Committee for Risk Assessment

RAC

Annex 2

Response to comments document (RCOM)

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

5-fluoro-1,3-dimethyl-N-[2-(4-methylpentan-2-yl)phenyl]-1H-pyrazole-4-carboxamide; 2'-[(RS)-1,3-dimethylbutyl]-5-fluoro-1,3-dimethylpyrazole-4-carboxanilide; penflufen

EC Number: -
CAS Number: 494793-67-8

CLH-O-0000001412-86-233/F

Adopted

15 October 2018

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON 5-FLUORO-1,3-DIMETHYL-N-[2-(4-METHYLPENTAN-2-YL)PHENYL]-1H-PYRAZOLE-4-CARBOXAMIDE; 2'-[(RS)-1,3-DIMETHYLBUTYL]-5-FLUORO-1,3-DIMETHYLPYRAZOLE-4-CARBOXANILIDE; PENFLUFEN

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: 5-fluoro-1,3-dimethyl-N-[2-(4-methylpentan-2-yl)phenyl]-1H-pyrazole-4-carboxamide; 2'-[(RS)-1,3-dimethylbutyl]-5-fluoro-1,3-dimethylpyrazole-4-carboxanilide; penflufen
EC number: -
CAS number: 494793-67-8
Dossier submitter: United Kingdom

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
29.11.2017	Germany		MemberState	1
Comment received				
The proposed classification for penflufen is Carc.2, H351, Aquatic Acute 1; H400 and Aquatic Chronic 1, H410. The corresponding signal word for these hazard classes is "Warning" and not "Danger" which is proposed on page 8 of the report.				
Dossier Submitter's Response				
Thank you for the clarification; noted.				
RAC's response				
Thank you. Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
01.12.2017	Belgium		MemberState	2
Comment received				
BE CA welcomes this proposal for harmonized classification and labelling. As a general comment, we would have appreciate a more detailed dossier, especially regarding acute toxicity studies knowing that they are used to further support STOT SE and respiratory tract irritation assessments. We agree with the Eye Irritation and Mutagenicity no classification proposal. Editorial comment: On page 27 (non-human information regarding corrosivity), section 4.4.1 refers to section 4.4.1. We assume the point refers to section 4.3.1.				

ECHA note – An attachment was submitted with the comment above. Refer to public attachment Penflufen_STOT RE_Annex.docx
Dossier Submitter's Response
The CLH report provides sufficient detail for an assessment of the classification proposal to be made. Information about the clinical signs seen in the acute toxicity tests is provided in Table 10 and section 4.3.3 of the CLH report. They were transient in nature and did not lead to any significant functional changes in any organs. Editorial comment – yes, the reference should be to Section 4.3.1.
RAC's response
Thank you. Your support for the Eye Irritation and Mutagenicity no classification proposal is noted.

Date	Country	Organisation	Type of Organisation	Comment number
27.11.2017	France		MemberState	3
Comment received				
p5: The Commission Implementing Regulation (EU) No 1031/2013 of 24 October 2013 indicates a minimum purity of 950 g/kg for the active substance penflufen. The minimum purity of 980 g/kg indicated in addendum 2 to Volume 4 (July 2015) cannot be taken into account and should not be used in the CLH report. p15: There is a typing error for water solubility: 10.09 mg/L instead of 10.9 mg/L at pH7.				
Dossier Submitter's Response				
p5. Thank you for the clarification; noted. However, as indicated on page 13 of the CLH report, in full-scale production the purity of the specification has increased to >98%. p15. Noted.				
RAC's response				
Thank you, your comment regarding purity is noted, as is the dossier submitter's explanation.				

CARCINOGENICITY

Date	Country	Organisation	Type of Organisation	Comment number
30.11.2017	Germany	Bayer AG	Company-Manufacturer	4
Comment received				
The general toxicity profile of penflufen is characterized by very low acute toxicity, no mutagenicity, no reproduction and developmental toxicity. The Rapporteur Member State (UK Competent Authority) proposed to classify penflufen as "suspected of causing cancer" Carc 2; H351 based on the presence of: - small increases in the incidence of hepatocellular adenoma in female rats, and increased incidence of liver carcinoma in male mice (top and mid doses), which exceeded the concurrent and historical control incidence rates. - very small increased incidences of tubulostromal adenoma at the top dose in female rats only. - very small increased incidences of astrocytoma in male rat only at the top dose.				

- very small increased incidences of histiocytic sarcoma in male rat only at top dose.
The RMS concluded that the increased tumours frequencies were slight, only just outside control ranges and they could have arisen by chance. A case could be made for no classification, on the basis of a lack of relevance to humans. However, the relevance to humans cannot be dismissed for all the tumours types and the small increases above background levels make it difficult to conclude that they were incidental. (CLH report, page 10, 50-69)
In the present document (which is attached as "penflufen - position paper on the proposed classification with H351") the summarized data show the following:
- A long term dietary administration of penflufen to male and female C57/Bl6 mice, a slightly higher incidence of adenoma and carcinoma in the liver was found in all doses in males, when compared to controls. However, these neoplastic findings were found without any dose effect relationship over a quite large range of dose levels. They were not associated with an increased incidence of pre-neoplastic changes. Overall, the incidences of those tumours were only marginally outside the historical control range for this strain of mice and this laboratory. Therefore, these liver tumours were considered not to be treatment-related. In females there was no increased incidence of hepatocellular tumour.
- A long term dietary administration of penflufen to male and female Wistar rats, numerically higher incidences of neoplastic lesions were observed in the liver. The hepatocellular adenoma observed in female rats following a 2-year treatment period with penflufen was considered to be subsequent to a phenobarbital-like mechanism of action which is a well known mechanism of action specific to the rodent and of no relevance to humans.
- A long term dietary administration of penflufen to male and female Wistar rats, numerical higher incidences of neoplastic lesions were observed in ovaries, hematopoïetic system and brain is some treated dose groups, generally the high dose group. Given that these incidences were similar to internal and/or external historical control data, that these neoplastic lesions were generally not dose-related and that penflufen is devoid of any genotoxic potential, it was concluded that the neoplastic lesions found in the ovaries, hematopoietic system and brain were not related to treatment with penflufen.
Altogether, the weight of evidence of all existing information on the toxicological profile of penflufen and on the occurrence of spontaneous tumours, lead to the conclusion that tumours (begins and malignants) observed are unlikely related to the administration of penflufen, and that penflufen is not considered to present a carcinogenic risk to humans.
Therefore Bayer proposes to not classify penflufen with H351 (cat.2 carcinogenic).

ECHA note – An attachment was submitted with the comment above. Refer to public attachment penflufen position paper ECHA public com_nov 2017_final.pdf

Dossier Submitter's Response

The CLH report provides a hazard assessment for this endpoint, in line with the relevant criteria and guidance. There are uncertainties and concerns provided in the animal data, as highlighted by other comments received publicly in favour of an even higher classification category. We believe that our assessment is balanced and comprehensive, and that carcinogen category 2 is the most appropriate classification for this substance.

RAC's response

Thank you for your comment and the detailed analysis in the attached position paper.
As for the liver neoplasms, RAC agrees that the data available are indicative of a phenobarbital-like mechanism of action. On the other hand, RAC notes that the MoA investigations have not been as extensive as for other potential CAR activators previously evaluated by RAC and that the evidence for exclusion of some alternative mechanisms is not definitive. Therefore, human relevance is not completely excluded, although

penflufen-induced liver tumours in rats and mice are considered of less concern than some other tumour types seen in the rat carcinogenicity study.
In agreement with the dossier submitter, RAC is of the view that there are concerns and uncertainties related to all four tumour types observed, and these justify a Category 2 classification.

Date	Country	Organisation	Type of Organisation	Comment number
01.12.2017	Belgium		MemberState	5

Comment received

BE CA disagrees with the Carc. 2 classification proposal.
The liver neoplastic findings include observations of benign hepatocellular tumors in female rats (3%, 8% and 7% at respectively 100, 2000 and 7000 ppm). Observations of hepatocellular carcinomas (6% and 6% at 1000 and 6000 ppm in males, 2% at 6000 ppm in females) and adenomas (10% and 8% at respectively 100 and 6000 ppm) have also been reported in mouse. Hepatocellular carcinoma is extremely rare in the strain of mouse tested. These results are consistent with the findings in the repetitive toxicity studies, showing that liver is a target organ, but also with the centrilobular hepatocellular hypertrophy increasing in a dose-dependant manner in male and female rats and mice.
Moreover, in male rat, histiocytic sarcoma appeared in low, mid and high dose groups (5%, 5% and 8,3%). 2/5 rats in the top dose died prematurely during the carcinogenicity phase of the study.
The incidence of astrocytoma in the top dose group in male rat (5%). All affected subjects died prematurely during the study. We would also point that metabolites of penflufen have been detected in the brain of exposed rats.
Many affected rats have also been reported to have metastasis. We regret the lack of further description of this fact into the dossier.
Considering the observations of tumors in two different species in liver, the fact that liver seems to be the target-organ, but also the occurrence of metastasis and rare tumors such as hepatocellular carcinoma, BE CA believes that penflufen should be classified as Carc. 1B.

ECHA note – An attachment was submitted with the comment above. Refer to public attachment Penflufen_STOT RE_Annex.docx

Dossier Submitter's Response

As discussed in the CLH report, it is agreed that these tumour findings cannot be dismissed. However, as further detailed in Comment Number 4, the evidence is not particularly strong and in our view a Category 2 classification is the most appropriate in these circumstances.

RAC's response

Thank you for your comment.
The CLP regulation states that carcinogenicity classification should be based on a weight of evidence approach (Annex I, 3.6.2.1) and many factors increasing or decreasing the concern have to be considered (for examples see Annex I, 3.6.2.2.6).
In this case, factors reducing the concern include sex- and species-specificity of the findings, lack of statistical significance and/or weak dose-response relationship in several cases, and information, albeit not definitive, on the MoA of the liver tumours. Negative genotoxicity tests are an additional factor to be taken into account.
Consideration of all available information leads RAC to agree with the dossier submitter's proposal of Category 2.

Date	Country	Organisation	Type of Organisation	Comment number
01.12.2017	Sweden		MemberState	6
Comment received				
The Swedish CA supports classification of Penflufen CAS no 494793-67-8 for carcinogenicity based on the data specified in the proposal. We agree that there is some evidence for carcinogenicity and that the findings support classification as Carc 2. There are small increases of hepatocellular adenoma in male and female rats, increased incidence of liver carcinoma in male mice, and small increased incidences of other tumor types in rats, mostly of benign character. Available data indicate that Penflufen is not mutagenic. However, since the mode of action is not clear, its relevance to humans cannot be ruled out.				
Dossier Submitter's Response				
Thank you for supporting the proposal.				
RAC's response				
Thank you for your comment. RAC agrees that Carc. 2 is the most appropriate classification in this case.				

Date	Country	Organisation	Type of Organisation	Comment number
27.11.2017	France		MemberState	7
Comment received				
P69 4.8.6 We agree with the proposed classification H351- Carcinogenicity category 2 according to the Regulation (EC) 1272/2008, taking into account the various tumours seen in animal studies, the increased xenobiotic-metabolizing enzymes induction involved in detoxification system, the increased hepatocellular proliferation accompanied by hypertrophy, the increased frequency of altered eosinophilic foci in liver as pre-neoplastic changes and cytotoxicity noted in all tested species. However, the limited evidence demonstrated in the provided animal and human studies is not sufficiently convincing to place the substance in category 1A or 1B (no clear dose-response). The MoA of Penflufen and its relevance to human are not clear but a non-genotoxic MOA can be assumed. Activation of CAR/PXR nuclear receptors seems consistent with the increased gene transcription and activity of phase I and II enzymes (CYP2, CYP3, BROD, PROD, BQ) but a potential AhR mediation cannot be excluded (CYP1A1 induction). Considering human data, hepatocytes from only one donor were analysed to investigate the relevance to human of the carcinogenic effects. This study is not sufficient to establish a robust conclusion since various types of tumour (liver, ovary, brain and hematopoietic) are observed in animal studies with potentially different MOA. p55 Carcinogenicity in the mouse: A typographic error is noted for survival percentage in the control group: it should be 72% instead of 60%				

Dossier Submitter's Response
Thank you for supporting the proposal. p55: Noted.
RAC's response
Thank you for your comment. RAC agrees that classification in Category 2 is appropriate.

Date	Country	Organisation	Type of Organisation	Comment number
01.12.2017	Germany	Lanxess Deutschland GmbH	Company-Manufacturer	8
Comment received				
Penflufen is undergoing its approval process as new active substance under the Biocidal Products Regulation (EU) No 528/2012 (BPR). Currently no harmonised classification is available for Penflufen. As part of this process, the UK, as the evaluating Member State (eMS), submitted a proposal to the European Chemical Agency's (ECHA) Risk Assessment Committee (RAC) for harmonised classification and labelling (CLH) with Carcinogen Category 2; H351 – Suspected of causing cancer, Aquatic Acute 1 and Aquatic Chronic 1. Penflufen is of very low acute toxicity and showed no neurotoxic or immunotoxic effects, and no effects on fertility or development. The UK is quoted in its argumentation for classification with Carcinogenic Cat 2 that "a clear mechanistic basis for Penflufen carcinogenicity is lacking (the possibility that a mode of action involving CAR activation was responsible for the slight increases in liver cancer has not been established unequivocally). If Penflufen did produce a biologically significant tumour response in rats and mice, this was very weak. A case could be made for no classification, on the basis of a lack of relevance to humans." LANXESS thus supports the case that Penflufen is not considered to present a carcinogenic risk to humans. Even though the public consultation should refer to toxicological arguments on inherent properties only, Lanxess Deutschland GmbH feel the need to highlight the importance of Penflufen for the wood protection market as a new and innovative product to replace various existing active substances currently under regulatory pressure due to (new) unfavourable classification. Penflufen is an innovative, highly efficacious active substance for use in wood preservation, protecting against basidiomycete fungi which cause decay. It could play a key role in future biocidal products approvals by protecting against decay in treated articles for exterior use (including wooden doors, window frames, fences, cladding for houses). At the moment, there are numerous wood preservative products that contain e.g. the class of azole fungizides, i.e. with Propiconazole and Cyproconazole both being under regulatory pressure as (potential) exclusion candidates. Those products alongside its potential replacement Penflufen are used either in penetrating processes (vacuum pressure pre-treatment) or superficial processes (brushing and spraying). Industrial wood coatings for factory application can be water-based, solvent-based or UV curing systems. Those for exterior wood tend to be water-based, using acrylics or alkyd dispersions. Penetrating processes are carried out in a closed system. There is justifiable concern that in case the new wood preservative active substance Penflufen would be restricted due to an unfavourable classification then there would be a large impact on downstream industries due to a lack of suitable alternative active				

substances. In 2002, 81 active substances were notified in PT8. There are currently 41 approved active substance listed on the biocidal active substances database . The review programme has been active for 13 years and there are currently still two existing active substances remaining in the review programme and one new active substance Penflufen, leaving 38 approved active substance in PT8. It cannot be guaranteed that any substance still in the review programme or currently going through the approval process will be approved.

Almost all existing active substance for wood preservation have been evaluated so far and of these:
•13 substances (i.e. one third of the total) meet exclusion or substitution criteria under BPR;
•6 substances are insecticides;
•7 substances are niche applications (e.g. fumigants);
•leaving only 12 active substances remaining: Copper components (5 entries), Quaternary Ammonium Compounds (5 entries), IPBC and DCOIT as organic fungicides.

As of 15th November 2017, there are 2.285 biocidal product authorisations for PT8 on the R4BP3 database which are currently still authorised, thereof 1.412 contain the active substance Propiconazole. Of the 873 product authorisations remaining, 641 contain IPBC; these can be disregarded as they contain only IPBC, which is highly effective against discolouration but has insufficient efficacy against decay, leaving 232 authorisations. A further two can be disregarded because the active substance Dichlofluanid has already been discontinued, leaving 230 product authorisations. The remaining authorised biocidal products may not be a suitable alternative. They are solely insecticides or they meet the criteria for exclusion or are candidates for substitution.

Wood preservation is a broad use category as wood is susceptible to attack from a number of organisms. An active substance is designed to treat a certain action and will act against certain species of organism. The efficacy spectrum is substance-specific and so active substance are not readily interchangeable. When considering alternatives to Penflufen, certain active substance can be discounted as they are either too substrate/organism specific or cannot be used for mainstream wood production. Six of the approved active substance are pure wood preservative insecticides and 7 are only suitable for niche applications such as fumigation or solvent based systems, meaning that they are not alternatives to the new active substance Penflufen.

As efficacy is a concern for substance in wood preservation, substances are often used in combination in order to be able to protect against a broad spectrum of organisms. The under BPR listed fungicidal active substance include IPBC, DCOIT and Thiabendazole, although each of these have limited uses and cannot substitute Penflufen efficacy spectrum. For example, IPBC, although being highly effective, has a limited spectrum and requires other active substance in order to achieve full efficacy; DCOIT has concerns for skin sensitisation; and Thiabendazole has limited use mostly in interior applications. Of the fungicide/insecticides, 5 are copper compounds and 5 are quaternary ammonium compounds. As such, only two modes of action exist which reduces their potential efficacy.

The limited efficacy of these AS poses limited options for alternatives to the new active substance Penflufen, particularly when one considers the issue of use class and the need to combine active substance in order to meet the needed efficacy levels. Azoles are currently the most popular option, as they do not always require other active substance

to achieve the required efficacy and –unlike copper based products- they can produce colourless products. However, azoles are currently under regulatory pressure based on its classification as reprotoxic substances. Tebuconazole is classified with Reprotoxicity Cat 2. Just recently Propiconazole was suggested for classification with Reprotoxicity Cat. 1B. Cyproconazole already is classified with Reprotoxicity Cat. 1B. All three Azole actives are thus under regulatory pressure under the BPR as meeting either the exclusion or substitution criteria. Due to a lack of suitable alternative wood preservative active substances, the new active substance Penflufen has an essential impact on the (downstream) wood industry. Beside that taking the weight of evidence of all existing data on the toxicological profile of Penflufen together Lanxess Deutschland GMBH believes that the proposal to classify Penflufen as a Carcinogen Category 2; H351 – Suspected of causing cancer is not justified. Therefore Lanxess Deutschland GmbH proposes to not classify Penflufen as a Carcinogen Category 2.
Dossier Submitter's Response
The CLH report provides a hazard assessment for this endpoint, in line with the relevant criteria and guidance. There are uncertainties and concerns provided in the animal data, as highlighted by other comments received publicly in favour of an even higher classification category. We believe that our assessment is balanced and comprehensive, and that carcinogen category 2 is the most appropriate classification for this substance.
RAC's response
Thank you for your comment. Your preference for no classification is noted. As you mentioned in your comment, classification of substances has to be based on inherent properties. RAC is obliged to base the classification on a comparison with the CLP criteria and is not allowed to take into account potential downstream consequences of the outcome.

Date	Country	Organisation	Type of Organisation	Comment number
01.12.2017	Denmark		MemberState	9
Comment received				
RAC should consider if a Carc Cat 1B classification is more appropriate considering - the occurrence of both carcinoma and sarcoma - liver adenoma and carcinoma in two species - tumors above historical control (even if only slightly)				
Dossier Submitter's Response				
As discussed in the CLH report, it is agreed that these tumour findings cannot be dismissed. However, as further detailed in Comment Number 4, the evidence is not particularly strong and in our view a Category 2 classification is the most appropriate in these circumstances.				
RAC's response				
Thank you for your comment. Please see response to comment no 5.				

Date	Country	Organisation	Type of Organisation	Comment number
29.11.2017	Germany		MemberState	10
Comment received				
Thank you for a very comprehensive presentation concerning potential carcinogenic properties! We agree that a classification for carcinogenicity is needed. Due to tumours observed in two species (rat, mouse) on multiple sites partly in both sexes (increased hepatic carcinomas in male mice, in male rats increased astrocytoma and histiocytic sarcoma, in female rats increased liver adenomas, and increased tubulostromal adenoma of ovary). Especially histiocytic sarcoma in male rats, hepatocellular carcinoma in male mice and brain astrocytoma in male rats were clearly above historical control incidences. Even though the mechanistic studies showed enzyme induction including CAR/PXR activation, activation of CYP1A1 (AhR regulated) was also demonstrated – in contrast to Phenobarbital. Hence, another mechanism for hepatic carcinoma and adenoma was also involved – at least at high doses. Also inhibition of the mitochondrial phosphorylation leading to increased oxidative stress provides a potential MoA. No MoA assessment of the other (non-hepatic) tumours was presented based on the lack of mechanistic investigations. Hence these tumours need to be considered as relevant for humans. It is noted that RAC has classified several substances as carcinogens based on slightly increased incidences of brain astrocytoma.				
Dossier Submitter's Response				
Thank you for supporting the proposal.				
RAC's response				
Thank you for your comment. RAC notes your support for classification.				

TOXICITY TO REPRODUCTION

Date	Country	Organisation	Type of Organisation	Comment number
01.12.2017	Belgium		MemberState	11
Comment received				
Fertility : BE CA agrees with the conclusion of the DS not to classify Penflufen as a reproductive toxicant for the specific fertility endpoint. Developmental toxicity : However, we express our surprise that the DS did not notice the fact that all developmental malformations observed in the OECD 416 study in rabbit all have the same developmental etiology. Gastroschisis, omphalocele, cleft palate, absent kidney and cardiac malformations are the most illustrating exemples of a vascular disruption during embryogenesis. Moreover, we see two major tendencies in the developmental findings. The first one is a disruption during the fusion of the embryo lateral body walls. This disruption is illustrated in rabbit fetuses by gastroschisis, cleft palate, diaphragmatic hernia and omphalocele and is represented in all penflufen doses investigated. The second tendency is a cardiovascular disruption with absent right atrioventricular valve (30 mg/kg/day), major cardiac malformations (100 mg/kg/bw) and dilated aortic arch and ascending aorta (600 mg/kg/bw). Taken together with the absence of LOAEL for developmental toxicity and the maternal				

toxicity set at 600 mg/kg/bw, BE CA considers that the observed malformations should not be dismissed. However, due to the absent of malformations in the OECD 414 rat study, we consider that a Repr.2 is warranted for the developmental toxicity. ECHA note – An attachment was submitted with the comment above. Refer to public attachment Penflufen_STOT RE_Annex.docx
Dossier Submitter's Response
Thank you for supporting the proposal with respect to fertility and reproductive function. Regarding your comment about the developmental findings in rabbits, we would suggest that the lack of a dose-response (and especially the limited number of malformations in the highest dose group) rather points towards no classification.
RAC's response
Thank you for your comment. Your support for no classification for fertility is noted. As to the developmental toxicity, in the absence of a dose-response relationship RAC concludes that there is no clear evidence for a treatment-related effect in the rabbit.

Date	Country	Organisation	Type of Organisation	Comment number
01.12.2017	Denmark		MemberState	12
Comment received				
Agree that there are no effects on fertility or development.				
Dossier Submitter's Response				
Thank you for supporting the proposal.				
RAC's response				
Thank you, your support for no classification is noted.				

OTHER HAZARDS AND ENDPOINTS – Skin Sensitisation Hazard

Date	Country	Organisation	Type of Organisation	Comment number
27.11.2017	France		MemberState	13
Comment received				
Skin sensitization (p28 4.5.1) A major deficiency is reported in the skin sensitization study. A non-irritant dose has been used for the induction phase and no sodium lauryl sulphate has been applied in order to create an irritation on the skin of the tested animals. In this context, the proposal of no classification is questionable since, even considering this lack of irritation, 25% of positive responses has been observed in the first challenge. The conclusion should be qualified in order to take into account this major deviation.				
Dossier Submitter's Response				
The criteria for classification do not appear to advocate making predictions of hazard based on extrapolation from studies that are deficient. However, this is an interesting alternative option to our proposal.				
RAC's response				
Thank you for your comment. Please see response to comment no 14.				

Date	Country	Organisation	Type of Organisation	Comment number
01.12.2017	Belgium		MemberState	14
Comment received				
Regarding skin sensitization, penflufen induced 25% positive response at a challenge dose of 50% (intradermal induction 2,5%) in a OECD 406 Magnusson and Kligman maximization test in Guinea-pig. First of all, this response magnitude is close to the guidance value for a Skin sens 1B classification (≥ 30% responding at > 1% intradermal induction dose). Moreover it should be noted that a major deficiency in the study has been pointed by the dossier submitter, as the dermal induction dose did not cause any skin irritation. Despite this deficiency, the number of responding guinea-pigs was close to criteria's warranting a Skin sens 1B classification. BE CA would have appreciate a more in-depth description of the study in order to properly conclude. ECHA note – An attachment was submitted with the comment above. Refer to public attachment Penflufen_STOT RE_Annex.docx				
Dossier Submitter's Response				
This is a similar comment to No. 13. Should RAC need further information about the study, we will endeavour to provide it.				
RAC's response				
Thank you for your comment. Upon request, RAC was provided with the full study report; the information contained therein only confirms what is already described in the CLH report. RAC agrees that the absence of SLS pretreatment is a major deficiency and that 25% positive response is close to the value triggering classification. Therefore, RAC considers the study inconclusive and agreed on no classification due to inconclusive data.				

OTHER HAZARDS AND ENDPOINTS – Specific Target Organ Toxicity Repeated Exposure

Date	Country	Organisation	Type of Organisation	Comment number
01.12.2017	Belgium		MemberState	15
Comment received				
BE CA disagrees with the DS not to classify penflufen for STOT RE (oral). As summarized below, the weigh-of-evidence is strongly in favor of a STOT RE 2 (liver) classification of penflufen, with 2 studies in rat, 1 study in mouse and 1 study in dog showing LOAEL's in STOT RE 2 range values. Moreover, 4 studies in rat, 2 studies in mouse and 2 studies in dog demonstrated a very low NOAEL, supporting the findings mentioned above. All studies, with only one exception, showed liver damage. The liver injury is mainly characterized by relative liver weight gain, centrilobular/panlobular hepatocellular hypertrophy, but also clinical chemistry alterations (decrease in cholesterol and increase in alkaline phosphatase). There are also several observations of hepatocellular macrovacuolation. Conclusively, BE CA supports a STOT RE 2 (liver) classification for penflufen. See table in annexed document. ECHA note – An attachment was submitted with the comment above. Refer to public attachment Penflufen_STOT RE_Annex.docx				

Dossier Submitter's Response
Thank you for the additional analysis. However, to our understanding, modest changes in liver weight, increased liver hypertrophy and the induction of liver enzymes are not sufficient grounds to justify classification with STOT RE.
RAC's response
Thank you for the comment and the attached analysis. STOT RE classification is reserved for 'significant health effects that can impair function' (CLP, Annex I, 3.9.1.1). As you have described in your comment, penflufen consistently induced liver hypertrophy in all three species tested. General consensus is that hepatocellular hypertrophy without histologic or clinical pathology alterations indicative of liver toxicity is considered an adaptive and non-adverse reaction. Increased ALP activity associated with liver enzyme induction, in the absence of accompanying degenerative histopathological findings, is a common finding in the dog (Hall et al., 2012). As this is the case here, RAC does not consider the increased ALP activity observed in the dogs treated with penflufen as an indication of liver injury. Serum cholesterol was increased in several rat studies and reduced in several mouse studies. Altered cholesterol levels were not accompanied by any histological findings in the liver apart from hypertrophy, so they are not considered adverse. Increased incidence of hepatocellular macrovacuolation was observed in the chronic rat and mouse studies, but this finding is not regarded as a severe effect and it only occurred above the guidance values for classification. For these reasons the liver findings in the repeated dose studies with penflufen are not considered to support classification for STOT RE. Reference Hall, A.P., et al. (2012) Liver hypertrophy: a review of adaptive (adverse and non-adverse) changes—conclusions from the 3rd International ESTP Expert Workshop. Toxicologic Pathology 40:971-994

OTHER HAZARDS AND ENDPOINTS – Hazardous to the Aquatic Environment

Date	Country	Organisation	Type of Organisation	Comment number
29.11.2017	Germany		MemberState	16
Comment received				
We agree 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. p. 79: 5.1 Degradation, Table 26: according to the information in the water/sediment simulation (OECD 308) study and the study summary under point 5.1.2.3 (p. 81- 82) mineralization was observed with a maximum of 3.2% and not 10.7% as it was stated in table 26. Please clarify the difference. p.81: 5.1.2.2 Screening Tests: A screening test OECD 301 C (CAR March 2017) for penflufen from Ichikawa (2015) is available. This result supports your conclusion of "not readily biodegradable" of the a.s. We think in view of the completeness that it would be reasonable to add this study in the CLH report. p.82: Summary and discussion of degradation: Please, add information of temperatures related to DT50 values. p.83 (chapter 5.3.2 summary aquatic bioaccumulation): In document 'penflufen_11_vol3_b9_ecotox 2011' it is stated in chapter "B.9.2.1.2 Bioconcentration potential of penflufen in fish" that the maximum derived BCF for TRR of 142 is used in the risk assessment. For the sake of consistency we recommend to add this value.				

Dossier Submitter's Response
Table 26, water/sediment simulation study: The mineralisation text is a typographical error and should read 0.7 to 3.2% AR. The range 0.7 to 3.2% AR reflects the range of CO2 measurements by day 120 for both systems and both radio labels which were as follows: 0.7 to 1.1% AR in the Hoenninger Wieher test system 0.8 and 3.2% AR in the Angleweiher test system Screening test: At the time the CLH report was drafted, we were not aware of the Ichikawa, 2015 study which is included in the CAR. A summary is presented below based on the CAR RSS: A GLP, ready biodegradation study is available following OECD Test Guideline 301C (modified MITI test). The 28 day study was run at 100 mg/l penflufen with a toxicity control included. It is noted that the test item concentration is above the experimental water solubility of ~10 mg/l at pH 7. Validation criteria were met. Based on DOC, no biodegradation was considered to have occurred. Based on BOD, negligible (4-7%) degradation was observed with an average of 6%. Based on analytical measurement of the test substance, no biodegradation occurred and no transformation products were observed. The study concludes that penflufen is not readily biodegradable. This supports the CLH position that penflufen is considered not rapidly degradable for hazard classification. Degradation summary: The basis of the presented DT50s is included in the text in section 5.1.2.3. For the simulation study, DT50s are based on study temperature. These were not adjusted to an environmentally relevant temperature given they are high values and would not impact the classification. Aquatic Bioaccumulation: The pesticides risk assessment process used a fish BCF of 142 as the maximum observed BCF which reflects a kinetic BCF at single point in time (day 14) for one treatment (0.45 µg/l). This was considered conservative in the absence of adequate information on the levels and toxicity of penflufen metabolites in fish and therefore appropriate in the risk assessment for fish-eating birds and mammals. This approach is not consistent with assessment of bioaccumulation for hazard classification and the data presented in the CLH report (Table 28 and section 5.3.1.2) are considered appropriate for hazard classification.
RAC's response
Thank you for detailed comments. Noted.

Date	Country	Organisation	Type of Organisation	Comment number
01.12.2017	Belgium		MemberState	17
Comment received				
Based on the results of the aquatic toxicity test on the most sensitive species (fish) with 96hLC50= 0.103 mg/l, 35dNOEC=0.0234 mg/l), the fact that the substance is considered				

as not rapidly degradable it is justified to classify, following the classification criteria of regulation 1272/2008, as Aquatic Acute 1, H400 and Aquatic Chronic 1, H411 . Furthermore, the substance does not meet the CLP criteria for bioaccumulation. Notwithstanding the fact that the 96hLC50 is very close to the cut off value of 0.1 mg/l, a M-factor for acute toxicity of 1 (0.1mg/l <LC50 ≤1 mg/l) can be assigned and an M-factor for chronic toxicity of 1 (not rapidly degradable substance and NOEC between 0.01 and 0.1 mg/l). BE CA agrees with the proposed environmental classification by the UK CA. ECHA note – An attachment was submitted with the comment above. Refer to public attachment Penflufen_STOT RE_Annex.docx
Dossier Submitter's Response
Thank you for your support.
RAC's response
Thank you. Noted.

Date	Country	Organisation	Type of Organisation	Comment number
27.11.2017	France		MemberState	18
Comment received				
We agree with the proposed classification and labelling: Aquatic acute 1, H400 M-factor = 1 Aquatic chronic 1, H410 M-factor = 1				
Dossier Submitter's Response				
Thank you for your support.				
RAC's response				
Thank you. Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
01.12.2017	Denmark		MemberState	19
Comment received				
Agree with the classification.				
Dossier Submitter's Response				
Thank you for your support.				
RAC's response				
Thank you. Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
29.11.2017	Finland		MemberState	20
Comment received				
Acute toxicity tests for fish (Cyprinus carpio) and chronic toxicity tests for fish (Pimephales promelas) used for classification of penflufen are considered valid. The lowest acute toxicity for fish was LC50 value of 0.103 mg/l. The lowest chronic toxicity for				

fish was NOEC value of 0.0234 mg/l. FI CA supports the conclusions that penflufen is neither rapidly degradable or potentially bioaccumulative. Based on classification criteria FI CA supports the proposed environmental classification Aquatic Acute 1, H400 with M-factor of 1 and Aquatic Chronic 1, H410 with M-factor of 1 for penflufen.
Dossier Submitter's Response
Thank you for your comments.
RAC's response
Thank you. Noted.

PUBLIC ATTACHMENTS
1. Penflufen_STOT RE_Annex.docx [Please refer to comment No. 2, 5, 11, 14, 15, 17]
2. penflufen position paper ECHA public com_nov 2017_final.pdf [Please refer to comment No. 4]