COMMENTS AND RESPONSE TO COMMENTS ON CLH: PROPOSAL AND JUSTIFICATION

Comments provided during public consultation are made available in this table as submitted by the webform. Please note that the comments displayed below may have been accompanied by attachments which are not published in this table.

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Last data extracted on 04.03.2019

Substance name: esfenvalerate (ISO); (S)-α-cyano-3-phenoxybenzyl-(S)-2-(4-chlorophenyl)-3-methylbutyrate
CAS number: 66230-04-4
EC number: -
Dossier submitter: 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				

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.				

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".				

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

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.

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.				

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.

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.				

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				

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.

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.				

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				

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.				

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.				

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.				

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

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.				

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.				

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				

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.				

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 $0.000001 < L(E)C50 \leq 0.00001$, 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.

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.

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