Committee for Risk Assessment

RAC

Annex 2

Response to comments document (RCOM)

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

Flutianil (ISO); (2*Z*)-{[2-fluoro-5-(trifluoromethyl)phenyl]thio} [3-(2-methoxyphenyl)-1,3-thiazolidin-2-ylidene] acetonitrile

EC Number: -
CAS Number: 958647-10-4

CLH-O-0000001412-86-101/F

Adopted

10 March 2016

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON FLUTIANIL (ISO); (2Z)-{[2-FLUORO-5-(TRIFLUOROMETHYL)PHENYL]THIO}[3-(2-METHOXYPHENYL)-1,3-THIAZOLIDIN-2-YLIDENE]ACETONITRILE

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: Flutianil (ISO); (2Z)-{[2-fluoro-5-(trifluoromethyl)phenyl]thio}[3-(2-methoxyphenyl)-1,3-thiazolidin-2-ylidene]acetonitrile
EC number: -
CAS number: 958647-10-4
Dossier submitter: United Kingdom

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
30.07.2015	Germany		MemberState	1
Comment received				
Proposed C&L: We support the proposed classification of Repr. 2, H361d and Aquatic chronic 1, H410 with the chronic M-factor of 100. In addition we propose to classify as Carc. 2 (H351), please find our reasoning below (specific comment Carcinogenicity). Substance identity: - In IUCLID section 1.2 some impurities are listed (flagged as confidential). For two of the stated impurities CAS names are given although there are no existing corresponding CAS entries. Therefore, both CAS names should be deleted. Furthermore, for one of the other impurities a CAS number is given, but the corresponding CAS name is missing and should be added. - In Part B, section 1.3, table 8 of the CLH report it is stated that "EC A.3, OECD 109, GLP" was used to determine the relative density. Because of the aspect that no specific method is provided, the corresponding information (according to the document "Flutianil_DAR_04_Volume_3_B-2_2013-06-18[1].pdf" on the physical and chemical properties attached in IUCLID section 13: pycnometer method) should be added. Furthermore, the information on the temperature (20°C) should be added. Further information: The UK CA for the PPP procedure presented a revised DAR in April 2014. Regarding human health assessment, it contained further toxicological information that might have been relevant for the evaluation (mode of action assessment on possibly endocrine mediated effects).				

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON FLUTIANIL (ISO); (2Z)-{[2-FLUORO-5-(TRIFLUOROMETHYL)PHENYL]THIO}[3-(2-METHOXYPHENYL)-1,3-THIAZOLIDIN-2-YLIDENE]ACETONITRILE

Dossier Submitter's Response
Proposed C&L: Thank you for your comments. With regard to carcinogenicity, see our specific response to comment number 3 later. Substance identity: Thank you for your comments. The IUCLID has been updated as suggested. We agree with the comments regarding the specific method and temperature for the relative density. However, we can not update the CLH report at this stage. Further information: The information included in the April 2014 DAR has been taken into account in the CLH report.
RAC's response
Thank you for comments suggesting classification of flutianil as Repr. 2, H361d and Carc. 2 (H351). In the analysis of developmental toxicity data it has been noted that only part of the available historical control data on incidence of hydrocephalus was used in CLH report. The developmental toxicity studies for flutanil were done between 19 February and 16 March 2007. The laboratory historical control data (HCD) provided by Dossier Submitter in rabbits from the same laboratory covering the period February 2005 – June 2006, thus roughly 6 months before study was done, showed that 2 foetuses with visceral hydrocephalus in a single litter was the maximum incidence in untreated rabbits. The litter incidence of hydrocephalus observed in animals treated with flutanil at the top dose of 1000 mg/kg bw/day was not higher than in this historical control; however, the foetal incidence (3/185) at the top dose exceeded the control range by one fetus (maximum 2/189 observed in the period February 2005 – June 2006). However, the data provided during public consultation, based on 51 developmental toxicity studies performed since January 2005 till January 2007 (thus closer to the period when developmental study of Flutanil was done between 19 February -16 March 2007) on New Zealand White rabbits from the same source, have shown that hydrocephalus was found in 8 litters out of 922 examined litters, and in 12 fetuses out of examined 7621 fetuses with maximum 4 fetuses with hydrocephalus in one litter. The other data provided during public consultation, based on 49 developmental toxicity studies performed since January 2007 till January 2009 on New Zealand White rabbits from the same source, have shown that moderate or marked hydrocephalus was found only in 2 litters out of 936 examined litters, and in 6 fetuses out of examined 7708 fetuses with maximum 5 fetuses with hydrocephalus in one litter. Although these data show that the frequency of visceral hydrocephalus in control time-mated pregnant New Zealand White rabbits is very low, they also demonstrate that the occurrence of hydrocephalus in 3 fetuses in one litter in the group of 22 litters of dams exposed at a dose of 1000 mg/kg bw/day by gavage to flutanil is not treatment related, because it is well within the litter and fetal incidence of this malformation reported in the historical control data on New Zealand White rabbits from the same source collected during the relevant period of time. Keeping in mind that the properly conducted developmental studies in rats and rabbits did not yield evidence of development toxicity of flutanil, RAC is of the opinion that it does not warrant classification for that hazard class. RAC's view on carcinogenicity is provided under comment No. 2 of this document.

CARCINOGENICITY

Date	Country	Organisation	Type of Organisation	Comment number
28.07.2015	France		MemberState	2

Comment received

Page 40 (4.10.5):
FR is disagreed with the proposition of no classification for carcinogenicity potential. Due to the occurrence of tumours in rats (pancreatic islet cell adenomas and cholangiomas), both types of tumours being rare, the EFSA Peer Review experts has considered during the PRAPeR meeting that classification as Carcinogenic Category 2 may be appropriate for flutianil. FR supports this position.

Dossier Submitter's Response

Thank you for your comments. In rats, an increase in islet cell adenoma of the pancreas was observed in males (but not in females) in the top dose (294 mg/kg bw/day) group (4/51 compared to 1/51 in controls). This finding marginally exceeded (by one animal) the historical control upper range of 3/51. Islet cell hyperplasia was also observed in top dose males, but the incidence was low (2/51 *vs* 0/51 in controls) and only marginally exceeded the laboratory historical control incidence rate (1/51). No toxic effects were noted in the islet cells or other tissues of the pancreas in both sexes. There was no increase in malignant tumours in males, but 2 tumours were observed in top dose (1130 mg/kg bw/day) females. However, as there were no pre-neoplastic lesions or benign Islet cell tumours in females; the increase above concurrent and historical controls was marginal; and it is possible that one of the tumours could have occurred as a consequence of metastasis from another tissue, the weight of evidence suggests that the female pancreatic carcinomas were not related to treatment. Overall, the absence of a consistent toxic response to flutianil in this organ and the sex-specific nature of the response (adenomas in males) bring into question the biological plausibility of its relation to treatment. In conclusion, there is insufficient evidence in this study for a treatment-related carcinogenic effect of flutianil in the islet cells of the pancreas.

Also in rats, bile duct cholangioma, a benign lesion, occurred in 1/17 and 1/51 females at 334 and 1130 mg/kg bw/day, respectively, but not in the concurrent or historical controls. In females, the incidence of bile duct hyperplasia (graded as 'slight') was slightly increased at the top dose at 52 weeks but not at 104 weeks. However, at 104 weeks, the severity of the hyperplasia was more pronounced than in controls. There were no malignant bile duct tumours in any female rat and, despite the slightly increased incidence/severity of bile duct hyperplasia in the top dose females, no toxic effects were reported in this organ in both sexes. In males, there were no benign tumours of the bile duct. Malignant cholangiocarcinoma was seen in 1/18 low dose males (at 2.5 mg/kg bw/day). However, there were no such tumours in any other dose group. In addition, there were ascites and severe hepatocellular necrosis in this animal. Therefore, this isolated carcinoma finding in a low dose group male is considered to be un-related to treatment. Overall, the absence of a clear toxic response to flutianil in this organ and the sex-specific nature of the response (adenomas in females) bring into question the biological plausibility of its relation to treatment. In conclusion, there is insufficient evidence in this study for a treatment-related carcinogenic effect of flutianil on the bile duct.

In view of these arguments, the DS remains of the opinion that classification for carcinogenicity is not justified.

RAC's response

Thank you for the comment. In the case of carcinogenicity RAC supports the opinion of the Dossier Submitter.

In the combined chronic toxicity/carcinogenicity study in the rat [28] there were no increase in incidence of tumors, except an increase in adenomas of islet cells of the pancreas, which was observed in males, but not in females, in the top dose group (4/51 - 8% compared to 1/51 – 2% in controls). This finding marginally exceeded (by one animal) the laboratory historical control upper range of 3/51 (6%). However, it is noted that this incidence was well within the historical control upper range value of 44% from the RCC database (RCC Ltd.) and of 15.8% from the publication of Carlus *et al.* (2013). There was no increase in islet cell carcinoma both in female and male rats at any dose level.

The hyperplasia of islet cells of the pancreas in the rat carcinogenicity study was also observed in top dose males, but the incidence was low (2/51 vs. 0/51 in controls) and only marginally exceeded the laboratory historical control incidence rate (1/51). Hyperplasia was not seen at 52 weeks. The grading of the hyperplasia was 'slight' in one animal that died in week 100 and 'moderate' at terminal kill in the other animal. No toxic effects were noted in the islet cells or other tissues of the pancreas. These findings may be indicative of a slight treatment related tumourigenic effect of flutianil on the islet cells of the pancreas; however, considering the adenoma exceeded only marginally the laboratory historical control range (by one animal); the hyperplasia was graded as slight/moderate; and no toxicity was noted in the pancreas; the evidence for a treatment related effect is considered equivocal.

There was one case of islet cell carcinoma in one male at 2000 ppm, but as the same tumour was also seen in one control male and none were evident at the top dose, this was not considered to have been treatment-related.

No islet cell hyperplasia or adenoma were reported in females, which raised further doubt about the relation to treatment of the findings in males.

Islet cell carcinoma of the pancreas was seen in 2/51 top dose group females (*vs*. 1/51 in controls), both of whom died before the end of the study. The laboratory historical control range for this finding was 0/51 - 1/51. There was some doubt about the aetiology of one of these tumours in one of the two females affected at a top dose. This female was killed *in extremis* during week 94 and had multiple tumours; in addition to islet cell carcinoma, the female presented with pituitary and uterine horn adenocarcinomas, both of which had metastasised. Therefore, it is possible that the pancreatic tumour was also a secondary one (although this was not confirmed unequivocally in the study report). Overall, as there were no pre-neoplastic lesions or benign islet cell tumours in females; the increase above concurrent and historical controls was marginal; and it is possible that one of the tumours could have occurred as a consequence of metastasis from another tissue, therefore the weight of evidence suggests that the female pancreatic carcinomas were not related to treatment. Overall, the absence of a consistent toxic response to flutianil in this organ and the sex-specific nature of the response (adenomas in males) bring into question the biological plausibility of its relation to treatment.
In conclusion, there is insufficient evidence in this study for a treatment-related carcinogenic effect of flutianil in the islet cells of the pancreas.

Bile duct cholangioma, a benign lesion, occurred at an incidence of 2% in 1/17 and 1/51 females in the 6000 and 20000 ppm dose groups, respectively, but not in the concurrent or historical controls (0%). However, it is noted that this incidence was within the

historical control upper range value of 2% from the RCC database (RCC Ltd.) and of 6% from public domain sources. There were no malignant bile duct tumours in any female rat and, despite the slightly increased incidence/severity of bile duct hyperplasia in the top dose females, no toxic effects were reported in this organ in both sexes. In males, there were no benign tumours of the bile duct. Malignant chloangiocarcinoma was seen in 1/18 low dose males. However, there were no such tumours in any other dose group. In addition, there were ascites and severe hepatocellular necrosis in this animal. Therefore, this isolated carcinoma finding in a low dose group male is considered to be un-related to treatment. Overall, the absence of a clear toxic response to flutianil in this organ and the sex-specific nature of the response (adenomas in females) bring into question the biological plausibility of its relationship to treatment.
In conclusion, there is insufficient evidence in this study for a treatment-related carcinogenic effect of flutianil on the bile duct.
In summary, flutianil was not carcinogenic in the rat up to the limit dose in females and up to a dose causing kidney toxicity in males.

In a GLP and guideline compliant carcinogenicity study in the mouse [29] flutianil was administered to 52 male and 52 female CD1 mice/group for a minimum of 78 weeks. Dose levels were 1000, 3000 and 10000 ppm. There were no treatment related effects on survival. At the end of the study body weights and body weight gains for males and females were comparable to the control group. No notable changes in any organ weight, irrespective of sex/dose were observed.

A marginal increase in hepatocellular carcinoma was seen in males in all dose groups. The increase did not reach statistical significance, but exceeded the maximum laboratory historical control rate by a single incidence in both the low and high dose groups. Hepatocellular adenoma was increased in the mid dose group but showed no dose response relationship. These findings in males are considered to be incidental as there was no association with an increase in pre-neoplastic findings or benign tumours, and similar findings were not seen in females.

No inhalation or dermal carcinogenicity studies were performed.

Taking into account that there is no sufficient evidence for a carcinogenic effect in rats and mice, and lack of genotoxicity of flutianil, RAC is of the opinion that flutianil does not warrant classification for carcinogenicity.

Date	Country	Organisation	Type of Organisation	Comment number
30.07.2015	Germany		MemberState	3
Comment received				
In the long-term rat study, increased incidences on islet cell adenoma were reported in top dose males and islet cell carcinoma in top dose females. Additionally, the incidence of cholangioma was increased in the two highest dose groups in females. The incidences were above concurrent controls and the laboratory's historical control range. When considering the reported HCD, these tumours occur only very seldom under the conditions of this laboratory. The other HCD which were mentioned in the CLH dossier, seem to be less relevant, as they come from other laboratories. In summary, the presented study in rats raises sufficient evidence for carcinogenic properties of flutianil, to classify it with Carc. 2 (H351). This would be in line with the recommendation of EFSA's Pesticides Peer Review Experts' Meeting 114 and the				

conclusion of EFSA's peer review.

Dossier Submitter's Response

DS: In rats, an increase in islet cell adenoma of the pancreas was observed in males (but not in females) in the top dose (294 mg/kg bw/day) group (4/51 compared to 1/51 in controls). This finding marginally exceeded (by one animal) the historical control upper range of 3/51. Islet cell hyperplasia was also observed in top dose males, but the incidence was low (2/51 *vs* 0/51 in controls) and only marginally exceeded the laboratory historical control incidence rate (1/51). No toxic effects were noted in the islet cells or other tissues of the pancreas in both sexes. There was no increase in malignant tumours in males, but 2 tumours were observed in top dose (1130 mg/kg bw/day) females. However, as there were no pre-neoplastic lesions or benign Islet cell tumours in females; the increase above concurrent and historical controls was marginal; and it is possible that one of the tumours could have occurred as a consequence of metastasis from another tissue, the weight of evidence suggests that the female pancreatic carcinomas were not related to treatment. Overall, the absence of a consistent toxic response to flutianil in this organ and the sex-specific nature of the response (adenomas in males) bring into question the biological plausibility of its relation to treatment. In conclusion, there is insufficient evidence in this study for a treatment-related carcinogenic effect of flutianil in the islet cells of the pancreas.

Also in rats, bile duct cholangioma, a benign lesion, occurred in 1/17 and 1/51 females at 334 and 1130 mg/kg bw/day, respectively, but not in the concurrent or historical controls. In females, the incidence of bile duct hyperplasia (graded as 'slight') was slightly increased at the top dose at 52 weeks but not at 104 weeks. However, at 104 weeks, the severity of the hyperplasia was more pronounced than in controls. There were no malignant bile duct tumours in any female rat and, despite the slightly increased incidence/severity of bile duct hyperplasia in the top dose females, no toxic effects were reported in this organ in both sexes. In males, there were no benign tumours of the bile duct. Malignant cholangiocarcinoma was seen in 1/18 low dose males (at 2.5 mg/kg bw/day). However, there were no such tumours in any other dose group. In addition, there were ascites and severe hepatocellular necrosis in this animal. Therefore, this isolated carcinoma finding in a low dose group male is considered to be un-related to treatment. Overall, the absence of a clear toxic response to flutianil in this organ and the sex-specific nature of the response (adenomas in females) bring into question the biological plausibility of its relation to treatment. In conclusion, there is insufficient evidence in this study for a treatment-related carcinogenic effect of flutianil on the bile duct.

In view of these arguments, the DS remains of the opinion that classification for carcinogenicity is not justified.

RAC's response

Thank you for the comment. In the case of carcinogenicity RAC supports the opinion of the Dossier Submitter.

In the combined chronic toxicity/carcinogenicity study in the rat [28] there were no increase in incidence of tumors, except an increase in adenomas of islet cells of the pancreas, which was observed in males, but not in females, in the top dose group (4/51 - 8% compared to 1/51 – 2% in controls). This finding marginally exceeded (by one animal) the laboratory historical control upper range of 3/51 (6%). However, it is noted that this incidence was well within the historical control upper range value of 44% from the RCC database (RCC Ltd.) and of 15.8% from the publication of Carlus *et al*. (2013). There was

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In conclusion, there is insufficient evidence in this study for a treatment-related carcinogenic effect of flutianil on the bile duct.

In summary, flutianil was not carcinogenic in the rat up to the limit dose in females and up to a dose causing kidney toxicity in males.

In a GLP and guideline compliant carcinogenicity study in the mouse [29] flutianil was administered to 52 male and 52 female CD1 mice/group for a minimum of 78 weeks. Dose levels were 1000, 3000 and 10000 ppm. There were no treatment related effects on survival. At the end of the study body weights and body weight gains for males and females were comparable to the control group. No notable changes in any organ weight, irrespective of sex/dose were observed.

A marginal increase in hepatocellular carcinoma was seen in males in all dose groups. The increase did not reach statistical significance, but exceeded the maximum laboratory historical control rate by a single incidence in both the low and high dose groups. Hepatocellular adenoma was increased in the mid dose group but showed no dose response relationship. These findings in males are considered to be incidental as there was no association with an increase in pre-neoplastic findings or benign tumours, and similar findings were not seen in females.

No inhalation or dermal carcinogenicity studies were performed.

Taking into account that there is no sufficient evidence for a carcinogenic effect in rats and mice, and lack of genotoxicity of flutianil, RAC is of the opinion that flutianil does not warrant classification for carcinogenicity.

Date	Country	Organisation	Type of Organisation	Comment number
31.07.2015	United Kingdom	-	BehalfOfAnOrganisation	4
Comment received				
It is agreed that there is insufficient evidence in the rat study to suggest that flutianil is carcinogenic. The arguments presented for both the islet cells of the pancreas and bile duct cholangioma are compelling, well contrasted and balanced in the arguments put forward. It is concluded that there is insufficient evidence that for a treatment related carcinogenic effect of flutianil on the bile duct or in the islet cells of the pancreas.				
Dossier Submitter's Response				
Noted.				
RAC's response				
Thank you for the comment.				

MUTAGENICITY

Date	Country	Organisation	Type of Organisation	Comment number
28.07.2015	France		MemberState	5
Comment received				
No comment				

Date	Country	Organisation	Type of Organisation	Comment number
30.07.2015	Germany		MemberState	6
Comment received				
Considering the presented study results, we support the proposal not to classify for mutagenicity.				
Dossier Submitter's Response				
Noted. Thank you.				
RAC's response				
Noted. Thank you				

Date	Country	Organisation	Type of Organisation	Comment number
31.07.2015	United Kingdom	-	BehalfOfAnOrganisation	7
Comment received				
A robust analysis given in the proposal describes convincing evidence that flutianil is not genotoxic				
Dossier Submitter's Response				
Noted. Thank you.				
RAC's response				
Noted. Thank you.				

TOXICITY TO REPRODUCTION

Date	Country	Organisation	Type of Organisation	Comment number
30.07.2015	United States		Individual	8
Comment received				
The CLH document discussed the developmental toxicity of flutianil in rats and rabbits in Section 4.11.2.1 and concluded on page 50: *In conclusion, there was a slight increase in the foetal incidence of visceral hydrocephalus at the top dose of 1000 mg/kg bw/day in rabbits in the absence of maternal toxicity. Although this increase marginally exceeds (by 1 foetus) the historical control range and there is no difference in the total number of foetuses with any malformations between this dose group and the controls, relation to treatment cannot be excluded.* In response to this conclusion, I asked Dr. Alan Hoberman, a renowned expert in developmental animal studies, to review the data and provide his opinion. Dr. Hoberman is the Executive director of Charles River Preclinical Testing Services, PA (formerly Argus Research). Highlight of relevance: The incidence of hydrocephalus at the top dose of 1000 mg/kg/day was one fetus more in a single litter than observed in the historical control data presented in the report. Therefore the littler incidence which is the more appropriate unit for evaluation in developmental toxicity studies did not differ from the historical control data base for the Testing facility.				

Additional historical data was provided from the Charles River historical database for the same time period and from animals from the same breeder as the Testing Facility. Based on this additional historical control information, it was clear that during the time this study was conducted, the incidence of hydrocephalus had increased and has since come back to a lower level. Based on this it is concluded, there is no relationship to treatment of the apparent increased incidence of hydrocephalus. *ECHA note: The following attachment was submitted with the following comment:* *2. Expert report: A prenatal developmental toxicity study of OK-5203 technical grade in rabbits*
Dossier Submitter's Response
Thank you for your comments and we note the submission of the expert report which we ask RAC to consider. However, in a guideline developmental toxicity study in rabbits, there was a slight increase in the foetal incidence of visceral hydrocephalus at the top dose of 1000 mg/kg bw/day (3 foetuses in 1 litter *vs.* 0 in controls) in the absence of maternal toxicity. Although this increase marginally exceeds the historical control range (maximum of 2 foetuses in a single litter) and there is no difference in the total number of foetuses with any malformations between this dose group and the controls, relation to treatment of this malformation cannot be excluded. Overall, there is limited evidence that flutianil is a developmental toxicant in rabbits. Therefore the DS remains of the opinion that classification is justified. Although the litter rather than the foetus is the prescribed statistical unit by the guideline, in this case, statistics play no role as the numbers of foetuses/litters affected are so low. HCD from other laboratories have been presented for completeness, but it is the laboratory own HCD that play the most important role when making a decision.
RAC's response
Noted. Thank you. Please see RAC response to comment No. 1

Date	Country	Organisation	Type of Organisation	Comment number
17.07.2015	United Kingdom	-	BehalfOfAnOrganisation	9
Comment received				
Page 45 - 47. Please refer to attached document which provides a detailed argument as to the relevance of the increases in hydrocephaly observed in the rabbit developmental study. *ECHA note: The following attachment was submitted with the following comment:* *1. Discussion of the hydrocephaly incidence in the rabbit developmental toxicity study conducted on flutianil*				
Dossier Submitter's Response				
Thank you for the report, we ask that RAC take account of this.				
RAC's response				
Noted. Thank you. Please see RAC response to comment No. 1				

Date	Country	Organisation	Type of Organisation	Comment number
28.07.2015	Finland		MemberState	10
Comment received				
We support the proposed classification for developmental effects as Repr. 2, H361d for Flutianil. We also agree that the substance should not be classified for fertility, since no consistent or clear findings related to this hazard end-point were reported.				
Dossier Submitter's Response				
Noted. Thank you.				
RAC's response				
Thank you. RAC agrees that no classification for fertility is warranted, and for developmental toxicity see RAC response to comment 1 in this document.				

Date	Country	Organisation	Type of Organisation	Comment number
28.07.2015	France		MemberState	11
Comment received				
Page 49 (4.11.5): FR is agreed with the proposed classification of flutianil as toxic for the reproduction (regarding developmental toxicity) category 2 based on both rat and rabbit studies. Furthermore, there is evidence that treatment with flutianil produced adverse effects on gonads (testes softening and atrophy in mice, seminiferous tubules atrophy and cellular infiltrate of prostate in dogs, reduced number of implantation sites and pups delivered, increased histopathological findings and increased uterus weight, decreased ovary weight and atrophy) and carcinogenic effect on the pancreatic islet system in rats. For these effects an endocrine-mediated MoA cannot be ruled out. Following the EFSA PRAPeR expert meeting, a critical area of concern has been identified with regard to Annex II, Point 3.6.5 of Regulation (EC) No 1107/2009 interim provisions for active substances that shall be considered to have endocrine disruption properties. On this basis, a data gap has been identified by EFSA for the Level 2 tests currently indicated in the OECD Conceptual Framework for EAS (oestrogen, androgen and steroidogenesis) modalities, to clarify a possible endocrine-mediated MoA. FR supports this position and the need of further data in order to analyze a possible endocrine-mediated MoA.				
Dossier Submitter's Response				
Please note that the repro classification is based only on the presence of visceral hydrocephaly in the rabbit. With regard to the rat study, a very low incidence of only one type of skeletal variation (asymmetry of the sternal centra) was noted from a dose 333 mg/kg bw/day in the absence of maternal toxicity. This finding is considered to be of minimal toxicological significance and does not represent a significant developmental hazard. With regard to evidence of adverse effects on the gonads, the DS notes that Minor findings in the reproductive organs were reported in mice, rats and dogs in the available guideline				

repeated dose toxicity studies (see **Error! Reference source not found.** of the CLH report).

In the mouse, testis atrophy was noted in single males in a 90-day study from a dose of 409 mg/kg bw/day, but the incidence was within the laboratory historical control range. Testis atrophy was also noted in the chronic toxicity/carcinogenicity study at the top dose of 1086 mg/kg bw/day, but, again, it was considered unrelated to treatment as it fell within the laboratory historical control range.

In the dog, organ weight changes of testis, prostate and uterus, and histopathological findings in testes (atrophy of seminiferous tubules) and prostate (cell infiltration) were seen from relatively low doses (10-30 mg/kg bw/day) in the 28-day and 90-day studies, but were not confirmed in the 1-year study at similar dose levels after a much longer period of treatment. Therefore, these findings were considered to be of no toxicological significance.

In the rat chronic/carcinogenicity study, isolated histopathological findings of the uterus (cysts, luminal dilatation, hyperplasia and polyps) were seen in females at 1130 mg/kg bw/day and a slight increase in the incidence of histopathological findings of the male reproductive organs (atrophy of testes, seminal vesicle and coagulating gland and oligospermia of epididymis) was observed at the top dose of 249 mg/kg bw/day. Given the low incidences of these isolated findings in the uterus and male reproductive organs, it is unclear whether these observations were treatment-related or incidental. However, after taking into account that they were not reproduced in the rat two-generation study, in which no clear functional effects on fertility were observed, it can be concluded that these findings in the reproductive organs of rat do not represent a hazard to reproduction.

Overall, the available evidence shows that flutianil has no effects on reproductive organs, performance and fertility. Therefore, in the absence of adverse effects on relevant organs, there is no ED MoA to discuss/consider.

RAC's response

Thank you. RAC supports the Dossier Submitter arguments for lack of justification for classification for fertility.

As far as incidence of hydrocephalus in rabbits is concerned, please see RAC response to comment 1 in this document. The available HCD data show that the frequency of visceral hydrocephalus in control time-mated pregnant New Zealand White rabbits is very low, but they demonstrate that the occurrence of hydrocephalus in 3 fetuses in one litter in the group of 22 litters of dams exposed at a dose of 1000 mg/kg bw/day by gavage to flutanil is not treatment related, because it is well within the litter and fetal incidence of this malformation reported in the historical control data on New Zealand White rabbits from the same source collected during the relevant period of time.

Keeping in mind that the properly conducted developmental studies in rats and rabbits did not yield evidence of development toxicity of flutanil, RAC is of the opinion that it does not warrant classification to that hazard class.

Date	Country	Organisation	Type of Organisation	Comment number
30.07.2015	Germany		MemberState	12

Comment received

Considering the presented study results (hydrocephaly in rabbits above relevant HCD), we support the proposal to classify for reproductive toxicity category 2 (H361d). According to the CLH dossier, maternal toxicity was not very high in the top dose group.

Detailed reasons for a classification of flutianil as Repr. Cat. 2:

Two prenatal developmental toxicity studies in rats and in rabbits are available.
In the rat study asymmetric sternal centra were found as only effect after exposure to the substance. This effect occurred in 2 foetuses/22 litters in the highest (1000 mg/kg bw/d) and in 1 foetus/22 litters (333 mg/kg bw/d) in the next lower dose group.

In rabbits hydrocephalies were observed in 4 foetuses, one in the lowest (100 mg/kg bw/d) and 3 in the highest dose group (1000 mg/kg bw/d). The effect hydrocephalus as a finding in developmental toxicity studies was identified as a malformation with a high level of concern (Moore et al., 2013).

Conclusions:
In two animal studies (rat and rabbit) effects concerning development of the foetuses are described. In rats only one kind of effect is observed - asymmetric sternal centra – without maternal toxicity. Neither the level of concern nor the consequences of this finding for the animals are clear or defined. Furthermore only a small number of foetuses were affected.

The most critical finding with regard to classification for developmental effects is a slight increased incidence of hydrocephalies in rabbit foetuses. There is no clear dose response relationship to find. The incidences of 3 foetuses with this malformation from one litter exceeded the historical control range with maximal 2 foetuses from one litter only marginally. In addition, these 3 foetuses came from the same litter, which could question a relation between the occurrence of this malformation and the treatment with the substance. The effect hydrocephalus found in the developmental study in rabbits is identified as a malformation which would justify a classification of flutianil as Repr. Cat. 1B. The criteria for a classification in Category 1B is a clear evidence of an adverse effect of a substance on development of the foetuses. As stated above these clear indications are not available for flutianil. The effects found in rat and rabbit in the developmental toxicity studies are not convincing, clear and strong enough to justify a classification in Cat. 1B. For a Classification in Category 2 only some evidence from experimental animals of an adverse effect on development is required.
Therefore a classification of flutianil for development toxicity Category 2 is supported.

Reference:
- Moore et al., "Guidance on classification for reproductive toxicity under the globally harmonized system of classification and labelling of chemicals (GHS)" Crit Rev Toxicol, 2013; 43(10): 850–891.

Dossier Submitter's Response

Noted. Thanks you.

RAC's response

In a developmental toxicity study in rats a very low incidence was noted of skeletal variations (asymmetry) of the sternal centra amounting to 1/22 litters vs. 0/21 in control and to 1/129 foetus vs. 0/114 in control at 333 mg/kg bw/day without maternal toxicity and to 2/22 litters vs. 0/21 in control and to 2/135 foetus vs. 0/114 in control at 1000 mg/kg bw/day concurrent with maternal toxicity. RAC agrees that neither the level of concern nor the consequences of this finding for the animals are clear or defined. These findings are considered to be of minimal toxicological significance and do not represent a significant developmental hazard.

As far as the incidence of hydrocephalus in rabbits is concerned please see RAC response to comment 1 in this document. The available HCD data show that the frequency of visceral hydrocephalus in control time-mated pregnant New Zealand White rabbits is very low, but they demonstrate that the occurrence of hydrocephalus in 3 fetuses in one litter in the group of 22 litters of dams exposed at a dose of 1000 mg/kg bw/day by gavage to flutanil is not treatment related, because it is well within the litter and fetal incidence of this malformation reported in the historical control data on New Zealand White rabbits from the same source collected during the relevant period of time.

Having in mind that the properly concucted developmental studies in rats and rabbits did not yield evidence of development toxicity of flutanil, RAC is of the opinion that it does not warrant classification to that hazard class.

Date	Country	Organisation	Type of Organisation	Comment number
31.07.2015	United Kingdom	-	BehalfOfAnOrganisation	13
Comment received				
Comments provided earlier.				
Dossier Submitter's Response				
Noted.				
RAC's response				
Noted.				

RESPIRATORY SENSITISATION

Date	Country	Organisation	Type of Organisation	Comment number
28.07.2015	France		MemberState	14
Comment received				
No comment.				

Date	Country	Organisation	Type of Organisation	Comment number
30.07.2015	Germany		MemberState	15
Comment received				
According to the CLH dossier, the relevant data are lacking to judge for this hazard.				
Dossier Submitter's Response				
Noted. Thank you.				
RAC's response				
Noted. Thank you.				

Date	Country	Organisation	Type of Organisation	Comment number
31.07.2015	United Kingdom	-	BehalfOfAnOrganisation	16

Comment received
Agree with the lack of data to trigger classification.
Dossier Submitter's Response
Noted.
RAC's response
Noted. Thank you.

OTHER HAZARDS AND ENDPOINTS – Acute Toxicity

Date	Country	Organisation	Type of Organisation	Comment number
30.07.2015	Germany		MemberState	17
Comment received				
Considering the presented study results after oral, dermal or inhalation exposure, we support the proposal not to classify for acute dermal or inhalation toxicity.				
Dossier Submitter's Response				
Noted. Thank you.				
RAC's response				
Noted. Thank you.				

Date	Country	Organisation	Type of Organisation	Comment number
31.07.2015	United Kingdom	-	BehalfOfAnOrganisation	18
Comment received				
Agree with the acute endpoints presented and the lack of need to classify.				
Dossier Submitter's Response				
Noted. Thank you.				
RAC's response				
Noted. Thank you.				

OTHER HAZARDS AND ENDPOINTS – Skin Hazard

Date	Country	Organisation	Type of Organisation	Comment number
30.07.2015	Germany		MemberState	19
Comment received				
Considering the presented study results, we support the proposal not to classify for skin corrosion/irritation.				
Dossier Submitter's Response				
Noted. Thank you.				
RAC's response				
Noted. Thank you.				

Date	Country	Organisation	Type of Organisation	Comment number
31.07.2015	United Kingdom	-	BehalfOfAnOrganisation	20
Comment received				
Agree with the skin irritation endpoint presented and the lack of need to classify.				
Dossier Submitter's Response				
Noted. Thank you.				
RAC's response				
Noted. Thank you.				

OTHER HAZARDS AND ENDPOINTS – Eye Hazard

Date	Country	Organisation	Type of Organisation	Comment number
30.07.2015	Germany		MemberState	21
Comment received				
Considering the presented study results, we support the proposal not to classify for serious eye damage/eye irritation.				
Dossier Submitter's Response				
Noted. Thank you.				
RAC's response				
Noted. Thank you.				

Date	Country	Organisation	Type of Organisation	Comment number
31.07.2015	United Kingdom	-	BehalfOfAnOrganisation	22
Comment received				
Agree with the eye irritation endpoint presented and the lack of need to classify.				
Dossier Submitter's Response				
Noted. Thank you				
RAC's response				
Noted. Thank you.				

OTHER HAZARDS AND ENDPOINTS – Skin Sensitisation Hazard

Date	Country	Organisation	Type of Organisation	Comment number
30.07.2015	Germany		MemberState	23
Comment received				
Considering the presented study results, we support the proposal not to classify for skin sensitisation.				
Dossier Submitter's Response				
Noted. Thank you.				

RAC's response
Noted. Thank you.

Date	Country	Organisation	Type of Organisation	Comment number
31.07.2015	United Kingdom	-	BehalfOfAnOrganisation	24
Comment received				
Agree with the lack of evidence to suggest any skin sensitisation potential				
Dossier Submitter's Response				
Noted. Thank you.				
RAC's response				
Noted. Thank you.				

OTHER HAZARDS AND ENDPOINTS – Specific Target Organ Toxicity Single Exposure

Date	Country	Organisation	Type of Organisation	Comment number
30.07.2015	Germany		MemberState	25
Comment received				
Considering the presented study results, we support the proposal not to classify for STOT-SE.				
Dossier Submitter's Response				
Noted. Thank you.				
RAC's response				
Noted. Thank you.				

Date	Country	Organisation	Type of Organisation	Comment number
31.07.2015	United Kingdom	-	BehalfOfAnOrganisation	26
Comment received				
Agree that the information from the acute toxicity studies in rats shows no indication that flutianil causes toxicity to specific organs after a single exposure.				
Dossier Submitter's Response				
Noted. Thank you.				
RAC's response				
Noted. Thank you.				

OTHER HAZARDS AND ENDPOINTS – Specific Target Organ Toxicity Repeated Exposure

Date	Country	Organisation	Type of Organisation	Comment number
30.07.2015	Germany		MemberState	27

Comment received
Considering the presented study results, we support the proposal not to classify for STOT-RE.
Dossier Submitter's Response
Noted. Thank you.
RAC's response
Noted. Thank you.

Date	Country	Organisation	Type of Organisation	Comment number
31.07.2015	United Kingdom	-	BehalfOfAnOrganisation	28
Comment received				
From the data presented it is agreed that the mouse and dog showed no significant (or consistent) toxic effects at any dose. Where effects occurred in sub-acute studies, the effects were not replicated in sub-chronic / chronic studies. In the rat, where significant toxic effects occurred (in the liver), these were well in excess of the specified guidance values for classification with STOT RE Cat.2				
Dossier Submitter's Response				
Noted. Thank you				
RAC's response				
Noted. Thank you.				

OTHER HAZARDS AND ENDPOINTS – Aspiration Hazard

Date	Country	Organisation	Type of Organisation	Comment number
30.07.2015	Germany		MemberState	29
Comment received				
According to the CLH dossier, the relevant data are lacking to judge for this hazard.				
Dossier Submitter's Response				
It is not proposed to classify for aspiration toxicity.				
RAC's response				
Noted. Thank you. Flutanil is a solid, therefore measurement of a kinematic viscosity may not be possible.				

Date	Country	Organisation	Type of Organisation	Comment number
31.07.2015	United Kingdom	-	BehalfOfAnOrganisation	30
Comment received				
Agree with the lack of evidence to suggest the requirement to label for aspiration hazards.				
Dossier Submitter's Response				
Noted. Thank you.				
RAC's response				
Noted. Thank you. Flutanil is a solid, therefore measurement of a kinematic viscosity may not be possible.				

OTHER HAZARDS AND ENDPOINTS – Hazardous to the Aquatic Environment

Date	Country	Organisation	Type of Organisation	Comment number
28.07.2015	France		MemberState	31
Comment received				
We agree with the classification and the chronic M factor proposed for Environmental hazards.				
Dossier Submitter's Response				
Noted. Thank you.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
31.07.2015	United Kingdom	-	BehalfOfAnOrganisation	32
Comment received				
Agree with the classification and labelling proposed for environmental hazards				
Dossier Submitter's Response				
Noted. Thank you.				
RAC's response				
Noted.				

OTHER HAZARDS AND ENDPOINTS – Hazardous to the Ozone Layer

Date	Country	Organisation	Type of Organisation	Comment number
31.07.2015	United Kingdom	-	BehalfOfAnOrganisation	33
Comment received				
Agree with the lack of evidence to suggest any effects on the ozone layer				
Dossier Submitter's Response				
Noted. Thank you.				
RAC's response				
Noted.				

OTHER HAZARDS AND ENDPOINTS – Physical Hazards

Date	Country	Organisation	Type of Organisation	Comment number
31.07.2015	United Kingdom	-	BehalfOfAnOrganisation	34
Comment received				
Agree with the lack of evidence to suggest the requirement to label for physical hazards				
Dossier Submitter's Response				
Noted. Thank you.				
RAC's response				
Noted. Thank you.				

NON-CONFIDENTIAL ATTACHMENTS RECEIVED

1. Discussion of the hydrocephaly incidence in the rabbit developmental toxicity study conducted on flutianil – Submitted on 17/07/2015. [Refer to comment 9]

2. Expert report: A prenatal developmental toxicity study of OK-5203 technical grade in rabbits – Submitted by an individual on 30/07/2015. [Refer to comment 8]