptions was comparable				

between treated and control groups up to 1000 mg/kg/day, the highest dose tested. There were no other treatment-related effects on late resorptions, or visceral malformations/variations. We agreed with the dossier submitter that the failure to confirm the increase in early resorptions in a second study in the same strain of rabbit, even at the limit dose of 1000 mg/kg/day reduces concern that the late resorptions observed in the first rabbit study are treatment-related. Besides, similar changes were not observed in rats. Therefore, it can be concluded that ethametsulfuron-methyl is not a developmental toxicant and No classification is required.

Date	Country	Organisation	Type of Organisation	Comment number
25.02.2019	United States	FMC Corporation	Company-Manufacturer	9

Comment received

Reproductive effects
No toxicologically significant adverse effects on sexual function or fertility were observed in male or female parental rats in either a one-generation reproduction pilot study or in the two-generation reproduction study. In addition, no test-substance-related effects on litter size, pup survival, pup growth and development, and clinical observations were observed in either study. The applicant agrees with the RMS that ethametsulfuron-methyl does not meet the classification criteria for sexual function and fertility.
Developmental Effects
Ethametsulfuron-methyl did not induce any structural or visceral malformations or variations in rat and rabbit developmental studies. In the original rabbit developmental study, a slight increase in early resorptions were observed. However, this observation was not confirmed in a second study in which ethametsulfuron-methyl was administered to the same rabbit strain at the limit dose of 1000 mg/kg/day for the gestation period of GD 7-28, which was 9 days longer than the dosing period in the original study. The applicant agrees with the RMS that no effects were observed in these studies that meet the requirements for classification.

Date	Country	Organisation	Type of Organisation	Comment number
20.02.2019	Germany		MemberState	10

Comment received

Classification as reproductive toxicant in Category 2 with hazard statement H361d is suggested.
Justification
In the developmental toxicity study in the rabbit, an increase in the number and percentage of total and early resorptions per litter was observed at all dose levels. The resorption rate exceeded the historical control range. In addition, heart and heart vessels malformations were seen in two foetuses in two different litters at a dose level of 250 mg/kg bw/day. Even though no dose response was obvious, this finding is of concern since it is rare and was clearly above the historical control range.
Unfortunately, no meaningful evaluation of resorption rate or malformations was feasible in the highest dose group receiving 4000 mg/kg bw/day. Due to excessive toxicity with maternal deaths and abortions, the number of litters and foetuses was too small. Therefore, we can rely only on what observed at the low and mid dose levels.
Based on a higher resorption rate in both dose groups and supported by the potentially

teratogenic findings in the low dose group, classification for developmental toxicity should be at least considered. According to the ”Guidance on the application of the CLP Criteria”, developmental effects which occur in the presence of maternal toxicity (as it is the case here) must not be ignored but might result in a less severe classification. On balance, we think that Category 2 would be appropriate.

In its 2014 conclusion on the substance the EFSA also proposed classification Repr 2.

There is new data in the CLH report coming from a follow-up study in which no significant increase in resorptions and no heart malformations were observed up to 1000 mg/kg bw/day. Unfortunately, this study was not guideline-compliant because only a small number of animals were used (10 rabbits instead of 20 per dose group). According to the OECD TG 414, groups with fewer than 16 female animals may be inappropriate to evaluate the developmental toxicity. In addition, the rate of resorptions was rather high (in particular when compared to the previous study) in nearly all groups including the concurrent control but was highest at the top dose level (i.e., 5.9 total resorptions/litter at 1000 mg/kg bw/day as compared to 3.4 in the controls).
Regarding its limitations it is questionable whether the negative results obtained in this study should be used to weaken the findings of the standard study.
The presented time frame (2006-2017) for historical controls for late resorptions in the study Anonymous 2018 is too broad. The time frame should contain only data of the last five years in this case.

Date	Country	Organisation	Type of Organisation	Comment number
27.02.2019	Sweden		MemberState	11
Comment received				
The developmental study in rabbits performed in 2018 to follow up the findings in the 1991 study did not show the increased frequency of early resorptions clearly shown in the first study. However, the follow-up study was a non-standard study performed with only 10 dams/group in contrast to the 1991 study which was performed according to OECD 414 (1983) with 22 dams/group. Therefore, we do not consider the results from the new study to overrule the findings in the first. The increase in resorptions in the 1991 study occurred at doses where also a reduced bodyweight gain was observed. In the absence of further information, it is not possible to assess if the effects were restricted to outliers with severely reduced bodyweight gains. Nevertheless, according to HCD, early resorptions are rare events in rabbits and the CLP states “In rabbits, the body weight gain may not be useful indicators of maternal toxicity because of normal fluctuations in body weight during pregnancy.” Therefore, we do not find it safe to exclude that the early resorptions observed in rabbits may be related to treatment and we suggest that classification in category 2 should be considered by RAC.				

Date	Country	Organisation	Type of Organisation	Comment number
20.02.2019	Netherlands		MemberState	12
Comment received				
Reproductive toxicity The NL CA agrees with the proposed ‘no classification’ for adverse effects on sexual function and fertility and the ‘no classification’ for adverse effects on/via lactation. With respect to adverse effects on developmental toxicity, the following is noted.				

In a rat developmental study, up to 1000 mg/kg/day no statistical significant developmental effects were observed (NOAEL 1000 mg/kg/day). We agree with the Dossier Submitter that the findings in rat do not warrant classification of ethametsulfuron-methyl for developmental toxicity.
However, based on the effects observed in the 1991 rabbit study (as mentioned in CLH report as "Anonymous (1991m)" in table 27, page 27), a concern for developmental toxicity was raised by EFSA and they suggested that a classification as reproductive toxicant, category 2 (H361d) may be required (EFSA Journal 2014;12(7):3787). In the EFSA report, it is stated that, in addition to reduced number of live foetuses and increased resorptions, also an increase in heart-related malformations from 250 mg/kg/day on is observed which is not specifically mentioned in the CLH report. The Dossier Submitter is requested to clarify this issue and to discuss the relevance of these findings with respect to classification for developmental toxicity. As the EFSA report is from 2014, the non-standard follow-up study is not included in their conclusion.

OTHER HAZARDS AND ENDPOINTS – Acute Toxicity

Date	Country	Organisation	Type of Organisation	Comment number
25.02.2019	United States	FMC Corporation	Company-Manufacturer	13
Comment received				
The oral LD50 of >5000 mg/kg bw for rats is above the value for classification, the dermal LD50 of >2000 mg/kg in rats and rabbits is above the value for classification, and the inhalation LC50 of >5.7 mg/L in rats is above the value for classification. The applicant agrees with the RMS that these values do not meet the criteria for classification.				

OTHER HAZARDS AND ENDPOINTS – Skin Hazard

Date	Country	Organisation	Type of Organisation	Comment number
25.02.2019	United States	FMC Corporation	Company-Manufacturer	14
Comment received				
No evidence of skin irritation was observed in two separate rabbit studies. The applicant agrees with the RMS that these results do not meet the criteria for classification.				

OTHER HAZARDS AND ENDPOINTS – Eye Hazard

Date	Country	Organisation	Type of Organisation	Comment number
01.03.2019	Spain		MemberState	15
Comment received				
Based on the observed corneal opacity with a score of ≥ 1 in 4/6 animals in the unwashed group of the rabbits study (Anonymous, 1991e) the Spanish CA supports the dossier submitter proposal to classify ethametsulfuron-methyl as Eye Irritation 2: H319 – 'Causes serious eye irritation'.				

Date	Country	Organisation	Type of Organisation	Comment number
25.02.2019	United States	FMC Corporation	Company-Manufacturer	16
Comment received				
Ethametsulfuron-methyl caused reversible eye irritation (with a score of >1 for corneal opacity in 4 of 6 animals in the unwashed group and 2 of 3 animals in the washed group. All irritation reversed by observation day 10. The applicant agrees with the RMS that the				

observations meet the classification criteria for Category 2 (H319 “causes serious eye irritation”).

Date	Country	Organisation	Type of Organisation	Comment number
20.02.2019	Germany		MemberState	17
Comment received				
The proposal for classification with Eye Irrit. 2 is supported based on cornea effects that were fully reversible after at maximum 10 days in the study Anonymous 1991e.				

OTHER HAZARDS AND ENDPOINTS – Skin Sensitisation Hazard

Date	Country	Organisation	Type of Organisation	Comment number
25.02.2019	United States	FMC Corporation	Company-Manufacturer	18
Comment received				
Skin sensitization was investigated in a LLNA study in mice, and in two Buehler assays in guinea pigs. No positive responses were noted in any assay. The applicant agrees with the RMS that ethametsulfuron-methyl does not meet the requirements for classification.				

OTHER HAZARDS AND ENDPOINTS – Specific Target Organ Toxicity Single Exposure

Date	Country	Organisation	Type of Organisation	Comment number
25.02.2019	United States	FMC Corporation	Company-Manufacturer	19
Comment received				
No deaths, clinical signs of toxicity, respiratory tract irritation, narcotic effects, or other findings of specific target organ toxicity were noted in any of the acute toxicity studies for any relevant route of exposure. The applicant agrees with the RMS that there are no observations that meet the criteria for classification for specific target organ toxicity.				

OTHER HAZARDS AND ENDPOINTS – Specific Target Organ Toxicity Repeated Exposure

Date	Country	Organisation	Type of Organisation	Comment number
25.02.2019	United States	FMC Corporation	Company-Manufacturer	20
Comment received				
The repeated dose toxicity of ethametsulfuron-methyl has been evaluated in 90-day studies in rats, mice, and dogs, lifetime studies in rats and mice, and in a one-year dog study. Increased absolute and relative spleen weights observed in male mice at 3.5 mg/kg/day and above in the 2-year mouse study did not correlate with any functional or microscopic changes, and therefore did not meet the criteria for classification. The applicant agrees with the RMS that none of the observations in these studies meets the classification criteria for STOT-RE.				

Date	Country	Organisation	Type of Organisation	Comment number
01.03.2019	Spain		MemberState	21
Comment received				
The only treatment-related change observed at or below any repeated dose classification guidance value was a statistically significant increase in absolute and relative spleen weights				

in male mice at a dose of 3.5 mg/kg/day and above in a lifetime oral dosing study. There were no supporting histopathological changes, or clinical chemistry/haematology findings to suggest that the spleen function was perturbed. Therefore, although dose-related, the lack of evidence of perturbed spleen function in mice, and absence of similar changes in standard studies in rats or dogs reduces the overall level of concern. The Spanish CA agreed with the dossier submitter that no classification for STOT-RE is required.

OTHER HAZARDS AND ENDPOINTS – Hazardous to the Aquatic Environment

Date	Country	Organisation	Type of Organisation	Comment number
25.02.2019	United States	FMC Corporation	Company-Manufacturer	22
Comment received				
Ethametsulfuron-methyl should be classified for the environment as Aquatic Acute 1 with an acute M-factor of 1000 based on Lemna ErC50 data in the range 0.0001 mg/l < EC50 ≤ 0.001 mg/l. The applicant agrees with the RMS conclusion that Ethametsulfuron-methyl is not a rapidly degradable compound. Ethametsulfuron-methyl and should be classified for the environment as Aquatic Chronic 1 with a chronic M-factor of 100 based on Lemna NOEC data in the range 0.0001 mg/l < NOEC ≤ 0.001 mg/l.				

Date	Country	Organisation	Type of Organisation	Comment number
20.02.2019	Netherlands		MemberState	23
Comment received				
Agreed to base the aquatic classifications on the selected effect concentrations obtained for Lemna gibba and agreed with the proposed Aquatic Acute 1 (M=1000) and Aquatic Chronic 1 (M=100) classifications.				

Date	Country	Organisation	Type of Organisation	Comment number
20.02.2019	Germany		MemberState	24
Comment received				
Page 39, point 11.1 Rapid degradability of organic substances, Table 29: As stated under point 11.1.4.3 the study by Sarff (2010) was according to the Method described in OECD 308 and not OECD 309. The study is therefore not a "freshwater aquatic biodegradation simulation study" but an “aerobic sediment/water study”. Please correct the stated method for this study in the Table 29. Page 42; 11.1.4.3 Water, water-sediment and soil degradation data (including simulation studies): The study by Sarff (2010) was conducted according to OECD 308 and is therefore an aerobic sediment/water study and not a freshwater aquatic biodegradation simulation study. Please correct the study-type. Page 48, point 11.5.3 Acute toxicity to algae or other aquatic plants (Table 34): Actually the EC50 (shoot length, 10 days) is > 23 mg a.s./L (mm) instead of 0.23 mg as./L for the aquatic macrophyte Myriophyllum spicatum (Hoberg, 2010c). But there is no influence on classification and labelling as Aquatic acute 1 and M-factor of 1000, because the relevant study is the study with Lemna gibba (Porch et al., 2009) with				

ErC50 (7 days) of 0.000808 mg a.s./L (mm).

Date	Country	Organisation	Type of Organisation	Comment number
01.03.2019	France		MemberState	25
Comment received				
FR agrees with the classification proposal and the M factors (acute and chronic) proposed in the CLH report.				

OTHER HAZARDS AND ENDPOINTS – Hazardous to the Ozone Layer

Date	Country	Organisation	Type of Organisation	Comment number
25.02.2019	United States	FMC Corporation	Company-Manufacturer	26
Comment received				
Agree with RMS. 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.				

OTHER HAZARDS AND ENDPOINTS – Physical Hazards

Date	Country	Organisation	Type of Organisation	Comment number
25.02.2019	United States	FMC Corporation	Company-Manufacturer	27
Comment received				
Sufficient study data is available to assess the potential physical hazards of Ethametsulfuron-methyl. The compound is a solid that exhibits no evidence of explosive, flammability, self-reactive, pyrophoric or oxidative hazards. The applicant agrees with the RMS that ethametsulfuron-methyl does not meet the classification criteria for any physical hazards.				