Committee for Risk Assessment

RAC

Annex 2

Response to comments document (RCOM)

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

esfenvalerate (ISO); (*S*)-α-cyano-3-phenoxybenzyl-(*S*)-2-(4-chlorophenyl)-3-methylbutyrate

EC Number: -

CAS Number: 66230-04-4

CLH-O-0000006715-69-01/F

Adopted

20 September 2019

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON ESFENVALERATE (ISO); (*S*)-α-CYANO-3-PHENOXYBENZYL-(*S*)-2-(4-CHLOROPHENYL)-3-METHYLBUTYRATE

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: esfenvalerate (ISO); (*S*)-α-cyano-3-phenoxybenzyl-(*S*)-2-(4-chlorophenyl)-3-methylbutyrate
EC number: -
CAS number: 66230-04-4
Dossier submitter: The United Kingdom

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
01.03.2019	Belgium		MemberState	1
Comment received				
BE CA would thank the UK CA for this CLH dossier proposal. BE CA agree not to classify esfenvalerate for mutagenicity and STOT SE. Based on the tumours observed on the reproductive system (Leydig cell tumours), BE CA regrets that no reproductive toxicity studies is available in the CLH report and that the reproductive toxicity endpoint is not open to comment. Moreover, the CLH report is normally a stand-alone document. Some major informations regarding repeated dose toxicity studies and neurotoxicity are only include in Annex I to the CLH report. CLH report alone does not provide sufficient data to conclude on the neurotoxicity without the Annex I. ECHA note – An attachment was submitted with the comment above. Refer to public attachment Esfenvalerate_PC comment_BE1.docx				
Dossier Submitter's Response				
Noted, thank you. In the dossier submitter's opinion, generally the key information is presented in the main body of the CLH report, with any further information provided in Annex I (which indeed, forms part of the overall CLH proposal).				
RAC's response				
RAC notes the agreement not to classify esfenvalerate for mutagenicity and STOT SE.				

Date	Country	Organisation	Type of Organisation	Comment number
01.03.2019	France		MemberState	2
Comment received				
FR: Table 7 (p5): in the column "reason for no classification", it should rather be read "data conclusive but not sufficient for classification" or "not applicable" rather than "hazard class not assessed in this dossier" as data are available in the monograph of the substance. The conclusion for physico chemical properties should be based on the studies and results provided in the monograph. FR: Table 7 (p5) – corrosive to metal: no test has been provided to demonstrate that the active substance is not corrosive to metals. A demonstration using method C.1 described in manual UN RTDG or a scientific case should be provided by the applicant.				
Dossier Submitter's Response				
Thank you for your comments. Table 7 should contain the reason for not proposing harmonised classification and status under public consultation. The reason why we have not proposed harmonised classification for phys chem end points is that this is a targeted proposal, looking only at the following end points: acute toxicity (oral and inhalation routes), STOT SE, skin sensitisation, mutagenicity, carcinogenicity and STOT RE. The phys-chem hazards are not part of the proposal, therefore in our opinion, it is appropriate to state the reason for no classification as 'hazard class not assessed in this dossier', and to note that these end points were not within scope of the public consultation. Similarly, as this proposal did not assess the phys chem data, in our opinion it is not appropriate for us to request phys chem testing (i.e., a corrosive to metals test).				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
21.02.2019	Germany		MemberState	3
Comment received				
According to the CLH report, not the ideal substance Estenvalerat (The SS isomer) with a purity of 100 % is considered, but the actually manufactured substance with a purity of ≥ 83 %. In the composition it is stated that the impurity "Sum of Aβ + Bα + Bβ isomers" contributes to the classification of the substances. However, neither the exact identity of the impurities (isomers of the substance) nor their concentrations or classifications are given. These data are marked as confidential and are not available for review. The current understanding is that Annex VI to CLP lists the classification warranted by the substance as such (unless otherwise stated in the entry). It is therefore undesirable to leave the proposed entry as is. The guideline document "Impurities and (degree of) purity in CLP and in the CLH process" (https://echa.europa.eu/documents/10162/13626/clh_impurities_purity_en.pdf/cc0406ba-				

2e6c-4ee0-3082-2b2b3f123ee4) gives several ways forward on how to include substances with relevant impurities in Annex VI. However due to the scarcity of information available to us and the possible conflict of confidential information within the PPP process with the requirements of the CLH process ("An impurity/additive pivotal for the classification cannot for obvious reasons be claimed confidential") we are not in a position to suggest a correct entry. We however urge the dossier submitter and ECHA to review the entry and to bring it to conformity before inclusion in Annex VI.

In Table 6 in Column "Hazard Class and Category Code (s)" "STOT RE Cat 2" should be replaced by the proper abbreviation "STOR RE 2" as given in Annex VI Table 1.1. In column "Specific Conc. Limits, M-factors" "ATEinhal = 0.48mg / L" should be replaced by "inhalation: ATE = 0.48 mg/l (dusts or mists)". "ATEoral = 88.5 mg / kg" should be replaced by "oral: ATE = 88.5 mg / kg".

Dossier Submitter's Response

Thank you for your comments.

The inclusion of 'Sum of Aβ + Bα + Bβ isomers' in table 3 is actually an error, and the information should be deleted.

The applicant defines esfenvalerate as the single active isomer (Aα). This is supported by EFSA because the minimum content of the single active isomer (≥83%) is listed as "Minimum purity of the active substance as manufactured" in EFSA Conclusion (EFSA Journal 2014;12(11):3873). It is our understanding that the non-active isomers do not impact on the toxicity or classification of esfenvalerate.

An early draft of the CLH report summarised all of the toxicology data that had been evaluated by EFSA, including data on fenvalerate. Fenvalerate is a mixture of four optical isomers, one of which is esfenvalerate. The reference to 'Sum of Aβ + Bα + Bβ isomers' in Table 3 actually relates to fenvalerate, rather than esfenvalerate.

When the draft CLH report was refined, we removed all of the fenvalerate data but forgot to delete 'Sum of Aβ + Bα + Bβ isomers' in table 3. So the isomers are still referred to in Table 3 as relevant for classification, even though they are not. They should therefore be removed from the table.

We apologise for this error, and any confusion it has caused.

RAC's response

Noted.

CARCINOGENICITY

Date	Country	Organisation	Type of Organisation	Comment number
01.03.2019	Belgium		MemberState	4

Comment received

The rat chronic toxicity study (anonymous (2011a)) revealed a higher incidence of Leydig cell tumour at the 2 highest doses (4, 2, 0, 8 and 8% respectively at 0, 15, 50, 150 and 400 ppm). Although it is not significantly increased, the incidence exceeded the value of the historical control data (range of 0.0 – 4.0 calculated between 2005 to 2011). The Guidance on the Application of the CLP criteria (version 5.0 July 2017) states that "Historical control data can also be useful to judge the biological significance of marginal increases in

uncommon tumours. If there is a small increase in a particular tumour type which historical data shows to be very uncommon and unlikely to have occurred by chance then this may support a conclusion of carcinogenicity without the requirement for a statistically significant increase…. It is also known that tumour incidences in control animals can change over time, due to factors such as genetic drift, changes in diagnostic criteria for pathological changes/tumour types, and husbandry factors (including the standard diet used), so the historical data should be contemporary to the study being evaluated (e.g. within a period of up to around 5 years of the study). Historical data older than this should be used with caution and acknowledgement of its lower relevance and reliability." As valid historical control data measured during the 5 years prior the study was available, BE CA considers unacceptable to compare with older data (1989, 1994 and 1997). Furthermore, though this increase was not statistically significant, BE CA would like to emphasize that the tested dose are very low (0, 0.7, 2.3, 6.9 and 18.5 mg/kg bw/d respectively for 0, 15, 50, 150 and 400 ppm).

In the second chronic toxicity study performed in mice (anonymous (1997)), no treatment-related tumours was noted. However, survival was significantly decreased in both sexes (high number of mice sacrificed in extremis due to self-trauma). Due to this high rate of mortality, only a small number of animals survived to the end of the study and the presence or absence of tumours is difficult to analyse and conclude.

The CLP Regulation (EC) 1907/2006 states that for "limited evidence of carcinogenicity: the data suggest a carcinogenic effect but are limited for making a definitive evaluation because, e.g. (a) the evidence of carcinogenicity is restricted to a single experiment; (b) there are unresolved questions regarding the adequacy of the design, conduct or interpretation of the studies; (c) the agent increases the incidence only of benign neoplasms or lesions of uncertain neoplastic potential; or (d) the evidence of carcinogenicity is restricted to studies that demonstrate only promoting activity in a narrow range of tissues or organs."

Based on the nature of the tumours, the BE CA regrets that the reproductive toxicity studies are not available in the CLH report and that the reproductive toxicity endpoint is not open to comment.
Due to the previous arguments the observations of Leydig cell tumours should be carefully assessed and BE CA is of the opinion that a classification as Carc. 2 should be discussed.

ECHA note – An attachment was submitted with the comment above. Refer to public attachment Esfenvalerate_PC comment_BE1.docx

Dossier Submitter's Response

Thank you for your comments.

Brief responses:
In our opinion, the slight increase in benign Leydig cell tumours in the 2 year combined chronic toxicity/ oncogenicity study using Wistar rats is not biologically significant, and is therefore not relevant for classification.

The finding is for one tumour type (benign) in one species (the rat but not mouse) and occurred in one study with esfenvalerate, within biological variation.

The incidences of benign Leydig cell tumours are within the historical control range of the laboratory and the published range for Wistar rats.

There were no significantly increased pre-neoplastic changes (Leydig cell hyperplasia) in the rat 2 year study. From the results of multi-generational reproductive toxicity studies, esfenvalerate did not exhibit any evidence of known modes of action for testicular Leydig cell tumourigenicity via endocrine mediated effects.

The top dose level tested in the rat 2 year study appears to have been sufficiently high as to achieved maximum tolerated dose (MTD).

The oncogenicity in mice was properly analyzed by taking into account the studies on fenvalerate, the conclusion was that esfenvalerate was not tumourigenic in mice.

Detailed justifications:

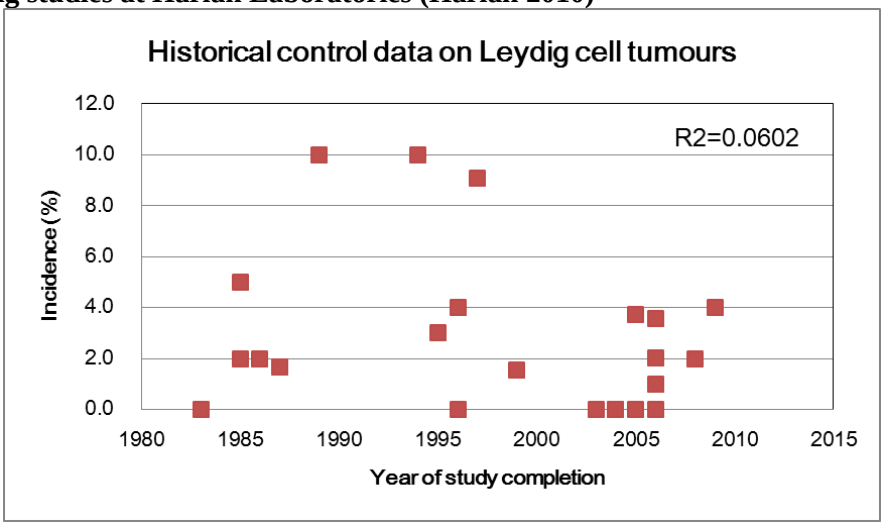
Historical control data

The incidences of benign Leydig cell tumours are within the historical control range of the laboratory and the published range for Wistar rats. We recognise that, ideally, historical control data should be ± 5 years of the study being conducted; indeed, this is why we presented the historical control data in two separate tables, so that it was easy to distinguish between those data that were within the 5 year limit, and those that weren't. As BE notes, the guidance states "historical data older than [5 years] should be used with caution and acknowledgement of its lower relevance and reliability"; it does not say that such data is unacceptable.

Furthermore, some parameters may change in a short period of time while others remain stable over prolonged periods, and the use of a "fixed moving time window" may lead to a loss of important information or the reference to inappropriate historical control data (Deschl *et al.,* 2002; Nolte *et al.,* 2011).

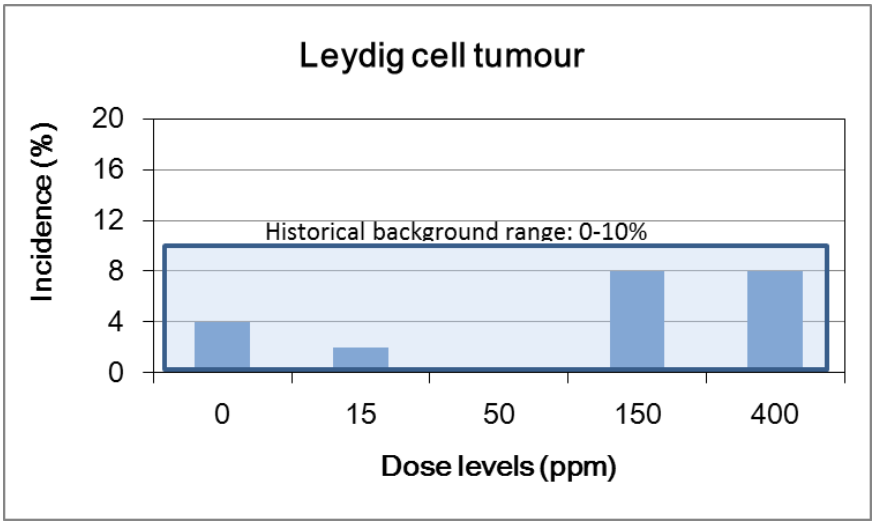
The applicant evaluated the correlation between the Leydig cell tumour incidence and the year of study start. They found a low correlation (R^2=0.0602) with the background values for the tumours in the same laboratory (Figure 1). Thus there appears to be no dependency between year of study start and incidence of these tumours for this laboratory, suggesting stability of the background incidence over time and, therefore, historical control data outside the 5 year 'window' may still be informative. If all of the historical control data is considered, then the incidence of testicular Leydig cell tumours at 150 and 400 ppm (4 of 50 animals per group; 8 %) was within the historical range of this laboratory (0-10.0%) (Figure 2).

Figure 1. Historical background values of testicular benign Leydig cell tumours in male Wistar rats from 2-year feeding studies at Harlan Laboratories (Harlan 2010)



Total number of studies: 23
Total number of animals examined: 1740
Number of animals bearing benign Leydig cell tumour: 52
Total incidence: 3.0 %
Mean value ±SD of incidence: 2.8 ±3.1 %
Range: minimum 0.0%, maximum 10.0%

Figure 2. Incidence of testicular Leydig cell tumours in the rat 2-year study with esfenvalerate and comparison with historical control data



Moreover, we note that the incidence of these tumours is highly variable in Wistar rats with a minimum of 0%, a maximum of 60% and a mean of 13.7% (Nolte *et al.*, 2011; see below Table 1).

Table 1. Strain- and breeder- dependent differences in the incidence of testicular Leydig cell adenoma (Nolte *et al.*, 2011)

Strain	Breeder	*N* studies	*N* animals	Incidence [%]		
				Mean	Min.	Max.
Wistar	A	19	1079	39.9	18	60
	B	12	800	2.8	0	6
	D1	11	608	5.8	0	29
	G	16	770	12.5	4	22
	I	30	1609	6.8	1.1	22
SD	D1	10	518	5.4	0	12
	D2	5	279	5	1.7	10
	D3	8	440	2.3	1.8	3.6
	H	6	398	6.3	2.0	8.6
F344	D6	2	100	83	76	90

Pre-neoplastic changes

There were no significantly increased pre-neoplastic changes (Leydig cell hyperplasia) in the esfenvalerate 2 year study. When testicular proliferative lesions are assessed as combined incidence of testicular Leydig cell hyperplasia and/or tumour, the lesions are observed in 3, 1, 0, 4 and 4 animals in control, 15, 50, 150 and 400 ppm esfenvalerate groups, respectively.

Based on these considerations, the slightly increased incidence of testicular Leydig cell tumours observed in the rat 2-year study with esfenvalerate is considered not to be treatment-related and is not toxicologically significant.

Reproductive Toxicity Studies

Regarding the reproductive toxicity, multi-generational reproductive toxicity studies with esfenvalerate have been conducted in rats. In these studies, the effects on mating indices, fertility indices and reproductive organs were investigated. There were no effects on fertility, nor any change in weight of the testis or treatment-related histopathological findings in the testis and other reproductive organs. Based on the results of the above-mentioned studies, it is considered that esfenvalerate does not have the potential of known modes of action for testicular Leydig cell tumourigenicity, by interacting with the endocrine system, including testis. We have attached an extract from the RAR ("Confidential document 1 - esfenvalerate RCOM - reproductive toxicity studies - extract from RAR") containing the reproductive toxicity studies, in case they can assist RAC in their analysis.

Dose levels

We agree that the tested doses are low, however the data suggest that the highest dose level in the 2 year chronic/oncogenicity study achieved the MTD, and was suitable to determine the carcinogenic potential of esfenvalerate. The top dose (400 ppm) was selected based on signs of toxicity including deaths seen at 500 ppm and above in the 4- and 13-week feeding studies. In the rat 2 year study, overall mean food consumption in treated males and females was not affected by treatment with esfenvalerate. However, clear treatment-related effects on body weight were observed in males at 400 ppm, and similar but slight effects were also observed in females at 400 ppm without statistical significance. Overall mean body weight gains in males and females were decreased by approximately 10% by treatment with esfenvalerate. Taken together with the effects at 500 ppm and

above in the 4- or 13-week studies, the body weight changes in this study indicated that the dose level of 400 ppm was a MTD.

Oncogenicity in mice
For mouse oncogenicity, two additional studies on **fenvalerate** are available. Esfenvalerate is one of the 4 isomers of fenvalerate, the [2S,S] isomer, and these studies have been used for the risk assessment. Fenvalerate has not demonstrated any potential to be tumourigenic when tested up to 1250 ppm. Taking into account the results of these studies, it was concluded that esfenvalerate was not tumourigenic in mice.

References
Deschl U, Kittel B, Rittinghausen S, Morawietz G, and Kohler M. (2002). The value of historical control data—scientific advantages. Toxicol Pathol 30: 80–7.
Nolte, T., Rittinghausen, S., Kellner, R., Karbe, E., Kittel, B., Rinke, M., and Deschl, U. (2011). RITA-Registry of Industrial Toxicology Animal data: the application of historical control data for Leydig cell tumors in rats. Experimental and toxicologic pathology 63: 645-56.

RAC's response

Thank you for your comments. RAC agrees with the Dossier Submitter's view. Additionally, RAC does not consider Leydig cell tumours to be "very uncommon", indeed the Dossier Submitter showed in their comment that in Wistar rats the % incidences vary greatly, but they are not uncommon. RAC agrees that the historical control data for more than 5 years previous to the current study should be used with caution.

Date	Country	Organisation	Type of Organisation	Comment number
01.03.2019	Spain		MemberState	5

Comment received

The EFSA peer review of esfenvalerate suggested that a classification of Carcinogenicity Category 2 may be appropriate, based on the incidence of bening Leydig cell tumours in the testes of male rats in the 150 and 400 ppm treatment groups in a combined chronic toxicity/ oncogenicity rat study (EFSA, 2014). The Applicant disagreed with this proposal and carried out an additional histopathological examination (including all animals of intermediate dose groups, not only decedent animals).

The revised incidence of benign Leydig cell tumours showed that at the top two doses the incidence was slightly greater than controls (4, 2, 0, 8 and 8% at 0, 15. 50, 150 and 400 ppm), with no clear dose- response, and the difference compared to controls was not statistically significant. Besides, there was no treatment-related increase in the incidence of Leydig cell hyperplasia and no malignant tumours were reported at any dose level. Furthermore, in the available repeated dose toxicity studies and reproductive toxicity studies there were no findings which were indicative of an adverse effect on the testes or the endocrine system.

The dossier submitter is of the opinion that the slight increase in benign Leydig cell tumours seen in the rat dosed with esfenvalerate is not treatment-related and proposed no classification regarding carcinogenicity. In the CLH report the dossier submitter considers worth noting that the incidence control incidences of 9.1, 10.0 and 10.0% were reported in

the same laboratory 14, 17 and 22 years prior. However, the incidences of benign Leydig cell tumours at 150 and 400 ppm (8%) were outside the range of the historical control data collected in the same laboratory during the 5 years prior to the study being conducted. The dossier submitter also pointed out that esfenvalerate was negative in standard in vitro and in vivo tests for genotoxicity and it tested negative in a range of mechanistic studies conducted to investigate the endocrine disrupting potential of esfenvalerate. However, we consider that not all potential modes of action with relevance to humans can be ruled out. In our opinion, the mechanism of action has not been sufficiently clarified and therefore the relevance for humans still remains unclear. Besides, there was not a confounding effect of excessive toxicity at the top two doses where the incidence of benign Leydig cell tumours increased (6.9 and 18.5 mg/kg bw/d). There were no treatment-related clinical signs, or effects on survival rates. Body weights were reduced in treated males; the effect was statistically significant at the top dose only (mean body weights in this dose group were 9.7% lower than controls at study termination). It is possible that with higher doses tested, the increase in tumours could have been much greater. Overall, the available data are some kind of borderline and the criteria leave a margin for different interpretations. All the considerations mentioned before reduce considerably the concern and it might be possible that the benign tumours in benign Leydig cell tumours male rats were chance observations. However, in our opinion a treatment-related tumour response cannot be excluded.
Dossier Submitter's Response
Thank you for the detailed comments. Please see response to comment number 4.
RAC's response
Thank you for your comments.

Date	Country	Organisation	Type of Organisation	Comment number
21.02.2019	Germany		MemberState	6
Comment received				
Speculations on the (absence of a) dose response relationship for benign Leydig cell tumors should be supported by suitable statistical analyses (e.g. trend testing or BMD). A Cochrane-Armitage linear trend test without correction for survival results in a p value of 0.1475 (two-sided), supporting the DS interpretation that the stat. significant finding at 6.9 mg/kg bw/d may be due to chance.				
Dossier Submitter's Response				
Thank you for the comment and support.				
RAC's response				
Thank you for your comment.				

Date	Country	Organisation	Type of Organisation	Comment number
27.02.2019	Sweden		MemberState	7
Comment received				
Since there was no increase of Leydig cell hyperplasia, no malignant Leydig cell tumours and no dose-response we agree that the findings do not fulfil criteria for classification.				

However, since the study summaries on reproductive toxicity referred to are not available in Annex I and since the study summaries on RDT do not state if the testis actually was investigated, it is not possible to conclude if these result support the conclusion that effects lack biological significance. With respect to other tumour frequencies observed in animals with gross lesions or found dead, the only remaining concern following a correction for 50 animals/dose is an increase of benign thymoma in females . Although within the range 0-16% of the HCD stated, the incidences are well above the concurrent control and the mean value of 3.6% in the HCD. However, considering the benign nature of this tumour type, that it was only observed in females, the lack of dose-response and the lack of other types of tumours, the criteria for classification are not considered fulfilled. Therefore, overall we agree that the data on esfenvalerate does not fulfil criteria for classification.
Dossier Submitter's Response
Thank you for your comments and support.
RAC's response
Thank you for your comments and support. RAC agrees that the thymoma findings do not support classification.

MUTAGENICITY

Date	Country	Organisation	Type of Organisation	Comment number
27.02.2019	Sweden		MemberState	8
Comment received				
With the exception of one in vitro study, neither the CLH report nor annex I contains a presentation of results (frequencies etc) in the in vitro and in vivo tests. Consequently, the reviewer must rely on the DS conclusion and an independent assessment of this endpoint cannot be made.				
Dossier Submitter's Response				
Thank you for your comments. In our opinion, the studies were clearly negative and we did not see any value in reproducing tables of negative data. However, we have provided the study reports (confidential documents 2 – 6) in case RAC find them useful to their assessment.				
RAC's response				
Thank you for your comment.				

OTHER HAZARDS AND ENDPOINTS – Acute Toxicity

Date	Country	Organisation	Type of Organisation	Comment number
01.03.2019	Belgium		MemberState	9
Comment received				
Acute toxicity via oral route The classification of esfenvalerate for Acute Tox. 3, H301, is supported. In the acute toxicity study performed in rats following OECD TG 401 (Anonymous (1985d)), the estimated LD50 was 88.5 mg/kg bw. These observations are supported by a following acute toxicity study performed in mice which demonstrated a LD50 of 250 mg/kg bw in females (320 mg/kg bw in males).				

BE CA is of the opinion that the anonymous (1985d)'s study should be considered as the key study and supports the ATE of 88.5 mg/kg bw proposed by the DS.

For Acute toxicity via inhalation route

The classification of esfenvalerate for Acute Tox. 2, H330, is supported.

The acute toxicity study performed in rats following OECD TG 403 fulfil the criteria for classification as Acute Tox. 2, H330 based on a LC50 was of 0.48 mg/l in males. The proposed ATE of 0.48 mg/l is further supported as well.

ECHA note – An attachment was submitted with the comment above. Refer to public attachment Esfenvalerate_PC comment_BE1.docx

Dossier Submitter's Response

Thank you for the support.

RAC's response

Thank you for your comment and your support has been noted.

For inhalation exposure, RAC noted that whole-body exposure to corn oil spray is likely to lead to high oral exposure via grooming, which is corroborated by the autolysis of the intestinal tract of the animals that died. Thus, the observed LC_{50} values probably reflect exposure both via inhalation and the oral route. As the values overestimate inhalation toxicity, RAC proposed to use the mean of the male and female values for calculating the LC_{50} which leads to 0.53 mg/L. Recalculated for 100% active isomer, this value is 0,46 mg/l, so the proposed ATE (inhalation) is 0,46 mg/L.

The oral ATE value has also been recalculated by RAC for the active isomer content and thus the proposed ATE (oral) is 77,2 mg/kg bw.

Date	Country	Organisation	Type of Organisation	Comment number
01.03.2019	Spain		MemberState	10

Comment received

Acute toxicity – oral route

The most sensitive species for assessing acute oral toxicity is the rat. We agree with the dossier submitter that the lowest LD50 value in the rat (88.5 mg/kg bw for both males and females) shall be used as the basis for classification. The acute oral LD50 in the rat of 88.5 mg/kg bw meets the criterion for Category 3 (50 < LD50 ≤ 300 mg/kg bw). Therefore, classification as
Acute Tox. 3; H301: Toxic if swallowed (ATE = 88.5 mg/kg bw) is required.

Acute toxicity – inhalation route

The acute inhalation LC50 of 0.48 mg/L in male rats meets the criterion for Category 2 (Inhalation (dust/mist) 0.05< LC50 ≤0.5 mg/l). Therefore, classification as Acute Tox. 2; H330: Fatal if inhaled (ATE = 0.48mg/L) is warranted.

Dossier Submitter's Response
Thank you for the support.
RAC's response
Please see RAC's response to comment #9.

Date	Country	Organisation	Type of Organisation	Comment number
21.02.2019	Germany		MemberState	11
Comment received				
The proposal for classification with Acute Tox 3, H301 and Acute Tox 2, H330 is supported.				
Dossier Submitter's Response				
Thank you for the support.				
RAC's response				
Thank you for your comment and your support has been noted.				

OTHER HAZARDS AND ENDPOINTS – Skin Sensitisation Hazard

Date	Country	Organisation	Type of Organisation	Comment number
01.03.2019	Belgium		MemberState	12
Comment received				
The classification for Skin Sensitisation, H317, is supported based on the results of the GPMT (anonymous (1986b)). After an intradermal induction of 25% esfenvalerate, positive reactions were observed in 75% and 85% of animals, respectively after 24h and 48h. As category 1A cannot be excluded, BE CA supports the category 1. ECHA note – An attachment was submitted with the comment above. Refer to public attachment Esfenvalerate_PC comment_BE1.docx				
Dossier Submitter's Response				
Thank you for the support.				
RAC's response				
Thank you for your comment and your support has been noted.				

Date	Country	Organisation	Type of Organisation	Comment number
01.03.2019	Spain		MemberState	13
Comment received				
The results from the maximisation test suggest that classification in Category 1B may be appropriate, based on the observation of a ≥30% response at a >1% intradermal induction dose and the criteria in Table 3.4.4 of Annex I of CLP. However, in this case, only one intradermal induction concentration was investigated in the guinea pig maximisation test. Therefore, we cannot exclude the possibility that sensitisation would have occurred at lower induction concentrations. According to the ECHA Guidance on the Application of the CLP Criteria (Version 5.0 – July 2017), when Category 1A cannot be excluded, Category 1 should be applied instead of Category 1B. Therefore, we agreed with the dossier submitter that a classification as Skin Sens. 1; H317: May cause an allergic skin reaction is more appropriate.				

Dossier Submitter's Response
Thank you for the support.
RAC's response
Thank you for your comment and your support has been noted.

Date	Country	Organisation	Type of Organisation	Comment number
21.02.2019	Germany		MemberState	14
Comment received				
The proposal for classification with Skin Sens 1 is supported.				
Dossier Submitter's Response				
Thank you for the support.				
RAC's response				
Thank you for your comment and your support has been noted.				

OTHER HAZARDS AND ENDPOINTS – Specific Target Organ Toxicity Single Exposure

Date	Country	Organisation	Type of Organisation	Comment number
01.03.2019	Spain		MemberState	15
Comment received				
In acute oral toxicity and acute oral neurotoxicity studies in rats and mice, significant and severe signs of toxicity (neurological effects, death) were observed at doses relevant for classification for STOT SE (i.e., ≤ 2000 mg/kg bw). We agreed with dossier submitter that, given that, based on deaths caused by neurotoxicity, esfenvalerate is already proposed to be classified for acute toxicity by the oral route as Acute Tox 3 (H301), it is not appropriate to classify for STOT SE 1 or 2 based on neurotoxic effects. In an acute inhalation study in rats, significant and severe signs of toxicity (neurological effects, death) were observed at doses relevant for classification for STOT SE (≤ 5 mg/l/4h). As in the oral studies discussed above, esfenvalerate is already proposed to be classified for acute toxicity by inhalation as Acute Tox 2 (H330). Therefore, classification for STOT SE is not considered appropriate, as it would result in a double classification. We also agreed with the dossier submitter that, the results of the acute dermal studies do not support classification in STOT SE 1 or 2.				
Dossier Submitter's Response				
Thank you for the support.				
RAC's response				
Neurotoxicity was consistently observed across all acute oral, dermal and inhalation studies, at both lethal and non-lethal doses. The non-lethal doses at which the neurotoxic effects are observed fall within the guidance values for STOT SE 1 for the oral (C ≤ 300 mg/kg bw) and inhalation (≤ 1 mg/L) routes, and within the guidance values for STOT SE 2 C ≤ 2000 mg/kg bw) for the dermal route. The sublethal dose levels with neurotoxic findings were, with the exception of the inhalation route, more than a factor 2 lower than the lethal dose levels. Given the consistent picture, across all routes of exposure, supported by the fact that esfenvalerate belongs to the group of pyrethroids, which are known to induce neurotoxic effects, RAC classified esfenvalerate as STOT SE 1; H370 (nervous system) without specifying the route of exposure.				

OTHER HAZARDS AND ENDPOINTS – Specific Target Organ Toxicity Repeated Exposure

Date	Country	Organisation	Type of Organisation	Comment number
01.03.2019	Belgium		MemberState	16

Comment received

The classification of esfenvalerate for STOT RE 2, H373, based on mortality is supported. However, based on the effects observed in neurotoxicity studies and repeated dose toxicity studies, BE CA consider that an in-depth discussion is needed regarding the neurological system.

• In a short term study (anonymous (2008)), mortality was observed at the 2 highest dose. At 1000 ppm (44.0/46.5 mg/kg bw/d respectively in males/females), 7 males died between day 7 and 12, 2 males had to be killed in extremis on day 11 and the remaining male on day 12 while 2 females died spontaneously on day 7, 2 other on day 8 and the 6 remaining females had to be killed in extremis on day 8. At 700 ppm (46.0/54.0 mg/kg bw/d respectively in males/females), 1 male died on day 28.
• In a sub chronic toxicity study (anonymous (1984)), mortality was observed in females at the highest dose (25 mg/kg bw/d). At this dose level, 4, 1, and 1 females died respectively in weeks 6, 7 and 11, and 1 female had to be killed in extremis in week 9.
Although a proposal to classify esfenvalerate for acute toxicity is warranted, BE CA agrees that mortality observed in 2 repeated dose exposure studies, performed in rats, must be taken into account as the deaths occurred too late to be considered as an acute effect.

Moreover, BE CA is of the opinion that the neurological effects must be take into account for the classification :
• In another 90-day dietary neurotoxicity study (anonymous, 2000c), following OECD TG 424, rats were given esfenvalerate at a concentration of 0, 50, 100 or 300 ppm (corresponding to 0, 3.2/3.7, 6.4/7.3 and 20.1/22.8 mg/kg bw/d in males/females). Animals exposed to 300 ppm exhibited abnormal gait, significant reduction in forelimb and in hindlimb grip strength (see table B.6.7.2-3 page 93 of the Annex I to the CLH report).

For a readable table see uploaded attachement

Males Females
Dose level in ppm 0 50 100 300 0 50 100 300
Forelimb grip strength (kg) W4 1.15 1.06 1.02 0.71* 1.00 0.82 0.81 0.73*
W8 1.29 1.17 0.95* 0.86* 0.79 0.77 0.72 0.69
W13 1.04 1.04 0.90 0.89 0.79 0.69 0.58 0.70
Hindlimb grip strength (kg) W4 0.75 0.73 0.69 0.58* 0.65 0.63 0.64 0.54*
W8 0.87 0.83 0.77 0.79 0.77 0.75 0.73 0.63
W13 0.91 0.88 0.88 0.86 0.82 0.75 0.76 0.72*
* : $p<0.05$

• In a combined chronic toxicity/oncogenicity study (anonymous, 2011a), following OECD TG 453, rats were exposed to esfenvalerate at a concentration of 0, 15, 50, 150 or 400 ppm (corresponding to 0, 0.7, 2.3, 6.9 and 18.5 mg/kg bw/d). Animals exhibited significant lower hindlimb grip strength at the highest dose in both sexes (1.09, 1.10, 1.10, 1.09 and 0.98* kg in males respectively at 0, 15, 50, 150 and 400 ppm and 0.93, 1.03, 0.99, 0.91 and 0.68** kg in females respectively at 0, 15, 50, 150 and 400 mg/kg bw/d) (see table B.6.5.1-4 page 40 of the Annex I to the CLH report).
• In a 13-week dietary neurotoxicity study (anonymous, 1999c), following OECD TG 424,

rats were given esfenvalerate at a concentration of 0, 40, 120 or 360 ppm (corresponding to 0, 3.0/3.7, 8.9/10.7 and 28.8/35.0 mg/kg bw/d in males/females). At week 2 FOB revealed a significant lower forelimb grip strength in both sexes exposed to 360 ppm.
• In 28-day dietary study (anonymous, 2008), clinical signs were noted. Ataxia was noted in 5 females exposed to 700 ppm (ca. 46.0/54.0 mg/kg bw/d in males/females) and in all animals exposed to 1000 ppm (ca. 44.0/46.5 mg/kg bw/d in males/females values recorded after 1w of exposure due to mortality). No information on the histopathological examination was available.
• In 90-day dietary study (anonymous, 1984), rats exposed to 25 mg/kg bw/d exhibited jerky leg movements, unsteady gait, body tremors, hypersensitive to sounds and convulsions. Moreover, animals of the mid dose (15.0 mg/kg bw/d) showed also jerky leg movements and unsteady gait.
• In another 90-day dietary study (anonymous, 1987), neurological signs were noted in rats exposed to 15 mg/kg bw/d, such as hyperactivity and/or abnormal limb movements (jerky leg movements).
As a general conclusion, neurotoxicity studies (anonymous, 2000c and 1999c) revealed significant lower forelimb and hindlimb strength. These severe reductions were observed at low doses (22.8 and 18.5 mg/kg bw/d). Furthermore, other repeated dose toxicity studies showed neurological effects as well at dose levels which fulfil the criteria for a classification in category 2. Finally, esfenvalerate is a pyrethroid substance, a chemical class well known to induce neurotoxic effects. Based on these information, BE CA is of the opinion that a classification as STOT RE cat. 2 (neurological system) should be discussed.

ECHA note – An attachment was submitted with the comment above. Refer to public attachment Esfenvalerate_PC comment_BE1.docx

Dossier Submitter's Response

Thank you for the detailed comments and analysis.

The treatment-related neurological effects observed in repeated dose toxicity studies via the oral route were typical of those observed after acute exposure. There were no significant neuropathological changes and there was no increase in the incidence or severity of neurological effects with time in short term and chronic studies. The neurological effects in the rat were generally observed at dose levels ≥15 mg/kg/d (effective dose).

Where the same target organ toxicity of similar severity is observed after single and repeated exposure to a similar dose, it may be concluded that the toxicity is essentially an acute (i.e. single exposure) effect with no accumulation or exacerbation of the toxicity with repeated exposure (ECHA Guidance on the Application of the CLP Criteria, 2017). Therefore, we concluded that the neurological effects seen in the repeated dose studies do not warrant classification for STOT RE, as they are already covered by the classification for acute toxicity (Acute Tox 3; H301).

RAC's response

Your support for the classification of esfenvalerate for STOT RE 2, H373, based on mortality has been noted.

However, considering the neurological effects, RAC noted that in the repeated dose studies the effects started early during treatment (except for one neurotoxicity study), and the severity and incidences of findings did not increase with duration, only with dose. There are no histopathological alterations in any of the studies in relation to functional effects. According to the Guidance on the Application of the CLP Criteria, where the same target organ toxicity of similar severity is observed after single and repeated exposure to a similar

dose, it may be concluded that the toxicity is essentially an acute (i.e. single exposure) effect with no accumulation or exacerbation of the toxicity with repeated exposure. Therefore RAC considered that the neurological effects seen in the repeated dose studies do not warrant classification as STOT RE, as they are already covered by the classification as STOT SE 1 H370 (nervous system) adopted by RAC.

Date	Country	Organisation	Type of Organisation	Comment number
01.03.2019	Spain		MemberState	17
Comment received				
In a 90 day repeated dose toxicity study via the oral route, deaths occurred in female rats at 25 mg/kg bw/d. On this basis, the Spanish CA agreed with the dossier submitter that classification in STOT-RE Cat 2 (H373) is warranted.				
Dossier Submitter's Response				
Thank you for the support.				
RAC's response				
Thank you for your comment and your support has been noted.				

Date	Country	Organisation	Type of Organisation	Comment number
21.02.2019	Germany		MemberState	18
Comment received				
While "non-lethal toxic effects observed after a single-exposure event […] are […] excluded…", there the DS reported a major increase in severity of effects in rats with muscular fibrillation / tremor / limb paralysis after SE to death following RE at comparable doses. Therefore, the proposal is supported.				
Dossier Submitter's Response				
Thank you for the support.				
RAC's response				
Thank you for your comment and your support has been noted.				

OTHER HAZARDS AND ENDPOINTS – Hazardous to the Aquatic Environment

Date	Country	Organisation	Type of Organisation	Comment number
01.03.2019	Belgium		MemberState	19
Comment received				
BE CA supports the proposed environmental classification of Esfenvalerate with Aquatic Acute 1, H 400 (M= 10 000) and Aquatic Chronic 1, H410 (M= 10 000). Some editorial or/and minor comments : p.58 : 11.5.3 Acute (short term) toxicity to algae or other aquatic plants 2nd paragraph: "The reported 72 hr EbC50 values for 3-phenoxybenzoic acid, Dec-Fen, (+)CPIA, CONH2-Fen and PA-Fen were 33.8, >0.24, 64.6, >0.15 and >0.421 mg/L, respectively and the 72 hr EbC50 values were 51.92, >0.24, >100, >0.15 and >0.421 mg/L, respectively. " The latter should read ErC50 instead of EbC50. ECHA note – An attachment was submitted with the comment above. Refer to public attachment Esfenvalerate_PC comment_BE1.docx				
Dossier Submitter's Response				

We thank BE for their support for our classification proposal and also for pointing out the error in Section 11.5.3 of the Report. It is correct that the second set of values should indeed refer to the E**r**C50s for this degradant of esfenvalerate. As these data were not considered further in relation to the classification of esfenvalerate itself, this does not affect the classification proposal.
RAC's response
Noted.

Date	Country	Organisation	Type of Organisation	Comment number
01.03.2019	France		MemberState	20
Comment received				
FR agrees with the classification proposal and the M factors (acute and chronic) proposed in the CLH report.				
Dossier Submitter's Response				
Noted – thank you for the support.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
27.02.2019	Netherlands		MemberState	21
Comment received				

Conclusion:
We agree with Aquatic Acute 1, with an M-factor of 10000 but based on Daphnia instead of fish.
We agreed with Chronic 1, with an M-factor of 10000.

Proposed comments
The Annex I to the CLH was consulted to obtain more details on the aquatic toxicity studies. We can agree that fish and invertebrates were the most acutely sensitive trophic groups. However, we have the following the remarks.

Acute toxicity to aquatic invertebrates
Four EC50 values are available for Daphnia magna: 27, 3.5, 0.9 and ≈0.045 µg/L. However, 3.5 and 0.9 µg/L values are derived from unreliable studies since in both tests the test compound was not measured during the test. If these two values are excluded then the geometric mean cannot be applied and the lowest reliable toxicity value should be used for classification purposes. The lowest EC50 value for Daphna magna is 0.045 µg/L.

Acute toxicity to fish
Four studies with fish were performed.
1) A reliable study with bluegill sunfish was based on nominal concentrations: 0.21 µg/L.
2) An unreliable study (test compound not measured during test) with rainbow trout was based on nominal concentrations: 0.26 µg/L.
3) A study with rainbow trout was performed under flow through conditions. A range of ten concentrations was tested (0.010 – 0.750 µg/L). Only two out of ten concentrations were measured. The two measured concentrations of esfenvalerate were between 107 and 125%

of the nominal value of 0.032 and 0.056 µg /L. This means that the LC50 values based on nominal concentrations are less reliable as is already indicated (possibly slightly overestimated). Nevertheless, the endpoint of 0.1 µg /L can be used.
4) The last study with fish (fathead minnow), concentrations were measured at test initiation and after two days. Esfenvalerate concentrations dropped to 85% at test initiation and to 50% after two days. It is not reported which concentrations were measured. The applicant reasoned that fish in the highest concentration were already dead after 48 h. For that reason, the drop in concentrations would therefore not affect the results. However, at the level of the LC50 value of 0.18 µg /L, cumulative mortality is reaching 55% (at 0.22 µg /L). If the study had been performed under flow through conditions higher mortality could have been obtained. This means that the LC50 value could be considerably lower. The study is therefore considered unreliable.

In conclusion, the LC50 value of 0.1 µg /L is the lowest value for fish.

Classification
Based on the above, the classification could be based on the lowest value for Daphnia magna, 48-h EC50 of 0.045 µg/L. On the basis of the Daphnia endpoint being in the range 0.000001 < L(E)C50 ≤ 0.00001, esfenvalerate should be classified as acute environmental as, Acute Category 1 with an M-factor of 10000. The M-factor remains 10000 but it would be based on Daphnia and not fish as the dossier submitter proposed.

Dossier Submitter's Response

We thank NL for their support for our classification proposal and also for their comments on the basis for the acute aquatic classification. The two *Daphnia magna* studies by Hutton (1987) were included in the original 1995 pesticide DAR for esfenvalerate and in the subsequent 2014 RAR. It was originally thought that these were reliable but a later examination of the data revealed that there was no analytical verification of actual exposure concentrations. Whilst esfenvalerate showed variable stability over 48 hours in other tests, it is correct that these two nominal acute EC50 values are potentially unreliable. This was not corrected in the daphnid geomean calculation, which we now agree is not appropriate (see also comment 22 from DE). As NL point out, based on either the lowest fish LC50 value of 0.0001 mg/L or the lowest daphnid EC50 of 0.000045, the current acute aquatic classification (inc. M-factor) remains as proposed (although the range for an <u>acute</u> M-factor of 10000 is >0.00001 to ≤ 0.0001 rather than that mentioned by NL). We note that the daphnid EC50 was based on a '<' value and so is approximate and the fish LC50 is possibly a slight overestimate based on measured concentrations, however both values are in the same classification range and so could both be used to support the current proposal.

RAC's response

Noted. RAC assumed that the geometric mean of toxicity values of *Daphnia magna* should not be used to represent aquatic acute toxicity value for that species. 48-hours EC_{50} of 0.0009 and 0.0035 mg/L values (Hutton D. G., 1987) were derived from unreliable studies since in both tests the test compound was not measured during the test. Also 48-hours EC_{50} of 0.0035 mg/L for *Daphnia magna* is not reliable, because the daphnids were fed during the study. As these two aquatic acute toxicity values cannot be compared and should be excluded the geometric mean approach cannot be applied and aquatic acute classification should be based on the lowest reliable toxicity value 48-hour EC_{50} of 0.000045 mg/L for *Daphnia magna*.

Date	Country	Organisation	Type of Organisation	Comment number
21.02.2019	Germany		MemberState	22
Comment received				
From our point of view, there are not 4 valid and reliable study results for Daphnia magna.				

The EC50 (48 hours) = 3.5 µg/L for Daphnia magna (Hutton, D.G. (1987) LLW-71-0028) is not reliable, because the daphnids were fed during the study. The OECD 202 guideline regulates "the daphnids should not be fed during the test". Therefore, this result cannot be compared to the other EC50 results for Daphnia magna and there are not enough data to take the geometric mean (ECHA CLP-guidance, 2017). The relevant result for acute toxicity of esfenvalerate to Daphnia is EC50 (48 hours) = 0.045 µg/L (Sayers, L.E. 2011). However, the result from the acute fish study (Anonymous, 1986) is more sensitive and therefore the acute M-factor of 10000 is justified.
Dossier Submitter's Response
We thank DE for their comments and support for our classification proposal. Please see our response to NL's comments (no. 21) regarding the *Daphnia magna* studies by Hutton (1987). We agree that feeding the daphnia could have affected the results in the study referenced by DE along with the stability of the test substance - which, as pointed out by NL, was not determined in this test. For both reasons we agree that the Hutton endpoints are potentially unreliable and the geomean calculation for daphnids was not appropriate. This leaves the lowest acute L/EC50 values being 0.000045 mg/L for invertebrates (an approximate but sufficiently accurate value) and 0.0001 mg/L for fish (a slight over-estimation based on measured data but considered precautionary). The lowest value is actually the daphnid EC50 rather than the fish LC50 - but both are in the range >0.00001 to ≤ 0.0001 and therefore both values support the proposed classification of Acute 1 with an Acute M-factor of 10000.
RAC's response
Noted. RAC assumed that the geometric mean of toxicity values of *Daphnia magna* should not be used to represent aquatic acute toxicity value for that species. 48-hours EC_{50} of 0.0009 and 0.0035 mg/L values (Hutton D. G., 1987) were derived from unreliable studies since in both tests the test compound was not measured during the test. Also 48-hours EC_{50} of 0.0035 mg/L for *Daphnia magna* is not reliable, because the daphnids were fed during the study. As these two aquatic acute toxicity values cannot be compared and should be excluded the geometric mean approach cannot be applied and aquatic acute classification should be based on the lowest reliable toxicity value 48-hour EC_{50} of 0.000045 mg/L for *Daphnia magna*.

PUBLIC ATTACHMENTS

1. Esfenvalerate_PC comment_BE1.docx [Please refer to comment No. 1, 4, 9, 12, 16, 19]