Committee for Risk Assessment

RAC

Annex 2

Response to comments document (RCOM)

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

halosulfuron-methyl (ISO); methyl 3-chloro-5-{[(4,6-dimethoxypyrimidin-2-yl)carbamoyl]sulfamoyl}-1-methyl-1H-pyrazole-4-carboxylate

EC Number: -
CAS Number: 100784-20-1

CLH-O-0000001412-86-182/F

Adopted
22 September 2017

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON HALOSULFURON-METHYL (ISO); METHYL 3-CHLORO-5-{[(4,6-DIMETHOXYPYRIMIDIN-2-YL)CARBAMOYL]SULFAMOYL}-1-METHYL-1H-PYRAZOLE-4-CARBOXYLATE

COMMENTS AND RESPONSE TO COMMENTS ON CLH: PROPOSAL AND JUSTIFICATION

Comments provided during public consultation are made available in the table below as submitted through the web form. Any attachments received are referred to in this table and listed underneath, or have been copied directly into the table.

All comments and attachments including confidential information received during the public consultation have been provided in full to the dossier submitter (Member State Competent Authority), the Committees and to the European Commission. Non-confidential attachments that have not been copied into the table directly are published after the public consultation and are also published together with the opinion (after adoption) on ECHA's website. Dossier submitters who are manufacturers, importers or downstream users, will only receive the comments and non-confidential attachments, and not the confidential information received from other parties.

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Substance name: halosulfuron-methyl (ISO); methyl 3-chloro-5-{[(4,6-dimethoxypyrimidin-2-yl)carbamoyl]sulfamoyl}-1-methyl-1H-pyrazole-4-carboxylate
EC number: -
CAS number: 100784-20-1
Dossier submitter: Italy

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
22.09.2016	France		MemberState	1
Comment received				
p14: Part B. 1.2 Table 5. Constituents (non-confidential information): Please note that the concentration range in the five batch analysis of Halosulfuron-methyl is 99.1-99.6% in the DAR of Halosulfuron-methyl (in the Volume 4, Annex C, point C.1.2.3.1of the DAR, 2007 and of the updated DAR, 2012).				
Dossier Submitter's Response				
Thank you for the comment. In the "remarks" column in table 5 in the CLH report there is a comment "The typical purity is the mean value for purity determined in the five batch analysis of halosulfuron". The applicant interprets this to mean that the concentration ranges seen in the 5 batch analysis are typical for all batches of halosulfuron-methyl. The data for the five-batch analysis reported in the DAR is only from one study. Therefore the applicant believes that a broader range of 98-100% in the table is appropriate to cover the possibility of exceeding the range in the single 5-batch analysis while still achieving the minimum purity specification of halosulfuron-methyl. The concentration range 98-100% in the CLH report was in accordance with the purity > 980 g/kg in Regulation (EU) No. 356/2013 of 18 April 2013 approving the active substance halosulfuron-methyl, in accordance with Regulation (EC) No 1107/2009.				
RAC's response				
Noted. Not applicable for classification and labelling.				

TOXICITY TO REPRODUCTION

Date	Country	Organisation	Type of Organisation	Comment number
22.09.2016	France		MemberState	2

Comment received

P73. Toxicokinetics of halosulfuron-methyl.
The applicant uses autoradiography data to support that the effect on fetuses at 750 mg/kg/d was secondary to maternal toxicity. Indeed these data show that in pregnant females no radioactivity was detected in foetal tissues. However in this toxicokinetic study (Mc Carthy, 1991), the pregnant rats were dosed at 5 mg/kg/d and not at higher doses (eg: 250 and 750 mg/kg/d, the dose levels at which fetal effects are observed). The rationale given by the applicant is therefore considered inconsistent.

P70. Summary and discussion of reproductive toxicity.
The relevance of the historical control data should be discussed. It should be noted that historical control data shall be from the same species and strain, maintained under similar conditions in the same laboratory and shall be from contemporaneous studies. All of these criteria must be met to make them usable data to argue the non-relevance of the effects discussed. However, the historical control data provided for the effects observed in the two-generation study and in the rat teratogenicity study do not cover a five-year period and do not cover the date of the studies of interest. Furthermore, it is not clear whether the HCD strain is identical to that used in the corresponding studies. Moreover, not only the fetal incidences of the findings, but also the litter incidences have to be compared to HCD data. Finally the skeletal variations HCD (rat teratogenicity study) were expressed as fetal incidences (not provided as absolute values), and were not provided on the litters. Consequently, such information should not be considered as fully usable.
Moreover, as the fetal findings observed at the intermediate dose level are also noted at the highest dose level with higher incidences, it cannot be excluded that these effects are treatment-related.
Based on the available data showing dose-related fetal effects occurring in the absence of maternal toxicity at mid dose level, and taking into account the questionable HCD relevance, classification with Repr cat 2 H361d should be further discussed.

Dossier Submitter's Response

The historical control data on the 2-gen study are included the study report and so are from the same laboratory, same strain and same conditions. They do not cover a 5 year period but are entirely relevant to the 2-gen study covering the period immediately prior to the conduct of the study which was initiated in August 1989. These multigeneration studies are large complex studies of long duration and individual CROs (even large ones) generally only carry out a very small number each year. At the time of conducting the study, there was no requirement to collect 5 years of historical control data. The historical control data for the rat developmental study are similarly relevant since they are included in the study report and are taken from 12 studies conducted around the time of the conduct of the study which was initiated in April 1988. Additional historical control data to supplement the HCD in the original report were found in a publication by MARTA/MTA issued in 1996 covering a two year period shortly after the teratology study. The data were from studies using the same strain and supplier. Local conditions for studies carried out in different laboratories could not be regarded as identical. The HCD on caudal vertebrae ossification in the rat developmental toxicity study was provided by the CRO conducting the study on request and was compiled from studies conducted from 1994-1998, after the completion of the study. The CRO was asked for further data including the time period when the study was conducted but was not able to provide it. The time period 1994-1998 was the earliest they said they could provide.

We concur that historical data should be considered with great caution when assessing the relevance of findings of toxicological studies. Indeed, IT recommends no classification based on the findings of the available studies, with no reference to any historical data. In the meanwhile, it is noteworthy that the Applicant ensures that the historical data used in interpreting results of the developmental toxicity studies, came from studies carried out in different laboratories, but using the same strain and supplier: indeed, these two parameters (supplier and strain) would provide a sufficient degree of comparability. Nevertheless, the IT recommendation for no classification for developmental toxicity comes from the analysis of study findings, considering dose-response relationships, consistency of data and severity of effects in relation to maternal toxicity.
For more details see answer 5

RAC's response

In relation to the toxicokinetic autoradiography data for halosulfuron-methyl, RAC has similar reservations to that of the commenting Member State. The results of a single low dose (5 mg/kg bw/day) oral gavage autoradiography study with pregnant rats do not provide a convincing argument against trans-placental transfer of the active substance (McCarthy, 1991b - The autoradiography, disposition in tissues and biliary excretion of NC-319 in male and female rats). Without data of concomitant plasma levels of substance in both maternal and foetal blood, it is not possible to determine the relationship of the findings manifest in both organisms. Consequently the toxicokinetics of the substance in the foetus is unknown and the amount actually present in the foetal blood stream is also unknown though it is assumed there would be very little restriction to the movement of substance across the placenta for higher dosed pregnant females. RAC finds the data insufficient to conclude that there is little to no trans-placental transfer of the active substance.
The DS is correct in that the HCD was supplied as an addendum to the original study reports but only in a bridged form by way of summary tables. It is not completely clear however if the HCD for the rat developmental study is from the same laboratory that performed the repro tox studies, it is not explicitly stated as such (unlike for the rat 2-gen study). However, RAC agrees with the DS, in that the HCD is considered relevant for the time period concerned. The HCD is not so critical however, it is supportive of substance related effects observed in the rat developmental study. The RAC agrees with the Member State, the foetal findings observed in the rat developmental study are considered of significance and treatment-related. RAC concludes that these effects support Repr. 1B, H360D.

Date	Country	Organisation	Type of Organisation	Comment number
02.09.2016	Spain		MemberState	3

Comment received

We agree with the dossier submitter that, the minor changes in reproduction and fertility parameters in treated groups in rat 2-generation study were not dose-related, generally within background historical control data range for the laboratory and did not represent an adverse effect of treatment. Besides, there are no substantive data to indicate higher sensitivity of offspring to halosulfuron-methyl, taking into account supplementary evidence submitted to the RMS after the EU review. Therefore, the Spanish CA supports the dossier submitter conclusion that halosulfuron-methyl does not fulfil the criteria for classification as H361f Category 2.

The available data on developmental toxicity reported in rats and rabbits did not show clear and consistent pattern regarding developmental toxicity following exposure to

halosulfuron-methyl. In developmental rat study, visceral and skeletal findings observed at intermediate dose animals were associated with low foetal weight , attributable to slight immaturity and were within the range of background control values; while at the high dose animals those findings were secondary to maternal toxicity. Therefore, the Spanish CA supports the dossier submitter conclusion that halosulfuron-methyl does not fulfil the criteria for classification as H361d Category 2.
Dossier Submitter's Response
Thank you for your kind support.
RAC's response
RAC agrees with the DS and the MS regarding no classification for adverse effects on sexual function and fertility. The adverse effects on development in both rat and rabbit are not considered secondary non-specific consequences of maternal toxicity by RAC. Reductions in foetal body weight were seen in only one study and species (rat), but these changes were statistically significant, outside the HCD and associated with skeletal variations. The increase in rat external, skeletal and visceral variations which is indicative of a very extensive and biologically significant delayed development of the skeletal system, was observed at the top dose level of 750 mg/kg bw/day and in a few cases at 250 mg/kg bw/day (in this case maturation delay without any effect from maternal toxicity or foetal body weight reductions). In the rabbit developmental study, the increase in post-implantation loss at high dose was accompanied by a marked retardation of uncorrected maternal body weight gain during the dosing period. However, there were no clinical signs of toxicity during the dosing period. Halosulfuron-methyl induced early resorptions impacting the post-implantation losses as also observed in rats in the presence of only minimal maternal toxicity. Although these effects were not statistically significant in either species, the incidences were above the concurrent control values and HCD in rabbits and above the concurrent control values in rats. There were incidences of malformations at the high dose - the increased rat external, skeletal and visceral malformations are considered by RAC to be severe effects and toxicologically significant and relevant because the incidences were higher than in concurrent controls and above the incidences reported in the HCD. In summary, there is sufficient evidence of a substance-mediated effect. Development of rat foetuses was impaired at high dose levels. Rat foetal body weight was dramatically reduced. There was a biologically significant increase in early resorptions which impacted on the rat post-implantation loss and this effect was also noted in the rabbit developmental study. Several widespread developmental variations were observed and there were indications of malformations in both rats and rabbits. RAC considers the data sufficient for classification with Repr. 1B; H360D.

Date	Country	Organisation	Type of Organisation	Comment number
20.09.2016	United Kingdom	Nissan Chemical Europe S.A.R.L.	Company-Manufacturer	4
Comment received				
The Applicant, Nissan Chemical Europe S.A.R.L., agrees based on the data review shown below to the Rapporteur's proposal that classification for reproduction is not necessary.				

Two-generation study in rats
This study was conducted at 0, 100, 800 or 3600ppm and based on the absence of any adverse effects at 100 and 800 ppm in either generation, the study report concluded the NOAEL to be 800 ppm.
There was a transient decreased offspring bodyweight gain at 800 ppm in F1, F2a, F2b generation.
However there was no consistent evidence of effects on offspring bodyweight or bodyweight gain in the group receiving 800 ppm through F1 and F2 generations during lactation.
Further the newly submitted historical control data provided by the laboratory which conducted the study show that the covariate adjusted offspring body weights of halosulfuron-methyl treated animals are within the historical control range for the strain and conditions specific to the laboratory.
It is therefore considered that the NOAELs for both offspring and parental animals are 800 ppm (50.4 mg/kg bw/day).

Developmental toxicity study in rats
This study was conducted at 0, 75, 250 or 750 mg/kg bw/day and based on the absence of any adverse effects at 250 mg/kg bw/day, the study report concluded the NOAEL to be 250 mg/kg bw/day.
There were some visceral and skeletal variations at 250 mg/kg bw/day.
However the relatively small number and slight or small increases in variants mostly associated with low fetal weight and were generally attributable to slight immaturity.
Further the newly submitted historical control data provided by the laboratory which conducted the study show that the visceral and skeletal variations of halosulfuron-methyl treated animals are within the historical control range for the strain and conditions specific to the laboratory.
It is therefore considered that the NOAELs for both maternal and developmental toxicity are 250 mg/kg bw/day. No teratogenic effect was observed.

Developmental toxicity study in rabbits
This study was conducted at 0, 15, 50 or 150 mg/kg bw/day.
Both maternal and fetal NOAELs were 50 mg/kg bw/day based on early resorptions, decreased number of foetuses and reduced maternal body weight gain at 150 mg/kg bw/day. No teratogenic effect was observed.
Conclusion
Based on the above results, halosulfuron-methyl does not meet the CLP criteria classification for fertility toxicity, developmental toxicity or toxicity via lactation.

Dossier Submitter's Response

Thank you for your kind support.

RAC's response

The applicant does not address the significance of the findings in the high dose group of the rat development study. There is a consistent effect on foetal growth and delayed maturation of all skeletal parameters in addition to evidence of malformations. In addition there was a significant increase in early resorptions which impacted on the rat post-implantation loss and a similar effect was observed in the rabbit developmental study.

Evidence for developmental effects associated with halosulfuron-methyl were observed in both the rat (Morseth, 1990a) and rabbit (Morseth, 1990b) developmental studies:

1. Delayed development: there was a dramatic and statistically significant reduction in rat foetal body weight in both sexes:
   i. Males: 3.4 ± 0.3 vs 2.6 ± 0.3 g, controls vs high dose (-24%)
   ii. Females: 3.2 ± 0.4 vs 2.5 ± 0.3 g, controls vs high dose (-22%)
2. Delayed development: there was an extensive and widespread increase in rat skeletal variations:
   i. (skeletal - total variations: 105/23 – 115/25 – 114/23 – **146/22**)
3. Malformations: there was evidence for increased rat external, skeletal and visceral malformations (foetuses/litters)
   i. External – tail: 0/0 – 0/0 – 0/0 – 4/3
   ii. Skeletal – forked / fused ribs: 0/0 – 0/0 – 0/0 – 2/2
   iii. Visceral – heart / great vessel: 0/0 – 0/0 – 0/0 – 2/2
4. There was an increase in mean rat early resorptions and post-implantation loss
   i. resorptions: 1.0 vs 1.5 (controls vs high dose) [HCD: 0.3 – 1.5]
   ii. post-implantation loss: 6.9% vs 10.1% (controls vs high dose) [HCD: 2.9 – 13.6%]
5. There was a reduction in rabbit mean live litter size at the high dose:
   i. foetuses per litter: 7.2 – 7.4 – 7.2 – 5.8
6. There was a substantial increase in rabbit early resorptions and post-implantation loss:
   i. resorptions: 0.8 vs 2.0 (controls vs high dose) [HCD: 0.1 – 1.0]
   ii. post-implantation loss: 12.2% vs 31.5% (controls vs high dose) [HCD: 2.4 – 23%]
7. There was evidence of increased rabbit skeletal malformations:
   i. skeletal – forked / fused ribs: 1/1 – 0/0 – 0/0 – 4/4

Although developmental toxicity was limited in its extent in both rats and rabbits to a single (high) dose group only with no dose response at lower doses, RAC concludes the effects are significant enough to warrant classification for development (Repr. 1B; H360D).

No classification for lactation is supported by RAC.

Date	Country	Organisation	Type of Organisation	Comment number
14.09.2016	Germany		MemberState	5
Comment received				
1) Multi-generation study Pages 60-63; pages 79/80 In Table 31, two NOAELs are mentioned for the reproductive study. Usually, it is preferred to derive three NOAELs from a two- generation study, i.e., a parental, a reproductive and the third one for offspring effects. This would help to distinguish the findings more clearly.				

Here, it would demonstrate that the critical effect is the lower pup weight at doses which were not parentally toxic. This would rather point to a developmental than to a reproductive effect of the test substance.
Setting of a "marginal LOAEL" of 100 ppm for reproduction, however, means that the DS considers the reduced pregnancy rates and numbers of dams with litters as relevant. If relevant, this would be a clear reproductive effect in the absence of parental toxicity resulting in a need for classification and labelling. However, the tables 42 to 44 do not substantiate this assumption even though a pregnancy rate of 88 % in the F2B generation is hardly to believe if there were only 17 dams with litters following mating of 25 females.

Page 63
Table 32 is difficult to understand. Apparently the mean pup weights in the F1, F2a and F2b generations are reported. What is the meaning of the two right columns "F1 gen week 0 and week 14"?

2) Multi-generation study

Pages 65-68
Based on Table 33, there was a significant increase in external, skeletal and visceral malformations and variations at the top dose level of 750 mg/kg bw/day. This would normally lead to classification. Moreover, a developmental effect (lower pup weight) was seen in the two-generation study. Since maternal toxicity (even not very much pronounced) was observed at the same high dose level in the developmental study on rats, category 2 might be more appropriate than category 1B.

Page 68
The following inconsistency was noted: It is stated that the NOEL for maternal and developmental toxicity was 250 mg/kg (bw)/day. In the subsequent sentence, a NOEL for developmental toxicity of 75 mg/kg (bw)/day is mentioned. Please clarifiy! In addition, usually a NOAEL is given and considered relevant but not the NOEL which is hardly possible to establish.

Page 70
A higher rate of early resorptions in the rabbit study, even though in the presence of maternal toxicity, is an additional argument for classification and labelling. However, the LOAEL is rather seen at 50 mg/kg bw/day if the lacking dose response of this finding is taken into account.

On balance, Repro Cat. 2 (H361d) is considered the most appropriate classification. There was no convincing evidence of an effect on fertility or reproductive success but development of rat fetuses and pups was impaired at high dose levels. The occurrence of these adverse effects in the presence of some maternal toxicity suggests rather category 2 than 1B.

Dossier Submitter's Response

As a matter of principle, **IT** retains that hazard-based classification and labelling for developmental toxicity (as for other toxicological properties) should be based on scientific evidence, in order to pinpoint substances that present hazards of actual concern, considering dose-response relationships, consistency and biological plausibility of data and severity of effects in relation to maternal toxicity. On the other hand, it would be a wrong

approach to label each compound that presents any statistically significant increase for any developmental change; also, the simple comparison of maternal and developmental LOAEL and NOAEL* -*alone and per se*- should not normally be sufficient to decide whether or not a substance has to be classified as a developmental toxicant.

Concerning Halosulfuron-methyl in all three studies presented on reproductive and developmental toxicity (Two generation reproductive toxicity in rat, Lemen 1991; Teratogenicity by the oral route, rat, Morseth 1990; Teratogenicity by the oral route in the rabbit Morseth 1990) there were no adverse effects on foetal growth and viability at dose levels devoid of apparent maternal toxicity with no evidence that such effects can be at dose levels.
-Namely:
a) in the two generation study (dose levels 0, 100, 800 and 3600 mg/kg feed) in F1 litters from F0 parental animals there was no effect at all on litter size at birth; viability at weaning showed a slight decrease compared to controls but without any dose-relationship (93%, 94%, 95% at low, intermediate and high dose levels, respectively).
To support a substance-related effect, one would expect that these unclear findings become more evident in the F2 litters from F1 animals. However, in F2a and F2b pup viability values are essentially the same as in controls.
Litter size at birth in F2 is more complex. In F2a mean values are essentially the same as in controls (13.0 13.2 13.3 13.3). In F2b there is an actual decrease in top dose vs control group (11.7 vs. 13.1, respectively). The mean litter sizes at low (12.5) and intermediate (12,8) dose levels are slightly lower than in controls but without a dose relationship.
The reduced litter size at birth in F2b at the top dose level (3600 mg/kg) can be considered as a treatment-related effect.
Any apparent numerical reduction of litter size and/or viability at low and intermediate dose level should show an understandable dose-response relationship as the two dose levels show an 8-fold difference in magnitude (100 and 800 mg/kg). Moreover, the treatment groups show somewhat large and unexplained differences in female pregnancy rates: such differences do not show any treatment-related trend and may have a confounding influence on pup viability.
In the absence of statistical significance and meaningful dose-relationship, no treatment-related effects are identified at low and intermediate dose levels.
The top dose level (3600 mg/kg) is the LOAEL for litter and pup effects; at such dose levels general toxicity is also observed.
b) Developmental toxicity study in rats (dose levels 0, 75, 250 and 750 mg/kg)
Statistically significant adverse effects are seen at the top dose level, with concurrent maternal toxicity: lower foetal weight in both sexes, increased incidence of dilated brain lateral ventricles and increased pelvis cavitation, increased incidence of reduced tail ossification (such changes are considered indicators of intrauterine developmental delays). The total incidence of skeletal minor anomalies/ossification delays is also increased.
At the intermediate level fetal weight is unaffected, whereas there is a statically significant increase of fetuses with less than 5 ossified caudal vertebrae (litters-fetuses affected: 13-34, 18-35, 16-56 and 20-109 in controls, low-dose, intermediate and high-dose, respectively). Dose-related increases, albeit without statistical significance are seen for dilated brain lateral ventricles (0 in controls and low-dose, 2 fetuses in 2 litters at intermediate dose, 16 in 5 litters at high dose) and pelvis cavitation (litters-fetuses affected: 3-4, 5-8, 7-9 and 10-22 in controls, low-dose, intermediate and high-dose, respectively.

Due to the significant increase of reduced caudal ossification, accompanied by slight, but potentially treatment-related, increased in soft in soft tissue developmental delays, the intermediate dose level of 250 mg/kg bw should be considered the LOAEL for developmental toxicity in rats; the NOAEL is therefore 75 mg/kg bw. These values are *apparently* lower than the LOAEL and NOAEL for evident maternal toxicity in the rat (750 and 250 mg/kg bw)
c) Developmental toxicity study in rabbits (dose levels 0, 15, 50 and 150 mg/kg bw): in this study the only meaningful effect is the increase in litter resorption and the reduction of live litter size at the top dose, with concurrent maternal toxicity. The apparent effect on resorption rate seen at low dose (15.3% vs. 9.7% in controls) is unlikely to be treatment-related, because at intermediate dose level the resorption rate (10%) is essentially the same as in controls.
Therefore, the top dose and intermediate dose level of 150 and 50 mg/kg bw are the LOAEL and NOAEL, respectively, for both maternal and developmental toxicity in the rabbit.

To summarize: The findings in the two-generation rat study and in the prenatal rabbit study clearly do **not** justify any classification for developmental toxicity.
The only possible justification for a classification in cat. 2 for developmental toxicity (which is a *serious* classification) is that in the prenatal rat study, the NOAEL/LOAEL for developmental effects is lower than for maternal toxicity.
However, it is at least doubtful that the effects are of actual concern for developmental toxicity:
the magnitude and severity of changes is slight: only reduced ossification of caudal vertebrae is significantly increased,and the three changes that are increased (besides reduced tail ossification, dilate renal pelvis and lateral brain ventricles) are considered as reversible developmental delays *in the absence* of other indications of developmental toxicity.
Indeed, no malformation increases, i.e., no teratogenic effects, were observed across the three studies even at maternally toxic dose levels.
Therefore, the observed changes do **not** justify a classification in Cat. 2 for developmental toxicity based on scientific evidence.

IT Proposal

1) Halosulfuron methyl **is not classified** in any category for developmental toxicity.
2) The slight delaying effects on rat development observed in one study may be taken account in *the risk assessment* of Halosulfuron-methyl, e.g., the NOAEL (or according to a more up-to-date approach, a Benchmark Dose) can be considered in the definition of AOEL or even of a ARFD.

Note:* IT is aware of the many conceptual and statistical limitations of the LOAEL/NOAEL approach; whenever consistent methodologies are available, **IT endorses the use of Benchmark Dose, or related approaches, to define Points of Departure for adverse effects of chemicals.

For table 32: F1 week 0 means 4 weeks after birth, F1 week 14 means 18 weeks after birth. Apologies for the confusion.

RAC's response

The points made by the member state are noted. The reduced pregnancy rates and numbers of dams with litters in the rat 2-gen study are of concern and no adequate explanation is available. Total HCD data (F1 and F2 pups) indicates an expected variability from 77 – 100%. Both F1 matings show reduced pregnancy rates without a

clear dose response. Together with the very low control in the F0 mating a case for classification for fertility is considered but the argument is a weak one. In this particular instance RAC does not judge the data sufficiently robust to propose Repr. 2, H361f. A pregnancy rate of 88 % at the highest dose in the F2B generation is calculated from [(females pregnant / females paired) × 100] = [(22/25) x 100]. In contrast, RAC is of the opinion that there is sufficient evidence to warrant classification for development (Repr. 1B; H360D, see comments 3 and 4 above).

OTHER HAZARDS AND ENDPOINTS – Acute Toxicity

Date	Country	Organisation	Type of Organisation	Comment number
14.09.2016	Germany		MemberState	6
Comment received				
Toxicokinetics Pages 19 - 22 Even though it is not of concern with regard to classification and labelling, the following inconsistency in the CLH report was noted: In the sub-section on excretion, it is reported how the estimate of oral absorption was performed resulting in an assumption of 73.5%. It is also explained why and how this figure was used for risk assessment. In the sub-section 4.1.3 (Summary and discussion), however, a "high bioavailability" of >80 % is mentioned, in principle on the basis of the same data. If the latter estimate is correct, the EFSA should be approached in order to revise the AOEL since correction would be not needed then. However, we rather suspect a simple error.				
Dossier Submitter's Response				
>80 % is the correct value because at the beginning in the dRR, we estimated it as 73.5%, but after that we submitted an additional report estimating it as >80% in reply to the EFSA request. This figure (>80%) is also in the DAR (2007). For more details see answer 5				
RAC's response				
Noted and agree with the DS response. According to the DAR (addendum Vol 3, 2012) section B.6.1.4, "Based on data of urinary and biliary excretion, and residues in the carcass, it can be concluded that >80% of the administered dose was absorbed by the GI tract and that there was no indication of saturation of the absorption process". A supporting study (Ogawa, 1994) summarised in B.6.1.3 of the same addendum estimated absorption to be 92.4 % and 86.1% of the treatment dose for the two radiolabelled forms of halosulfuron methyl.				

OTHER HAZARDS AND ENDPOINTS – Hazardous to the Aquatic Environment

Date	Country	Organisation	Type of Organisation	Comment number
22.09.2016	France		MemberState	7
Comment received				
We agree with the classification proposal regarding environmental hazard and with the proposed acute and chronic M factors. However, it is FR opinion that the acute M factor should be based on the ErC50 value of 0.491 µg a.s./L for Lemna gibba and not on the EbC50 value of 0.217 µg a.s./L. It has to be noted that this would not change the proposal of the acute M factor value (1000).				
Dossier Submitter's Response				
Thank you for the comment,				

Following consideration of the comments received on the DAR, EFSA conducted an expert consultation in the areas of ecotoxicology. In this contest, the experts proposed to use the biomass endpoint from the standard laboratory study with Lemna gibba.
RAC's response
The support is noted. The DS response does not explain why the biomass end point was chosen. In the absence of this information, RAC would prefer to be consistent with previous cases and use the growth rate end point. This does not affect the proposed classification.

Date	Country	Organisation	Type of Organisation	Comment number
23.09.2016	Sweden		MemberState	8
Comment received				
The Swedish CA supports the environmental classification proposal of halosulfuron-methyl, CAS No. 100784-20-1 (Aquatic Acute 1, Aquatic Chronic 1 with Acute and Chronic M-factors of 1000), based on the toxicity on aquatic plants (Lemna gibba) with the endpoint EbC50=0.217 µg/l and a NOEC of 0.03 µg/l and the information showing that halosulfuron-methyl is not rapidly degradable and has low potential for bioaccumulation. Editorial comments: p. 10: 2.2 Short summary of scientific justification for the CLH proposal. The information on what the classification Aquatic Acute 1 is based on is missing. p. 91. 5.1. Degradation. Table 50: Summary of relevant information on degradation. It would have been helpful to have the information on what studies were considered as key studies for degradation. p. 94. 5.1.2.3 Simulation tests. Table 51: Distribution of degradation products (>=5% AR) in Bury Pond system. What does"*" on Halosulfuron-methyl rearrangement and Halosulfuron indicate? p. 95. 5.1.3. Summary and discussion of degradation. The ready biodegradability study according to OECD 301 B (DAR B.8.4.3.1. Barnes 2003) should have been mentioned in the discussion. p. 114. 5.5. Comparison with criteria for environmental hazard. A reasoning why the endpoint EbC50 was chosen instead of the CLP recommended ErC50 is lacking. p. 114. 5.5. Comparison with the criteria for environmental hazard (section 5.1-5.4). The ready biodegradability study according to OECD 301 B (DAR B.8.4.3.1. Barnes 2003) should have been mentioned. p 115. 5.6. Conclusions on classification and labelling for the environment hazard. The end point ErC50 of the aquatic plants (Lemna gibba) used should have been EbC50 since that is what the chronic aquatic endpoint in the classification proposal is based on.				
Dossier Submitter's Response				
Thank you for the comment. Noted. A detailed reply is provided at comment number 7.				

RAC's response
The support is noted. The DS has not provided a response to some of the points made. However, this does not affect the opinion. See also response to comment #7.

Date	Country	Organisation	Type of Organisation	Comment number
23.09.2016	Belgium		MemberState	9
Comment received				
Based on the results of the aquatic toxicity test on the most sensitive species (aquatic plants (Lemna gibba) with 7dErC50=0.000491 mg/l and with 7dNOErC=0.00003 mg/l, the fact that the substance is not rapidly degradable it is justified to classify, following the classification criteria of the regulation 1272/2008, as Aquatic Acute 1, H400 and Aquatic Chronic 1, H410. In view of the proposed classification and toxicity band for acute toxicity between 0.0001 mg/l and 0.001 mg/l, an M-factor for acute toxicity of 1000 can be assigned and an M-factor for chronic toxicity of 1000 (not rapidly degradable substance and NOEC between 0.00001 mg/l and 0.0001mg/l) In conclusion : we support the proposed environmental classification.				
Dossier Submitter's Response				
Thank you for your kind support.				
RAC's response				
The support is noted.				

Date	Country	Organisation	Type of Organisation	Comment number
14.09.2016	Germany		MemberState	10
Comment received				
We support the proposed environmental classification and labelling as Aquatic Acute 1 (H400) and Aquatic Chronic 1 (H410) and an acute/chronic M-factor of 1000.				
Dossier Submitter's Response				
Thank you for your kind support.				
RAC's response				
The support is noted.				