Committee for Risk Assessment

RAC

Annex 2

Response to comments document (RCOM)

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

(2RS)-2-[4-(4-chlorophenoxy)-2-(trifluoromethyl)phenyl]-1-(1H-1,2,4-triazol-1-yl)propan-2-ol; mefentrifluconazole

EC Number: -
CAS Number: 1417782-03-6

CLH-O-0000001412-86-199/F

Adopted

9 March 2018

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON (2RS)-2-[4-(4-CHLOROPHENOXY)-2-(TRIFLUOROMETHYL)PHENYL]-1-(1H-1,2,4-TRIAZOL-1-YL)PROPAN-2-OL; MEFENTRIFLUCONAZOLE

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: (2RS)-2-[4-(4-chlorophenoxy)-2-(trifluoromethyl)phenyl]-1-(1H-1,2,4-triazol-1-yl)propan-2-ol; mefentrifluconazole
EC number: -
CAS number: 1417782-03-6
Dossier submitter: United Kingdom

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
12.07.2017	France		MemberState	1
Comment received				
Identity of the active substance: - p. 5, Table 1 and Table 2: According to the data submitted in the frame of the approval of mefentrifluconazole under Reg. (EU) 1107/2009, the minimum purity of the substance is 97.0% and the concentration range is 97.87 – 99.33%. - p. 6, Table 3: According to the data submitted in the frame of the approval of mefentrifluconazole under Reg. (EU) 1107/2009, DMF (dimethylformamide) is regarded a toxicologically relevant impurity with a proposed certified limit of 0.5 g/kg in the technical active substance.				
Dossier Submitter's Response				
Thank you for your comment. Your first point is correct. Thank you for your observation on relevant impurities. This is not considered to result in any additional classification of mefentrifluconazole.				
RAC's response				
Noted. According to the data given in the IUCLID file the typical concentration is below the value mentioned in the comment. Environmental hazards: Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
14.07.2017	Germany		MemberState	2
Comment received				
Environmental hazards: The German CA agrees with the proposal of classification for environmental hazards as				

Aquatic acute 1 (H400) and Aquatic chronic 1 (H410) and the acute/chronic M-factor of 1. Health hazards: In addition to the classification as Skin Sens 1 (H317) we propose a classification as Repr. 2 H361f and STOT RE 2 (liver)(H373). For justification please view specific comments. ECHA note – An attachment was submitted with the comment above. Refer to public attachment Mefentrifluconazole_Justification Explosive.docx
Dossier Submitter's Response
Noted. Please see responses to the specific comments.
RAC's response
Noted.

CARCINOGENICITY

Date	Country	Organisation	Type of Organisation	Comment number
12.07.2017	France		MemberState	3
Comment received				
No comment				
Dossier Submitter's Response				
Noted.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
14.07.2017	Spain		MemberState	4
Comment received				
In rats, there was an increase in the incidence of malignant lymphoma in males and adenocarcinoma endometrial in females, although neither of these was statistically significant. A clear dose-response relationship was not evident in the malignant-lymphoma incidences, and the high-dose group incidence (6 %) was within the wider historical control range, exceeding the more recent historical control range (upper range 4 %, mean 3.2 %) by just one animal. Although many of the tumours were diagnosed in animals that died before the scheduled sacrifice, this was demonstrated to also be the case with the historical control data. Furthermore, the haemolymphoreticular system was not a target of mefentrifluconazole in any of the repeated-dose toxicity studies. The incidence of uterine adenocarcinoma did not show a dose-response relationship and was within the relevant historical control range. In mice, there was a very slight increase (not statistically significant) in the incidence of thyroid follicular-cell adenomas which was above the historical control range for males by only one animal, without a dose-response relationship. There was a statistically significant increase in the incidence of hyperplasia in the high-dose males, although again without a dose-response relationship. The dossier submitter considers that the increase in hyperplasia in the high-dose males was treatment-related and perhaps reflected an exacerbation of age-related thyroid changes. The increased incidence of hyperplasia was not associated with thyroid follicular-cell tumours in either the mefentrifluconazole exposed groups or the historical control data and the dossier submitter consider that reflected an exacerbation of age-related thyroid changes.				

Therefore, we agree with the UK CLP Competent Authorities that, mefentrifluconazole was not carcinogenic in rats or mice under the conditions of these studies.
Dossier Submitter's Response
Noted.
RAC's response
Noted.

MUTAGENICITY

Date	Country	Organisation	Type of Organisation	Comment number
12.07.2017	France		MemberState	5
Comment received				
No comment				
Dossier Submitter's Response				
Noted.				
RAC's response				
Noted.				

TOXICITY TO REPRODUCTION

Date	Country	Organisation	Type of Organisation	Comment number
12.07.2017	France		MemberState	6
Comment received				
Rat developmental toxicity study page 48: FR disagrees with the DS position that no developmental adverse effects are observed in the rat developmental toxicity study. Indeed, FR is of opinion that the increased incidence of variations (dilated pelvis and supra-occipital hole(s)), observed at 150 and 400 mg/kg bw/day in foetuses, should be considered as adverse effects. Rabbit developmental toxicity study page 52: FR considers that a maternal effect is observed at 25 mg/kg bw/day due to early body-weight changes (13% decreases) in the does at this dose. In addition, FR is of opinion that developmental effects (skeletal variations) are observed at 25 mg/kg bw/day. However, these developmental effects observed both in rats and rabbits are only minor defects with no consequence on post-natal survival or development. According to the CLP regulation, variants may not lead to classification if considered to be of low toxicological significance. In conclusion, FR is of opinion that these findings are not sufficiently severe to be a basis for classification of mefentrifluconazole as a developmental toxicant.				
Dossier Submitter's Response				
We note and thank you for the support for the proposal not to classify for reproductive toxicity. With regards to the highlighted findings in the rat study, the extensive, relevant historical control data demonstrated that dilated renal pelvis and supra-occipital holes are very common spontaneous findings (litter incidences of up to 57 and 100%, respectively). The foetal and litter incidences of these findings were well within the historical control ranges; moreover, the increase in supra-occipital holes did not show a dose-response relationship. For these reasons, we concluded that there was not a clear relationship between these				

findings and exposure to mefentrifluconazole. The minor skeletal variations in rabbits are possibly an artefact of the study design; i.e., in laboratories that perform Caesarean section on GD 29, as was the case in the present study, alterations of sternal elements (unossifications, misalignments, fusions, misshapes, attachments) are amongst the most commonly occurring developmental variations in New Zealand White rabbits. These changes would be less commonly observed in foetuses that were carried to term. The slightly higher incidence in the high-dose group might have been a secondary consequence of the marginally lower body-weight gain of the dams in this group during the pre-treatment period.
RAC's response
RAC took into consideration any adverse effect and performed the assessment using all the available information. The support in favour of no classification was noted.

Date	Country	Organisation	Type of Organisation	Comment number
14.07.2017	Germany		MemberState	7
Comment received				
Based on significant reduction of the mean number of implantation sites per dam in the high dose F1 parents (200 mg/kg bw/d) and the increase in post-implantation loss (2.4% in control group, 5% - 7.1% - 8.9 % for 25, 75 and 200 mg/kg bw/d rsp.), DE suggests Repr. 2 H361f. These effects occurred in the absence of pronounced parental toxicity. There was only one dam, which exhibited severe poor general condition and piloerection. ECHA note – An attachment was submitted with the comment above. Refer to public attachment Mefentrifluconazole_Justification Explosive.docx				
Dossier Submitter's Response				
The mean number of implantation sites per dam was slightly but statistically significantly lower in the high-dose-group F_1 parents (mean 10.0, range 1 to 14, compared with mean 12.0, range 9 to 16 in the controls). The mean of the high-dose group was affected by one female (number 388) that contained only one implant. Notwithstanding, the mean value of the high-dose group was within the historical-control range of the test facility (33 studies, 2008-2013: range 9.4 to 14.0). A dose-related change was also not seen, since the mean number of implantation sites in the mid-dose group was higher than that in the control group. Overall, therefore, the dossier submitter considers that the slightly lower value in the high-dose group reflected biological variation and was not a treatment-related effect. Although there were slight increases in post-implantation loss in the mid- (7.1 %) and high-dose (8.9 %) groups compared with the controls (2.4 %), these were also most likely to be a reflection of normal biological variation and were well within the historical control range (33 studies, 2008-2013: range 0.9 to 17.7). Also, the value of the high-dose group (which was not statistically significantly different from the control value) was strongly influenced by the female (number 388) with only one implant; this implant was resorbed, which resulted in a post-implantation loss of 100 % for this animal. Exclusion of this animal from the calculation would lead to a group mean of 4.8 %. Furthermore, the mean number of F2 pups delivered per dam was within the historical control range. There was therefore no evidence that mefentrifluconazole exposure affected the number of pups born per dam. With regard to maternal toxicity, body-weight gain of the F1 dams at 200 mg/kg bw/d was impaired throughout the study (including gestation). Consistent with this, food consumption of the high-dose F1 females was statistically significantly below the				

concurrent control during the premating period (up to 10%), the entire gestation period (up to 20%) and the lactation period (up to 20%). We consider that these data do not support a classification for effects on reproduction.
RAC's response
The effects mentioned in the comment were analysed in the assessment.

Date	Country	Organisation	Type of Organisation	Comment number
14.07.2017	Spain		MemberState	8
Comment received				
Fertility We agree with the UK CLP Competent Authorities that mefentrifluconazole did not show evidence of specific reproductive toxicity in the rat two-generation study. The slight changes in some of the reproduction parameters (which were, moreover, within the historical control ranges) and offspring toxicity and delayed development (dilated renal pelvis) were evident only at a dose that also resulted in parental toxicity (decreased food consumption and body weights), with an apparent lack of maternal care. Therefore, the Spanish CA consider not necessary to classify mefentriflucanozole for effects on fertility. Developmental toxicity In the rat developmental study, there was no evidence of intra-uterine toxicity to the embryos / fetuses or induction of malformations or variations. In the rabbit developmental study, there was a higher incidence of fused sternebra in the high-dose group above the historical control ranges from the test facility. However, the litter incidence represented only one litter above the historical-control range (18 % = 4/22 litters in the high-dose group, compared with 14.3 % = 3/21 in the historical-control data). Besides, the fusions were of minimal magnitude and confined to individual sternal embryonic areas rather than affecting the whole sternum; additionally, the pattern of sternal changes was identical between the affected control animals and those treated with mefentrifluconazole. In all cases, the underlying cartilage was normal without any indication of a change. Taken together with the lack of a dose-response relationship and statistical significance for the findings, we agree with the dossier submitter that the slightly higher incidence of this variation in the high-dose group being representative of a minor delay or minor disturbance of ossification, resulting from the lower maternal body weight of dams and that is likely to disappear post-natally. Therefore, the Spanish CA consider that mefentrifluconazole did not meet the criteria for classification for developmental toxicity in these studies. Adverse effects on or via lactation We agree with the dossier submitter conclusion that, the slight increase in pup mortality and decreased body weights in the surviving pups observed in the rat two-generation were secondary to maternal toxicity (inadequate nursing, arising from the much reduced food intake during lactation of the respective dams) and not a direct toxic effect of mefentrifluconazole or its metabolites on or via lactation.				

Mefentrifluconazole, therefore, does not meet the criteria for classification for effects on or via lactation.
Dossier Submitter's Response
We note and thank you for the support not to classify for reproductive toxicity or effects on or via lactation.
RAC's response
The support in favour of no classification was noted.

OTHER HAZARDS AND ENDPOINTS – Acute Toxicity

Date	Country	Organisation	Type of Organisation	Comment number
12.07.2017	France		MemberState	9
Comment received				
No comment				
Dossier Submitter's Response				
Noted.				
RAC's response				
Noted.				

OTHER HAZARDS AND ENDPOINTS – Skin Hazard

Date	Country	Organisation	Type of Organisation	Comment number
12.07.2017	France		MemberState	10
Comment received				
No comment				
Dossier Submitter's Response				
Noted.				
RAC's response				
Noted.				

OTHER HAZARDS AND ENDPOINTS – Eye Hazard

Date	Country	Organisation	Type of Organisation	Comment number
12.07.2017	France		MemberState	11
Comment received				
No comment				
Dossier Submitter's Response				
Noted.				
RAC's response				
Noted.				

OTHER HAZARDS AND ENDPOINTS – Skin Sensitisation Hazard

Date	Country	Organisation	Type of Organisation	Comment number
13.07.2017	Finland		MemberState	12
Comment received				
Skin sensitisation study (Guinea Pig Maximisation Test OECD TG 406) conducted with mefentrifluconazole resulted in a positive response in 60% of animals with intradermal				

induction dose of 5%. The result meets the criteria for Skin Sens. 1. Criteria for subcategory 1B is also met, but as stated in the CLH report subcategory 1A cannot be excluded. FI CA supports the proposed classification of Skin Sens. 1; May cause an allergic reaction for mefentrifluconazole.
Dossier Submitter's Response
Noted.
RAC's response
Noted.

Date	Country	Organisation	Type of Organisation	Comment number
12.07.2017	France		MemberState	13
Comment received				
No comment				
Dossier Submitter's Response				
Noted.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
04.07.2017	Sweden		MemberState	14
Comment received				
Based on the information available in the CLH report, the Swedish CA agree with the proposed classification Skin Sens 1. The GPMT shows that 60% of the animals had positive skin reactions after induction with 5% mefentrifluconazole - which fulfils the classification criteria for Skin Sens 1B. However, since the substance was not tested using lower induction doses than 5%, category 1A cannot be excluded and the substance should therefore be classified as Skin Sens 1.				
Dossier Submitter's Response				
Noted.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
14.07.2017	Spain		MemberState	15
Comment received				
We agree with the UK CLP Competent Authorities proposal to classify mefentriflucconazole as skin Sens 1; H317 – May cause an allergic skin reaction.				
Dossier Submitter's Response				
Noted.				
RAC's response				
Noted.				

OTHER HAZARDS AND ENDPOINTS – Specific Target Organ Toxicity Single Exposure

Date	Country	Organisation	Type of Organisation	Comment number
12.07.2017	France		MemberState	16
Comment received				
No comment				
Dossier Submitter's Response				
Noted.				
RAC's response				
Noted				

OTHER HAZARDS AND ENDPOINTS – Specific Target Organ Toxicity Repeated Exposure

Date	Country	Organisation	Type of Organisation	Comment number
12.07.2017	France		MemberState	17
Comment received				
No comment				
Dossier Submitter's Response				
Noted.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
14.07.2017	Germany		MemberState	18
Comment received				
DE suggests STOT RE 2 (liver) based on following pathological observations at doses below the guidance cut-off value: - hepatocellular necrosis, oval-cell proliferation, bile-duct hyperplasia, cytoplasmic alteration, fatty change in the 28-day and 90-day studies in mice - increased liver weight, hepatocellular hypertrophy in 28-day mice study - increase in severity of hepatocellular fatty change in 18-months mice study - increased liver weight with hepatocellular hypertrophy and eosinophilic change of hepatozytes in one–year dog study and 28-day dog study - increases in ALP and ALT values 12-months rat study ECHA note – An attachment was submitted with the comment above. Refer to public attachment Mefentrifluconazole_Justification Explosive.docx				
Dossier Submitter's Response				
No adverse liver effects were reported in rats at doses relevant for classification. Slight clinical-chemistry changes in the one-year rat study at 34 / 45 mg/kg bw/d probably reflected adaptive changes and alterations to liver-cell metabolism. They were not associated with liver-weight changes or histopathology findings at this dose. Small changes in clinical biochemistry, when such changes are of doubtful or minimal toxicological importance, do not support classification for STOT-RE.				

In dogs, liver effects below the cut-off value for category 2 were observed in the range-finding 28-day study and the one-year study. These effects in either or both studies comprised increased liver weight with hepatocellular hypertrophy and eosinophilic change of hepatocytes. The observed eosinophilic change was of minimal to slight severity and was not a clear indicator of hepatotoxicity; such a change in hepatocytes is associated with liver-enzyme induction, as is hypertrophy. None of these effects was reproduced in the 90-day dog study at doses below the cut-off value. Overall, considering the adaptive nature of the liver effects (with the eosinophilic change being of only slight severity) and the small numbers of animals investigated, the dossier submitter concludes that these changes in dogs do not warrant classification. Hepatocellular necrosis was observed in mice in the 28-day and 90-day studies at doses below the guidance cut-off value for category 2. In the 28-day study, the necrosis was multifocal and of minimal/slight severity. The necrosis that occurred after 90 days' administration was single cell, of minimal severity and in only 20 % of males, with no cases in females. Necrosis was not observed upon a longer duration of exposure (18 months). Given that the multi-focal necrosis was only observed in the 28-day range-finding study, was of minimal to slight severity, and was not observed upon longer durations of exposure, this finding does not constitute evidence of significant or severe toxicity and thus does not support classification. A slight increase in the severity of hepatocellular fatty change was recorded in male mice after 18 months of exposure at a dose below the guidance cut-off for category 2. This change was not seen after shorter exposure durations. Since almost all males, whatever the group, had at least slight (grade 2) diffuse fatty change, the increase in severity grade to 2.9 (verging upon moderate) at 9.1 mg/kg bw/d mefentrifluconazole probably reflects a slight exacerbation of age-related hepatocellular changes. The incidence of macrovesicular fatty change was also high in the control animals (approaching 50 %), but in this case there was a statistically significant increase in incidence in the 9.1 mg/kg bw/d group (to 70 %) together with a slight increase in severity (from 0.5 in controls to 1.5 (minimal / slight) in the exposed group). Considering that there was a high incidence of this finding in the controls, the changes in incidence and severity might, again, have represented a slight exacerbation of age-related pathology; the absence of fatty change in any group in the shorter-duration studies would support this view. In addition to fatty change, minimal-grade oval-cell proliferation and bile-duct hyperplasia were observed in the 28-day mouse study at doses below the guidance cut-off values for category 2, but not upon longer duration even at doses that exceeded the guidance value. The criteria specify that morphological changes should provide clear evidence of marked organ dysfunction. The dossier submitter considers that marked liver dysfunction was not demonstrated with mefentrifluconazole, since the fatty changes were scored as less than moderate. Furthermore, apart from an increase in liver weight, which might have been at least partially an adaptive change, there were no other indications of liver dysfunction. Long-term survival of the animals (to 18 months) was not affected. In conclusion, we consider that a classification for STOT-RE is not warranted.
RAC's response
The argumentation in favour of classification was taken into account and thoroughly analysed in the Opinion.

OTHER HAZARDS AND ENDPOINTS – Hazardous to the Aquatic Environment

Date	Country	Organisation	Type of Organisation	Comment number
12.07.2017	France		MemberState	19
Comment received				
FR agrees with the general conclusion for the classification and both chronic and acute M-factor = 1 for environmental hazard of the substance.				
Dossier Submitter's Response				
Thank you for your support.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
14.07.2017	Belgium		MemberState	20
Comment received				
BE CA supports the proposal of classification for the environment by UK CA : Aquatic Acute 1, H400 ; Macute=1 Aquatic Chronic 1, H410; Mchronic=1 Based on the results of the aquatic toxicity test on the most sensitive species [Fish (Oncorhynchus mykiss) with 96hEC50 = 0.532 mg/l (mm) , Invertebrates (Daphnia magna) with EC10=0.0175 mg/l(nom)], the fact that the substance is not rapidly degradable, the above classification proposal is justified. In view of the proposed classification and toxicity band for acute toxicity between 0.1mg/l and 1 mg/l, an M-factor for acute toxicity of 1 can be assigned. And an M-factor for chronic toxicity of 1 can be assigned (not rapidly degradable substance and EC10 between 0.01 and 0.1mg/l).				
Dossier Submitter's Response				
Thank you for your support.				
RAC's response				
Noted.				

OTHER HAZARDS AND ENDPOINTS – Hazardous to the Ozone Layer

Date	Country	Organisation	Type of Organisation	Comment number
12.07.2017	France		MemberState	21
Comment received				
No comment				
Dossier Submitter's Response				
Noted.				
RAC's response				
Noted.				

OTHER HAZARDS AND ENDPOINTS – Physical Hazards

Date	Country	Organisation	Type of Organisation	Comment number
12.07.2017	France		MemberState	22
Comment received				
No comment				
Dossier Submitter's Response				
Noted.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
14.07.2017	Germany		MemberState	23
Comment received				
In section 8.1 of the CLH Report is stated that Mefentrifluconazole was not found to be sensitive to the effects of heat, shock or friction. Consequently, it does not meet the criteria for classification as an explosive substance. We demur, that the comparison of EU test method A.14 with the CLP criteria is not valid and that for validation of the classification at least a "Time/pressure test" should be performed according to the specifications of test methods UN 1 (c) (i) and UN 2 (c) (i). This test is used to determine if ignition of substance under confinement leads to a deflagration with explosive violence at pressures which can be attained in normal commercial packages. For Justification please view attachment. ECHA note – An attachment was submitted with the comment above. Refer to public attachment Mefentrifluconazole_Justification Explosive.docx				
Dossier Submitter's Response				
Thank you for your comment. The conclusions in the CLH dossier were made based on data already available on the substance.				
RAC's response				
The comment and the justification attachement have been taken into account in the RAC evaluation.				

PUBLIC ATTACHMENTS
1. Mefentrifluconazole_Justification Explosive.docx [Please refer to comment No. 2, 7, 18, 23]