Committee for Risk Assessment

RAC

Annex 2

Response to comments document (RCOM)

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

beta-cyfluthrin (ISO); reaction mass of *rel*-(*R*)-cyano(4-fluoro-3-phenoxyphenyl)methyl (*1S,3S*)-3-(2,2-dichloroethenyl)-2,2-dimethylcyclopropane-1-carboxylate and *rel*-(*R*)-cyano(4-fluoro-3-phenoxyphenyl)methyl (*1S,3R*)-3-(2,2-dichloroethenyl)-2,2-dimethylcyclopropane-1-carboxylate

EC Number: -
CAS Number: 1820573-27-0

CLH-O-0000006798-55-01/F

Adopted

4 May 2020

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON BETA-CYFLUTHRIN (ISO); REACTION MASS OF REL-(R)-CYANO(4-FLUORO-3-PHENOXYPHENYL)METHYL (1S,3S)-3-(2,2-DICHLOROETHENYL)-2,2-DIMETHYLCYCLOPROPANE-1-CARBOXYLATE AND REL-(R)-CYANO(4-FLUORO-3-PHENOXYPHENYL)METHYL (1S,3R)-3-(2,2-DICHLOROETHENYL)-2,2-DIMETHYLCYCLOPROPANE-1-CARBOXYLATE

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: beta-cyfluthrin (ISO); reaction mass of rel-(R)-cyano(4-fluoro-3-phenoxyphenyl)methyl (1S,3S)-3-(2,2-dichloroethenyl)-2,2-dimethylcyclopropane-1-carboxylate and rel-(R)-cyano(4-fluoro-3-phenoxyphenyl)methyl (1S,3R)-3-(2,2-dichloroethenyl)-2,2-dimethylcyclopropane-1-carboxylate
EC number: -
CAS number: 1820573-27-0
Dossier submitter: Germany

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
13.05.2019	Netherlands		MemberState	1
Comment received				
Agreed with minor comments The cyfluthrin CLH proposal notes that the entire dataset of beta-cyfluthrin (PPP) and cyfluthrin (biocide) has been considered as the substances have the same chemical structure. These substances do, however, differ in their isomeric composition with cyfluthrin consisting of all four diastereomers (isomer I (23-27%); II (17-21%), III (32-36%) and IV (21-25%)), while beta-cyfluthrin consists of isomers II (30-40%) and IV (57-67%) only. In the ecotoxicity section of the proposal incoherent information is given on the potency, i.e. biological activity of the isomers. On one hand it is stated that: "Due to the common structure of the diastereomers it can be assumed that all diastereomers show a similar biological activity and share the same insecticidal mode of action", while on the other hand it is reasoned that isomers II and IV are more biologically active, and that isomer III can synergize the activity of isomer IV, which would justify an activity ratio of 1.3 between cyfluthrin and beta-cyfluthrin (instead of expected activity ratio of 2.4 based on the 40% beta-cyfluthrin content of cyfluthrin). It is proposed to align this section, and clearly indicate the assumptions made by the DS regarding the ecotoxicity of both substances in this proposal. The read-across does not affect the acute aquatic toxicity classification, as the lowest value				

is obtained for Hyalella azteca that was exposed to cyfluthrin yielding a LC50 of 0.55 ng/L (mean measured). H. azteca is a factor 290 more sensitive than Daphnia magna (EC50 of 160 ng/L conducted with cyfluthrin). The lowest chronic value is a NOEC of 0.41 ng/L (mean-measured) available for the marine invertebrate Americamysis bahia following exposure to beta-cyfluthrin for 28 days. A. bahia is a factor 50 more sensitive than Daphnia magna (NOEC of 20 ng/L conducted with cyfluthrin). These data suggest that if beta-cyfluthrin is indeed more toxic than cyfluthrin, A. bahia is considerably less sensitive than H. azteca. That said, as there is no chronic ecotoxicity data for the most sensitive acute species H. azteca the NL CA considers it appropriate to base the chronic aquatic classification on A. bahia. It is worth nothing that correcting the NOEC with a factor of 2.4 (to account for higher toxicity of the II and IV isomers) would not affect the chronic aquatic classification (as the corrected NOEC would be 0.984 ng/L).

Dossier Submitter's Response

Thank you for your comment.
In the ecotoxicity section (5.4 Aquatic toxicity) of the report it is clearly stated that beta-cyfluthrin is at least equally toxic as cyfluthrin, possibly up to 2.4 times more toxic than cyfluthrin (based on the content of biological active isomers: diasterioisomers II and IV). Because no chronic data for the acute most sensitive species Hyallela azteca that was exposed to cyfluthrin yielding a LC50 of 0.55 ng/L (mean measured) is available for beta-cyfluthrin, the NOEC of Americamysis bahia of 0.41 ng/L (mean measured) is used for aquatic chronic classification.

RAC's response

Thank you for your comment. The activity of different diastereomers have been investigated and cited as part of the dossier submitter's (DS's) proposal. The use of either ratio is not critical to classifying the substance.
The lowest acute value obtained for invertebrates for beta-cyfluthrin is with *A. bahia* 96-h LC_{50} = 0.0000022 mg/L and for Cyfluthrin (ISO) with *H. azteca* 96-h LC_{50} of 0.00000055 mg/L indicating that *H. azteca* can be considered the most sensitive specie with regards to acute toxicity to beta-cyfluthrin and can be considered as a basis for acute classification. RAC agrees with the DS that based on the content of biologically active isomers beta-cyfluthrin is possibly up to 2.4 or 1.3 times more toxic than cyfluthrin (ISO) and notes that the possible effects on the most sensitive species *H. azteca* need to be considered with regards to aquatic hazard classification. Chronic classification should therefore be based on a surrogate approach based on read-across data from cyfluthrin (ISO) resulting in the most stringent outcome.

TOXICITY TO REPRODUCTION

Date	Country	Organisation	Type of Organisation	Comment number
17.05.2019	Germany	Bayer AG	Company-Manufacturer	2

Comment received

We support the proposal of the Dossier Submitter that the classification Developmental toxicant cat. 2, H361 d (Suspected of damaging the unborn child) is not warranted based on the increase in malformations, including microphthalmia, that were observed in cyfluthrin developmental toxicity studies via the inhalation route (M-041542-02-1, M-038947-01-1). These findings were a consequence of the route of inhalation-triggered maternal toxicity e.g. bradypnea, leading to reduced oxygen supply, hypoxia and hypoxemia and not directly attributable to treatment. In addition it should also be noted that the Wistar Hsd Cpd:WU

rat strain used in these studies has a high spontaneous background incidences of microphthalmia. Based on mechanistic investigations, the increase in malformations was shown to be secondary to effects of inhalation exposure on the dams in the form of maternal hypoxia, with the resulting compensatory mechanisms of hypothermia and respiratory alkalosis, resulting in clinical signs of respiratory disturbances and hypoactivity. Hypoxia during development is known to be capable of inducing many types of malformations. In the inhalation study (M-038947-01-1), where an additional high dose group received supplementary oxygen, supplementation resulted in the reduction of maternal toxicity and developmental effects; in particular, the incidence of fetuses with microphthalmia was reduced from 5.4% to 2.9%. These observations support that hypoxia is the primary MOA for development of microphthalmia/other malformations and maternal toxicity for cyfluthrin when administered via the inhalation route. Furthermore in developmental studies via the oral route with cyfluthrin and beta-cyfluthrin, at dose levels up to 30 mg/kg bw/d and 40 mg/kg bw/d, respectively, no treatment-related increased incidences of any malformations, including microphthalmia, were observed, even though these dose levels were in the order of 10 fold higher than at the high dose (11 .9 mg/m3, , equivalent to 3 mg/kg bw/d) in the inhalation study (Holzum, 1993, M-038947-01-1), where a clear increase in malformations, particularly microphthalmia were seen. In addition, a comparison of systemically available cyfluthrin levels (plasma levels) after oral and inhalation indicated that the systemic beta-cyfluthrin/cyfluthrin concentrations after oral administration were much higher than after inhalation exposure, further demonstrated that the fetal malformations observed in the inhalation study were the result of maternal hypoxia and not directly related to treatment. More detailed argumentation is presented in the following Expert Statement, which is available for submission:
- Expert Statement entitled "Novel CLP R2 classification proposal by EFSA for beta-cyfluthrin" (M-635090-01-1)

Therefore, it can be concluded that 'the increased incidences of microphthalmia in the rat studies by inhalation were a secondary consequence of effects of the route of exposure, resulting in marked toxicity in the dams (eg hypoxia and bradypnea), which are known to be non-human relevant, hence the CLP Category R criteria are not met and no classification is warranted.

Documents mentioned are either referenced in the CLH Report or enclosed as attachments.

ECHA note – An attachment was submitted with the comment above. Refer to public attachment M-635090-01-2_Expert statement reprotox_sanitized.pdf
ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment M-635090-01-1_Expert statement reprotox.pdf

Dossier Submitter's Response

The DS proposal was supported. No response required.

RAC's response

Thank you for the detailed analysis. Despite some uncertainties, RAC finds it plausible that the increased incidence of microphthalmia in rat inhalation studies with cyfluthrin was secondary to maternal adaptive mechanisms, which are of low human relevance. RAC agrees with no classification for development.

Date	Country	Organisation	Type of Organisation	Comment number
17.05.2019	Germany	Bayer AG	Company-Manufacturer	3

Comment received

We strongly disagree with the proposed classification for Reproductive toxicity Lact. H362 (May cause harm to breastfed children).
Coarse tremors seen in the neonatal rat in the two generation reproduction study with cyfluthrin (M-032017-01-1), are classic transient signs of acute neurotoxicity associated with a Type ll pyrethroid with no adverse long term consequences. This is a high dose phenomenon based on the limited metabolic capacity of the young rat compared to the adult rat and is via a mode of action which is not relevant to humans. Pyrethroids are metabolized primarily by cytochrome P450 enzymes in the rat and by carboxylesterase enzymes in humans. Because carboxylesterase enzymes develop rapidly in humans after birth, pyrethroids are detoxified and cleared rapidly in both children and adults. More detailed argumentation is presented in the Expert Statement (M-512994-01-1). The following two recent publications, which are available for submission, provide further evidence that the sensitivity of young rats to pyrethroids associated with limited metabolic capacity is not relevant to predict the sensitivity of children to pyrethroids (different family of enzymes involved and those enzymes develop at a much earlier age (postnatal) in humans than rats):
- Publication entitled "Age-Dependent Human Hepatic Carboxylesterase 1 (CES1) and Carboxylesterase 2 (CES 2) Postnatal Ontology" (Hines et. al., Drug Metab Dispos 44: 959-966, 2016; M-625239-01-1)
- Publication entitled "Determination of Human Hepatic CYP2C8 and CYP1A2 Age-Dependent Expression to Support Human Health Risk Assessment for Early Ages (Song et. al., Drug Metab Dispos 45: 468-475, 2017; M-658739-01-1)
Furthermore, humans (including lactating females) would never be exposed to the high concentrations of beta cyfluthrin / cyfluthrin required to overwhelm the metabolizing capacity of the sensitive neonate rat.

Documents mentioned are either referenced in the CLH Report or enclosed as attachments.

ECHA note – An attachment was submitted with the comment above. Refer to public attachment CLH commenting_sanitized.zip
ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment CLH commenting.zip

Dossier Submitter's Response

We remain of the opinion that classification for Lact. H362 is warranted for the following reasons:
(1) beta-cyfluthrin has lipophilic properties, can be accumulated in the lipid-rich tissue of the breast implying that transfer into human or animal breast will occur
(2) Sheets and Lake (2003), DNT study with rats: measurements of beta-cyfluthrin concentration in whole brain tissue was performed; beta-cyfluthrin was detected in brain tissue from pups on both days measured (PND4 and PND21) at all dietary levels (dose-related)
(3) residues of cyfluthrin were detected in human breast milk samples

For these reasons there is clear evidence of exposure of pups during lactation which in turn

implies that beta-cyfluthrin can reach pups via dam's milk. The observed adverse effects in the offspring of the 2-generation toxicity study in rats during lactation is considered related to the transfer of cyfluthrin and/or its metabolite(s) in the milk.
The argumentation via metabolic capacity of CES is based on many speculation which cannot be used to exclude a hazard for human health.
The classification proposal for Lact. H362 was also supported by SE, ES and FR CA.

RAC's response

Thank you for the comment and the publications resulting from a research project on metabolism of pyrethroids.
The tremors observed in the neonatal rats exposed to cyfluthrin via milk in the two-generation study 70 in the absence of maternal toxicity, although transient, are considered an adverse effect.
According to Song *et al.* (2017), the major contributors to pyrethroid metabolism in humans are CYP2C8, CYP2C19, CYP3A4, CES1 and CES2. According to Hines *et al.* (2016) human infants younger than 3 weeks of age are expected to exhibit significantly lower CES1- and CES2-dependent metabolic clearance compared with older individuals. Song *et al.* (2017) found a significant increase in human hepatic CYP2C8 expression to occur around postnatal day 35. These data indicate that human infants younger than three weeks would exhibit significantly lower pyrethroid clearance, and thereby increased sensitivity to pyrethroid toxicity, compared to adults.
Risk-based arguments cannot be taken into account in hazard assessment.
Thus, RAC agrees with the DS's proposal of classification with Lact.; H362.

Date	Country	Organisation	Type of Organisation	Comment number
03.05.2019	Sweden		MemberState	4

Comment received

No effects on reproductive parameters were observed, thus the Swedish Chemicals Agency support the proposal of no classification for effects on fertility and sexual function. The Swedish Chemicals Agency also support the proposal of no classification for effects on development. The increased incidence of micropthtalmia outside HCD-range occurred in a rat strain (Wistar Hsd Cpb:WU) with a high background incidence of this malformation and was associated with maternal toxicity. No cases of micropthtalmia were observed at higher systemic dose levels following oral exposure in other strains of rat or rabbits following cyfluthrin or beta-cyfluthrin exposure. Thus, the effects can be considered specific to this particular stain of rats, likely due to an increase of a spontaneously occurring malformation in the presence of maternal toxicity and not a specific developmental effect of the substance. It would be valuable with a specification of the specific sub-strains of Wistar rats used in the different studies. A similar case was recently discussed in RAC with regard to the substance Prothioconazole, showing similar effects (microphthalmia) in this particular strain of Wistar Hsd Cpb:WU rats but not in other Wistar strains or in rabbits, leading to the conclusion of no classification for effects on development.

The Swedish Chemicals Agency support the proposal for classification of effects via lactation. Clinical signs of neurotoxicity were observed in the pups during the lactational period, likely attributed by the presence of cyfluthrin in the breast milk (supported by animal data on beta-cyfluthrin and by human data).

Dossier Submitter's Response
Thank you for your support.
RAC's response
Thank you for your comment. RAC agrees that Lact.; H362 and no classification for fertility and development are warranted.

Date	Country	Organisation	Type of Organisation	Comment number
24.05.2019	United Kingdom	<confidential>	Company-Downstream user	5
Comment received				
Page 81 - Conclusions of the Pesticides Peer Review: In the EFSA peer review of beta-cyfluthrin (EFSA Journal 2018;16(9):5405), based upon the discussion from the Pesticides Peer Review Meeting 172, it was mentioned that: "Reproductive toxicant category 2 H361d Suspected of damaging the unborn child was proposed by the majority of the experts, excluding the RMS." This was based primarily on the findings from an inhalation developmental study where some effects were seen at the highest dose tested in the presence of clear maternal toxicity. However, the CLH report for beta-cyfluthrin (CLH Report Beta-Cyfluthrin, Version number: 3.0, Date: November 2018) disputes that assumption and on the basis of a comprehensive review of the toxicology reports (e.g. there were five developmental studies and a multigeneration study via oral dosing) concludes that: "Manifestations of developmental toxicity seen in rats and rabbits were accompanied by maternal toxicity"…."Taken together, (the overall findings) based on the small number of animals affected, these findings are considered not severe enough to justify a classification in Category 2 (H361d)." Furthermore, in the CLH report, the effects seen in the inhalation developmental toxicity study are robustly addressed and the following conclusion reached: "It can be assumed that the occurrence of the mentioned malformations, especially microphthalmia, in the offspring does not represent a direct toxic effect of the test substance. This assumption is supported by reproductive toxicity studies with orally administered beta-cyfluthrin/cyfluthrin, which are systemically available by oral absorption (60 % (beta-cyfluthrin) and 90 % (cyfluthrin)). After oral administration no treatment-related malformations were observed." This conclusion is supported by the toxicology database where the evidence is clear, from both animal and human inhalation studies, that exposure to beta-cyfluthrin, at relatively high dosages, may result in local irritation of the airways. The evidence suggests that the local effects did not result in significant pathological lung changes and there was no data to suggest significant systemic exposure following inhalation exposure. Furthermore, the CLP reports states: "Due to the irritating properties of the test substance at these dose levels (via inhalation) a reflex bradypnoea occurred in the dams which was compensated by hypothermia and a reduction in metabolic activity." The weight of evidence from the toxicology database demonstrates that exposure to beta-cyfluthrin via inhalation may result in local respiratory irritative effects in the directly exposed subjects. There was no evidence for significant systemic exposure via inhalation exposure. Where systemic exposure to beta-cyfluthrin was manifest, after oral dosing, there was no evidence for teratogenicity or adverse developmental toxicity. The weight of evidence does not support a classification for developmental toxicity and the 2018 CLH				

report does not propose such a classification.
Dossier Submitter's Response
The DS proposal was supported. No response required.
RAC's response
Thank you for your comment. Please see response to comment 2.

Date	Country	Organisation	Type of Organisation	Comment number
26.04.2019	Spain		MemberState	6
Comment received				
Toxicity via lactation In a 2-generation toxicity study with cyfluthrin in rats, increased incidence of coarse tremors and decreased pup body weight was observed in F1 and F2 pups at 125 ppm (19 mg/kg bw/d) and 400 ppm (59 mg/kg bw/d). Coarse tremors were observed as early as lactation day 5 and had ceased by lactation day 18 and occurred in the presence of maternal toxicity only at 400 ppm. In F0 and F1 females, a compound-related and statistically significant increased incidence of splayed hind limbs occurred at 400 ppm during the lactation phase. Statistically significantly decreased terminal body weights were observed in F1 males at 125 ppm (6%) and 400 ppm (8%) and in F1 females only at 400 ppm (8%). No measurements of beta-cyfluthrin concentration in the rat milk after exposure have been provided. However, residues of cyfluthrin were detected in human breast milk samples. Additionally, measurements of beta-cyfluthrin concentration in whole-brain tissue were performed in a developmental neurotoxicity study in rats. Beta-cyfluthrin was detected in brain tissue from pups on both days measured (PND 4 and PND 21) at all dietary levels, with the concentration increasing in proportion to the dietary concentration. These findings provide clear evidence of exposure of the pups during lactation and that beta-cyfluthrin can reach the pups via the dam's milk. On overall, it can be concluded that the presence of neurotoxic effects in the offspring at 125 ppm in the 2-generation study in rats was due to transfer of cyfluthrin or of its metabolite(s) in the milk during the lactation period. This conclusion is supported by the absence of adverse treatment effects on prenatal or peri-natal litter parameters. Therefore, the Spanish CA agreed with the proposal of the dossier submitter to classify beta-cyfluthrin as a reproductive toxicant in category for effects on or via lactation as Lact H362: May cause harm to breast-fed children.				
Dossier Submitter's Response				
Thank you for you support.				
RAC's response				
Thank you for your comment. RAC agrees that classification with Lact.; H362 is warranted.				

Date	Country	Organisation	Type of Organisation	Comment number
20.05.2019	Denmark		MemberState	7
Comment received				
DK suggest that the EFSA proposal (PPR 172 Expert's meeting) for classification as Reproductive toxicant category 2 (H361d) is added – and with the same argument (p.81 in CLH report). DK emphasizes the increased incidences of microphthalmia in the rat developmental studies by inhalation. Microphthalmia is categorised as a finding with "high level of concern" (ECETOC, 2002).				
Dossier Submitter's Response				
The proposal for non-classification is supported by SE CA (see above).				
RAC's response				
Thank you for your comment. Despite some uncertainties, RAC finds it plausible that the increased incidence of microphthalmia in the rat inhalation studies with cyfluthrin was secondary to maternal adaptive mechanisms ('hibernation-like state' involving bradypnoea and hypothermia) triggered by sensory irritation. Although oxygen supplementation did not reduce the incidence of micropthalmia down to control levels, the reduced incidence in the oxygen-supplemented group indicates that hypoxia does play a role in the etiology. Oxygen supplementation did not fully counteract maternal toxicity; at least hypothermia was also present in the oxygen-supplemented group of study 78. An article on the mode of action (MoA) has recently been published in open literature (Pauluhn, 2018). It should also be noted that microphthalmia was always present in concurrent controls, so it was not a rare malformation in the strain tested. Importantly, no increase in malformations was observed in oral studies with cyfluthrin and beta-cyfluthrin (studies 72 and 76) leading to at least 10-fold higher systemic exposure than the inhalation studies (details about toxicokinetics are presented in the background document). As the strong physiological response to sensory irritation observed in rats is not expected to occur in humans exposed to (beta-)cyfluthrin, the related increase in eye malformations is considered to be of low human relevance. Consequently, RAC agrees with the DS that the increased incidence of micropthalmia in the rat inhalation studies with cyfluthrin does not warrant classification. Reference: Pauluhn (2018): Upper respiratory tract nociceptor stimulation and stress response following acute and repeated Cyfluthrin inhalation in normal and pregnant rats: physiological rat-specific adaptations can easily be misunderstood as adversities. Toxicology Letters 282:8-24				

Date	Country	Organisation	Type of Organisation	Comment number
17.05.2019	France		MemberState	8
Comment received				
FR: - Fertility: It is agreed that no classification is warranted.				

- Development:
Oral developmental toxicity studies:
Developmental toxicity (reduced fetal weight and delayed ossification) occurred in the presence of maternal toxicity and no evidence of teratogenicity was noted in the oral studies.
Inhalation developmental toxicity studies:
In study 77: effects on fetuses (decreased fetal weight, increased runts and skeletal anomalies) were observed from 1.1 mg/m3. At this dose level only decreased body weight gain is observed in dams. However, corrected BW gain is not reported. As both fetal weight and placenta weight are affected at 1.1 mg/m3, it is difficult to conclude if decreased body weight gain of dams is driven by general maternal toxicity or a consequence of decreased fetal weight.
At the high dose levels, malformations (microphthalmia) were observed in both inhalation studies (77 and 78) at maternally toxic levels.
The proposed mode of action (non-specific retardation of embryonic development attributed to a maternal hypoxia induced by the treatment rather to an embryotoxic potential of cyfluthrin) is not considered sufficiently supported by empirical support. Indeed, following additional oxygen exposure in the high dose group, the incidence of microphthalmia (study 78) was lower than without oxygen supplementation, but remained higher than control values.
As regard the absence of microphthalmia in oral developmental toxicity study, this could reflect a consequence of first pass effect.
The above-mentioned considerations provide some evidence of increased susceptibility of developing organisms and a classification as developmental toxicant category 2 (H361d "Suspected of damaging the unborn child") is proposed.

- Lactation :
Classification and labelling for reproductive toxicity H362: May cause harm to breast-fed children is supported based on the elements reported by DS (increased incidences of coarse tremors and decreased pup body weights at and above 125 ppm cyfluthrin during the lactation period in the rat 2-generation toxicity study, the lipophilic properties of beta-cyfluthrin and detection of cyfluthrin residues in human breast milk samples). Furthermore, FOB effects observed in the top dose pups (200 ppm) in the screening DNT (minimal resistance during handling and reduced startle response) should also be considered.

Dossier Submitter's Response

Thank you for your support regarding classification for Lact. H362.

With regard to classification for Repr.2 H361d, please refer to the CLH report summarising all available information. We agree that uncertainties in the DS's argumentation relating to first-pass clearance as described by FR should be acknowledged. The proposal for non-classification is supported by SE CA (see above).

RAC's response

Thank you for your comment.
RAC agrees that Lact.; H362 and no classification for sexual function and fertility are warranted. As for development, please see response to comment 7.

OTHER HAZARDS AND ENDPOINTS – Acute Toxicity

Date	Country	Organisation	Type of Organisation	Comment number
26.04.2019	Spain		MemberState	9
Comment received				
Oral The lowest LD50 value determined in acceptable studies with cyfluthrin was 14.3 mg/kg bw (solvent: Cremophor/water) in rats. We agreed with the dossier submitter to base the classification proposal of beta-cyfluthrin for acute oral toxicity on the cyfluthrin lowest value. Therefore, a classification as Acute Tox 2, H300 – Fatal if swallowed is warranted. Inhalation Based on the worst-case LC50 value determined in an acceptable inhalation study, the LC50 value in rats used for classification was 0.081 mg beta-cyfluthrin in ethanol/PEG 400/L air as mist (4h-exposure, head-nose only). The lowest rat LC50 value after dust exposure was 0.532 mg beta-cyfluthrin /L air (4h-exposure, head-nose only). Therefore, a classification as Acute Tox 2, H330 - Fatal if inhaled is warranted.				
Dossier Submitter's Response				
Thank you for your support.				
RAC's response				
Thank you for your comment. RAC agrees with Acute Tox. 2 via the oral and inhalation routes.				

Date	Country	Organisation	Type of Organisation	Comment number
17.05.2019	Germany	Bayer AG	Company-Manufacturer	10
Comment received				
We disagree with the proposal to use the acute oral LD50 value derived using Cremophor/water as vehicle, for classification and labelling. The LD50 value of 14.3 mg/kg bw is particularly low due to the fact that Cremophor being a non-ionic solubilizer and emulsifier, enhances absorption and was primarily developed for the pharmaceutical industry to aid in the GI absorption of drugs. Furthermore, OECD guidance for the choice of vehicle indicates the vehicle should neither reduce nor enhance the toxicity of the test substance. Therefore, the exaggerated toxic potency expressed in studies that used Cremophor/water as vehicle indicates that the resulting LD50 values are not appropriate for classification or labelling. Likewise, the relatively high LD50 values reported for cyfluthrin and beta-cyfluthrin administered in an aqueous or organic suspension may underestimate acute toxicity for classification or labelling. For pyrethroids, data generated using an oil based vehicle are best suited for references purposes and is in line with the approach taken by the US EPA for cyfluthrin. This is further detailed in the attached expert statement (M-494996-01-1) Therefore, the LD50 value of 77 mg/kg bw in fasted female rats (Report No.: 16181) - the lowest value generated using acetone/peanut oil as vehicle for either cyfluthrin or beta-cyfluthrin in acceptable studies - is the most appropriate scientifically for classification and labelling purposes. This data support a classification of Acute Tox. 3, H301 (Toxic if swallowed)				

Documents mentioned are either referenced in the CLH Report or enclosed as attachments.

ECHA note – An attachment was submitted with the comment above. Refer to public attachment CLH commenting_sanitized.zip
ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment CLH commenting.zip

Dossier Submitter's Response

We remain of the opinion that classification for Acute Tox. 2 (H300) is warranted. The lowest LD50 value determined in acceptable studies with cyfluthrin was 14.3 mg/kg bw (cremophor/water) in rats. As laid down in the Guidance on the application of CLP criteria (version 5.0, July 2017), […] "if there are different LD50 values from tests using different vehicles […] generally the lowest valid value would be the basis for classification […]" (page 241). For this reason, the classification for acute oral toxicity for cyfluthrin was based on the study using chemophor/water as vehicle.
This classification proposal is supported by ES and FR CA (see above and below).

RAC's response

Thank you for your comment.
RAC acknowledges that according to the relevant OECD TGs water and oil are generally preferred to other vehicles and that vegetable oils have been widely used for acute oral toxicity testing of pyrethroids. On the other hand, Cremophor is a surfactant and surfactants are found in plant protection products containing pyrethroids. Thus, Cremophor cannot be dismissed as a vehicle for human hazard assessment. Therefore RAC agrees with the DS to base the classification on studies where the substance was dissolved in aqueous Cremophor.

Date	Country	Organisation	Type of Organisation	Comment number
17.05.2019	France		MemberState	11

Comment received

FR: Acute toxicity

Oral route: page 32, the read across approach (use of cyfluthrin study 5 as key study) is supported. Indeed, the lowest valid value should be the basis for classification if there are different LD50 values from tests using different vehicles and no study with Cremophor/water solvent is available with beta-cyfluthrin.

Page 41: 4.2.5 Conclusions on classification and labelling. The proposal for classification Acute Tox 2, H300 – Fatal if swallowed and Acute Tox 2, H330 - Fatal if inhaled is supported.

Dossier Submitter's Response

Thank you for your support.

RAC's response

Thank you for your comment. RAC agrees with Acute Tox. 2 via the oral and inhalation routes.

OTHER HAZARDS AND ENDPOINTS – Skin Hazard

Date	Country	Organisation	Type of Organisation	Comment number
03.05.2019	Sweden		MemberState	12
Comment received				
Although clear symptoms of irritation of skin are observed after contact with cyfluthrin and/or beta-cyfluthrin, and it appears acknowledged that personal protective equipment is needed when handling the substances, the Swedish Chemicals Agency agree that these symptoms has a neurological basis and not caused by tissue damage to skin. Thus, no classification is warranted based on the CLP criteria.				
Dossier Submitter's Response				
Thank you for your support.				
RAC's response				
Thank you for your comment, RAC agrees that no classification for skin irritation is warranted.				

Date	Country	Organisation	Type of Organisation	Comment number
26.04.2019	Spain		MemberState	13
Comment received				
Skin symptoms (paraesthesia) have been observed in people handling the active ingredient Beta-cyfluthrin or cyfluthrin. We agreed with the dossier submitter that the dermal sensations are direct and transitory effects on sensory nerve endings and not the result of a primary skin irritation. This conclusion is supported by the results of the skin irritation study in rabbits with beta-cyfluthrin (all mean scores for erythema, eschar formation as well as for oedema formation were 0). Therefore, beta-cyfluthrin does not meet the criteria for dermal toxicity classification.				
Dossier Submitter's Response				
Thank you for your support.				
RAC's response				
Thank you for your comment, RAC agrees that no classification for skin irritation is warranted.				

Date	Country	Organisation	Type of Organisation	Comment number
17.05.2019	France		MemberState	14
Comment received				
FR: Skin corrosion / irritation Pages 45-46, results from experimental data do not trigger classification. Effects reported in human (paresthesia) typical of skin contact to alpha-cyano pyrethroids are driven by sensory nerve endings and do not result from a primary skin irritation. Therefore,				

classification is not warranted.
Dossier Submitter's Response
Thank you for your support.
RAC's response
Thank you for your comment, RAC agrees that no classification for skin irritation is warranted.

OTHER HAZARDS AND ENDPOINTS – Eye Hazard

Date	Country	Organisation	Type of Organisation	Comment number
03.05.2019	Sweden		MemberState	15
Comment received				
Although clear symptoms of irritation eyes are observed after contact with cyfluthrin and/or beta-cyfluthrin, and it appears acknowledged that personal protective equipment is needed when handling the substances, the Swedish Chemicals Agency agree that these symptoms has a neurological basis and not caused by tissue damage to eyes. Thus, no classification is warranted based on the CLP criteria.				
Dossier Submitter's Response				
Thank you for your support.				
RAC's response				
Thank you for your comment, RAC agrees that no classification for eye irritation is warranted.				

OTHER HAZARDS AND ENDPOINTS – Skin Sensitisation Hazard

Date	Country	Organisation	Type of Organisation	Comment number
17.05.2019	France		MemberState	16
Comment received				
FR: Skin sensitisation Pages 50-51: It should be highlighted that the sensitising potential could not be thoroughly assessed. Indeed, only a Buehler Patch Test with three applications is available with beta-cypermethrin while only Buehler test with nine application is considered valid for the evaluation of skin sensitization. Furthermore, this 3-application Buehler test presents several limitations as listed page 50. In the key study, a M&K test carried out with cyfluthrin, the challenge concentrations could have been higher. Indeed, it remains unclear – even though sodium lauryl sulphate was applied in the main study to provoke a local irritation for topical induction – why the dose-range-finding study was not extended to higher concentrations to investigate possible skin irritating effects induced by higher concentrations. In conclusion, the criteria for classification are not met based on the negative results in the provided inadequate test and there are still uncertainties on the intrinsic sensitising properties of beta-cyfluthrin since the concentrations applied for challenge were too low.				
Dossier Submitter's Response				
Thank you for your support.				

RAC's response
Thank you for your comment. RAC proposes no classification based on conclusive data. Buehler test with beta-cyfluthrin (study 58): It is considered plausible that a test concentration of 66% is near the highest attainable concentration for a solid in a paste. Three is the number of inductions required by OECD TG 406. RAC does not suspect the substance to be unstable at 66% when it was found to be stable at 40%. Occlusive conditions are mentioned for the pilot tests in the study report, so they are likely to have been applied also in the main test. Consequently, RAC considers the study adequate. GPMT with cyfluthrin (study 57): RAC notes that the robust study summary (from the biocidal dossier) does not provide any explanation as to why higher concentrations were not tested. As the substance was a liquid, it could have been tested neat. On the other hand, the high viscosity and high lipophilicity (log K_{ow} ca. 6) of cyfluthrin are likely to hinder dermal uptake. Thus, solubilisation in an agent such as PEG 400 can be seen as a step increasing dermal uptake and thereby sensitivity of the method, rather than a deficiency.

OTHER HAZARDS AND ENDPOINTS – Specific Target Organ Toxicity Single Exposure

Date	Country	Organisation	Type of Organisation	Comment number
03.05.2019	Sweden		MemberState	17
Comment received				
The Swedish Chemicals Agency support the proposal for STOT SE3, H335 ("May cause respiratory irritation") based on the human and animal data provided. In addition, beta-cyfluthrin causes as other pyrethroids neurotoxicity, which is observed in many studies. In the repeated dose studies, clinical signs such as tremors, ataxia, high-stepping gait, are commonly observed. The clinical effects observed in the acute toxicity studies are not described in the CLH-proposal. If similar neurological effects occur after single dosing, STOT SE3, H336 ("May cause drowsiness or dizziness") may be warranted.				
Dossier Submitter's Response				
Thank you for your support. STOT SE 3, H335 was also supported by ES CA (see below).				
RAC's response				
Thank you for your comment. According to the Guidance on the application of the CLP criteria (version 5.0), classification in STOT SE Category 3 for respiratory tract irritation is generally limited to local cytotoxic effects. Clear evidence of respiratory tract irritation (bradypnea) has been found in rats at non-lethal concentrations. However, given the lack of histopathological findings in the respiratory tract up to 24 mg/m^3 (28-d study 67), the effects are considered to represent sensory, not cytotoxic irritation. Respiratory irritation was observed at 0.1-0.2 mg/m^3 in the human volunteer study 44. However, taking into account the lack of histopathological evidence of cytotoxicity in animals at concentrations 2 orders of magnitude higher, these effects are also considered to represent sensory irritation. The human reports from occupationally exposed subjects referred to in the CLH report either do not mention respiratory irritation (studies 52, 53, 54) or are not described at a				

level of detail allowing independent assessment (study 45). Additional information, not specifically on cyfluthrin but on pyrethrins and pyrethroids in general, has been found in the ATSDR report (ATSDR: Toxicological profile for pyrethrins and pyrethroids, 2003). Some of the reported symptoms are indicative of irritation while severe asthmatic reactions from dermal and inhalation exposure to pyrethrins suggest a potential role of allergy.
In summary, there is sufficient evidence that the (beta-)cyfluthrin-induced respiratory irritation is a sensory, not cytotoxic irritation. Therefore, classification for respiratory tract irritation is not warranted.

The information on clinical signs of neurotoxicity in acute toxicity studies available to RAC is limited. However, it seems that in oral gavage and in inhalation studies the clinical signs of neurotoxicity occurred close to doses associated with mortality, thus being covered by the acute toxicity classification. On the other hand, the acute dermal studies 40 and 41 showed clinical signs significantly below lethal doses and no acute toxicity classification is proposed for the dermal route.
As to human data on pyrethroids, there appears to be a dose interval between mild poisoning (dizziness, headache, nausea) and severe poisoning (convulsive attacks and coma) sufficient to warrant a STOT SE classification, although the available exposure information is limited.
The nature and severity of the acute neurotoxic effects is considered to correspond to a STOT SE 1/2 rather than a STOT SE 3 classification. As the clinical signs in animals occurred at or below 300 and 1000 mg/kg bw after oral and dermal exposure respectively, and neurotoxic symptoms were reported also in humans exposed to pyrethroids, RAC proposes classification with STOT SE 1; H370 (nervous system).

Date	Country	Organisation	Type of Organisation	Comment number
26.04.2019	Spain		MemberState	18

Comment received

Medical data indicate the skin, eye, and the upper respiratory tract as main target organs towards cyfluthrin. Symptoms like paresthesia of the skin, eye irritation, watering eyes, hyperaemia of the nasal mucosa, nasal irritation, mild irritation of the throat, coughing, sneezing and asthma-like reactions may occur after dermal/inhalation exposure of cyfluthrin. Animal data also showed respiratory disturbances and bradypnoea due to irritative aerosol concentrations of cyfluthrin.

It is also possible that these effects were related to the intrinsic sensory irritation of synthetic pyrethroids and would be out of the scope of STOT SE classification. However, we are in line with the German CA that there are no mechanistic and/or sufficient data details available to differentiate the local cytotoxic irritant from the sensory central reflex symptoms in the respiratory system. Therefore, the Spanish CA agreed with the dossier submitter that classification of beta-cyfluthrin for respiratory irritation STOT-SE 3, H335 (May cause respiratory irritation) based on data from cyfluthrin studies is required.

Dossier Submitter's Response

Thank you for your support.

RAC's response

Thank you for your comment. Please see response to comment 17.

Date	Country	Organisation	Type of Organisation	Comment number
17.05.2019	Germany	Bayer AG	Company-Manufacturer	19

Comment received

We disagree with the proposed classification of STOT-SE Cat 3, H335 (May cause respiratory irritation) as the available data do not meet the relevant CLP criteria (v.4.1) for the following 3 key reasons:

1) STOT-SE Cat 3 for respiratory tract irritation should reflect the primary cause of effect and not secondary toxicological events such as the symptoms observed in human volunteers
2) those symptoms are rapidly reversible and
3) no evidence of 'cytotoxic irritation'.

The following Expert Statement and recent publication, which support the above reasoning against the proposed classification, are available for submission:
- Expert Statement entitled "Cyfluthrin-Induced Sensory Irritation in Rats and Humans" (M-546404-01-1)
- Publication entitled "Upper respiratory tract nociceptor stimulation and stress response following acute and repeated Cyfluthrin inhalation in normal and pregnant rats: Physiological rat-specific adaptions can easily be misunderstood as adversities" (M-658738-01-1).

The above also supports the non-classification of Beta-Cyfluthrin as Beta-Cyfluthrin is a mixture of the 4 isomers respectively two diastereomeric pairs of Cyfluthrin.

Documents mentioned are either referenced in the CLH Report or enclosed as attachments.

ECHA note – An attachment was submitted with the comment above. Refer to public attachment CLH commenting_sanitized.zip
ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment CLH commenting.zip

Dossier Submitter's Response

It is refered to the comments by SE, ES and FR CA supporting classification for STOT SE 3 as proposed by dossier submitter (see above and below).

STOT SE 3 classification is based on the following observations:
(1) Category 3 is primarily based on human data.
(2) Evidence for respiratory irritation in humans (asthma-like reactions, mild hyperaemia of nasal mucosa, moderate nasal irritation, mild irritation of throat, coughing, sneezing, watering eyes) can indicate cytotoxic/inflammatory reaction.

However, it may be also possible that these effects are related to the intrinsic sensory irritation of synthetic pyrethroids and would be out of scope of STOT SE classification. No mechanistic data and/or sufficient data details is available to differentiate the local cytotoxic irritant from the sensory central reflex symptoms in the respiratory tract (e.g. no appropriate histopathologic investigation of respiratory tract reported). Therefore, in order to make the user aware of the need for protection, STOT SE 3 is proposed by the dossier

submitter.
RAC's response
Thank you for the detailed analysis. RAC agrees that there there is sufficient evidence that (beta-)cyfluthrin causes sensory but not cytotoxic irritation and that classification with STOT SE 3; H335 is not warranted. See also response to comment 17.

Date	Country	Organisation	Type of Organisation	Comment number
17.05.2019	France		MemberState	20
Comment received				
FR: STOT-SE Page 44, the proposal for classification STOT-SE 3, H335 (May cause respiratory irritation) is supported.				
Dossier Submitter's Response				
Thank you for your support.				
RAC's response				
Thank you for your comment. Please see response to comment 17.				

OTHER HAZARDS AND ENDPOINTS – Specific Target Organ Toxicity Repeated Exposure

Date	Country	Organisation	Type of Organisation	Comment number
17.05.2019	France		MemberState	21
Comment received				
FR: STOT RE Page 66, the rationale not to classify for STOT RE since similar severity is observed after single and repeated exposure to a similar dose can be supported. Indeed, no accumulation or exacerbation of the toxicity with repeated exposure is observed and beta-cyfluthrin is already classified Acute Tox. 2, H300 Fatal if swallowed; Acute Tox. 2, H330 Fatal if inhaled.				
Dossier Submitter's Response				
Thank you for your support.				
RAC's response				
RAC agrees not to classify for STOT RE. However, RAC proposes to additionally classify with STOT SE 1; H370 (nervous system) for reasons explained in the response to comment 17.				

Date	Country	Organisation	Type of Organisation	Comment number
03.05.2019	Sweden		MemberState	22
Comment received				
The Swedish Chemicals Agency is of the opinion that classification of beta-cyfluthrin as STOT RE 2, H373 (nervous system) should be considered, based mainly on effects in oral toxicity studies in rats and dogs after exposure to cyfluthrin and beta-cyfluthrin. Clinical				

signs of neurotoxicity (motor disturbances) were observed at levels in the range for STOT RE2 classification. Also, mortality occurred (study 61, not explained in detail in the dossier) at doses significantly below the LD50 value for the substance. The justification for no STOT RE-classification by the dossier submitter is that the effects observed in the repeated dose studies are sequential acute toxicity effects, since the substances are extensively and rapidly metabolised. However, effects (including mortality) occur at doses, sometimes significantly, below the LD50-values. The effects are also stated to be reversible, however, in study 59 not all cases of sciatic nerve degeneration were reversed following the recovery period. In study 62, necrosis in head/neck region were observed within the level of STOT RE2-classification. Since necrosis is normally not a reversible effect, additional details as to why this effect should not be considered would be useful.
Dossier Submitter's Response
We agree with SE CA that there are some findings observed in rats and dogs at dose levels below the respective guidance values. Some of these findings were severe (such as clinical signs, motor disturbances and/or gait abnormalitites). However, these findings are considered to represent acute toxic/neurotoxic effects. Due to intensive metabolism and rapid excretion of (beta)-cyfluthrin, daily administrations are considered to represent a sequence of acute intoxications. Thus, no proposal for STOT RE was made. However, acute effects were addressed by making the proposal for STOT SE 3.
RAC's response
Thank you for your comment. In study 61 (28-d rat gavage study with beta-cyfluthrin, vehicle aqueous Cremophor) mortality (23 out of 60 animals) occurred at the top dose of 16 mg/kg bw/d; the proposed ATE for acute oral toxicity is 14 mg/kg bw. No mortality occurred at the next lower dose of 4 mg/kg bw/d according to the RAR. In study 59 (90-d rat dietary study with cyfluthrin) slight sciatic nerve degeneration was observed in 8 out of 40 animals at 61/68 mg/kg bw/d (m/f). However, minimal single fibre degeneration in the sciatic nerve was observed in 6 out of 8 rats already after a single gavage dose of 80 mg/kg bw cyfluthrin in PEG 400 in another study (Anonymous, 1983). Thus, the histopathological findings in study 59 need not necessarily represent a repeat dose effect. The necrosis and sores in the head and neck region observed in study 62 (90-d rat dietary study with beta-cyfluthrin) were attributed to increased preening movements which led to skin injuries. Based on the information available to RAC, the neurotoxicity in repeat dose studies with (beta-)cyfluthrin seems to represent a series of acute intoxications. RAC proposes to classify the substance as Acute Tox. 2 via oral and inhalation routes and STOT SE 1 (nervous system). See also response to comment 17. Reference: Anonymous (1983) FCR 1272 – Special toxicological study (morphological effects on the nervous system of rats). Bayer, report no. R 3362

OTHER HAZARDS AND ENDPOINTS – Hazardous to the Aquatic Environment

Date	Country	Organisation	Type of Organisation	Comment number
17.05.2019	United Kingdom		MemberState	23

Comment received

Beta-cyfluthrin (EC: -; CAS: 1820573-27-0)
Acute and chronic aquatic hazard classification:
The lowest and therefore key acute endpoint, is a 96-h LC50 of 0.00000055 mg/l (mm) for Hyalella Azteca using cyfluthrin. The study is considered valid and reliable for hazard classification. We agree this should form the basis of the acute hazard classification.

The lowest available chronic endpoint is a 28-d NOEC of 0.00000041 mg/l (mm) for Americamysis bahia using beta-cyfluthrin. The use of this endpoint results in Aquatic Chronic 1 with a chronic M-factor of 100,000. While we note beta-cyfluthrin is anticipated to be more ecotoxic than cyfluthrin, the surrogate approach using the H. Azteca acute endpoint for cyfluthrin results in a chronic M-factor of 1,000,000 for a NRD substance. We think this is preferable as H. Azteca appears to be more sensitive to the active isomers in cyfluthrin and beta-cyfluthrin on the basis of a less sensitive 96-h LC50 of 0.0000022 mg/l (mm) for A. bahia using beta-cyfluthrin.

Acute toxicity to algae (S. subspicatus):
Is analytical support available for the Heimback, 1987 algal growth inhibition study to support the use of nominal endpoints?

Acute toxicity to C. riparius:
Significant losses were observed in the water phase over the study 28 day period. On this basis we do not consider it is appropriate to base the endpoint on nominal concentrations. We note that the data may not be suitable for hazard assessment given the inclusion of a sediment phase and that C. riparius do not appear to be the most sensitive species. However, as it appears that the test item did not partition to the sediment phase or pore water significantly, is it possible to calculate a geometric mean measured endpoint to consider relative species sensitives?

Dossier Submitter's Response

Thank you for your support.
There was no analytical examination of the test concentrations at the algal growth inhibition study with Scenedesmus subspicatus (Heimbach, 1987). Therefore only nominal concentrations were reported.
At the toxicity study to Chironomus riparius (Kimmel, 2014) the concentration in water, pore water and sediment was determined over the study (d0, d1, d3, d7 and d28). The estimated mean measured concentration in water phase is 0.0057 µg/L for the nominal test concentration of 0.4 µg/L (NOEC).

RAC's response

Thank you for your comment. See also response to comment No. 1.

Date	Country	Organisation	Type of Organisation	Comment number
17.05.2019	Belgium		MemberState	24

Comment received

BE CA supports the proposed environmental classification with Aquatic Acute 1, H400 (M acute = 1 000 000) and Aquatic Chronic 1, H410 (M chronic= 100 000) but has nonetheless some questions/remarks.

Read-across can be used for classification purposes (4.1.3.1.2. of the CLP guidance).
Aquatic Acute Toxicity:
For acute toxicity we agree with the use of the read-across with cyfluthrin for the most sensitive invertebrate Hyalella azteca. A factor of 1.5 in difference in acute toxicity (D. magna, values are in the same order of magnitude) between cyfluthrin and beta-cyfluthrin can be noted. Furthermore, when considering the acute invertebrate toxicity of cyfluthrin, it was demonstrated that D. magna is not the most sensitive invertebrate species. Based on the above it can therefore be expected that H. azteca will be more sensitive than D. magna when exposed to beta-cyfluthrin

Aquatic Chronic Toxicity:
We have however some doubts about the assumption made that based on the content of biological active isomers beta-cyfluthrin is at least equally toxic as cyfluthrin and possibly up to 2.4 times more toxic than cyfluthrin to aquatic organisms. And especially towards the chronic toxicity to fish and the use of the read-across data. In our opinion it would be advisable to better substantiate the toxicity relation between cyfluthrin and beta-cyfluthrin substances by comparing available acute and chronic data for all trophic levels available and this by preference for the same species. F.i. comparing LC50 values for Oncorhynchus mykiss gives a factor of difference in toxicity of 4.4 and for Lepomis macrochirus of 3.5. The chronic fish toxicity of cyfluthrin will in all probability represent an underestimation of that of beta-cyfluthrin.

Although the same algae species are not tested for both substances the available data give an indication that the difference here is even much higher (445 to 805).

Do you have an explanation why the chronic results for invertebrates (D. magna and A. bahia) are "exactly" the same for both substances while the content of active isomers is different. (difference in acute tox for D. magna is a factor of 1.5)

Do the active isomers act via the same mode of action?

Seen the above we prefer the use of the surrogate approach (and classify according to the most stringent outcome) for chronic toxicity in this case, although it does not change the proposed classification,:
The substance is not rapidly degradable and meets the bioaccumulation criterion
- Based on lowest NOEC : Invertebrates (Americamysis bahia) with 28d NOEC = 0.00041 µg/L
Classification : Aquatic chronic 1, H410
M-factor = 100 000 (0.0000001 mg/l <NOEC ≤0.000001 mg/l)
- Based on lowest LC50 for the other trophic levels : Fish 96hLC50 = 0.068 µg/L (mm) = 0.00068mg/L

Classification : Aquatic Chronic 1, H410; M-factor =1 000 (0.0001 mg/l <LC50 ≤0.001 mg/l) Furthermore we question the validity of the read-across study for aquatic chronic toxicity with Pimephales promelas (Anonymous, 1990) equivalent to OECD TG 210 due to the high mortality (37.5 % post hatch) that was seen in the control group. According to OECD TG 210 the validity criterion concerning the survival of controls is not met: for Pimephales promelas hatching success should be 70% and post hatch success75%. Was there an analytical determination of beta-cyfluthrin concentration in the Scenedesmus subspicatus study (Heimbach, 1987)?
Dossier Submitter's Response
Thank you for your support. We fully agree that when considering the acute invertebrate toxicity of beta-cyfluthrin and cyfluthrin, it was demonstrated that D. magna is not the most sensitive invertebrate species. Based on data given in CLH-report it could be expected that H. azteca will be more sensitive than D. magna when exposed to beta-cyfluthrin. It is not really clear, if the active isomers act via the same mode of action. There is no explanation why the chronic results for invertebrates (D. magna and A. bahia) are "exactly" the same for both substances while the content of active isomers is different. We fully agree that the chronic fish toxicity of cyfluthrin will in all probability represent an underestimation of that of beta-cyfluthrin. But no reliable chronic fish study for beta-cyfluthrin is available. The aquatic chronic toxicity with Pimephales promelas (Anonymous, 1990) equivalent to OECD TG 210 is not fully reliable due to the high mortality (37.5 % post hatch) that was seen in the control group, but this occurred at day 153-301 post hatch (very long duration). The recommended duration of OECD 201 is 32 d (or 28 days post-hatch) with the validity criterion concerning the survival of controls (hatching success should be 70% and post hatch success 75%). In the control group the hatching success was 78% and the survival was 92% at day 7-61 post hatch. Therefore the study result is valid for the compareable duration to OECD 210 and reliable. There was no analytical examination of the test concentrations at the algal growth inhibition study with Scenedesmus subspicatus (Heimbach, 1987). Therefore only nominal concentrations were reported.
RAC's response
Thank you for your comment. Please also see response to comment No. 1. Acute fish toxicity data on Cyfluthrin (ISO) indicates slightly higher acute toxicity to fish of beta-Cyfluthrin. However, chronic fish data is available only for Cyfluthrin (ISO). Potentially higher chronic toxicity of beta-Cyfluthrin to fish as presented is noted. Water flea test results show similarly lower sensitivity towards beta-Cyfluthrin and Cylfuthrin (ISO). Based on the available data invertebrate are the most sensitive species to consider for both acute and chronic aquatic toxicity classification. Fish and algae data is not considered for the purpose of classification.

Date	Country	Organisation	Type of Organisation	Comment number
17.05.2019	France		MemberState	25
Comment received				
FR: - Please note that from the List of endpoint published by EFSA in 2018 (EFSA Journal 2018;16(8):5402) a worst-case acute endpoint for Hyalella azteca is available, 48h-EC50 = 0.0053 µg a.s./L. This allows to calculate a new acute M-Factor of 100000 instead of the one of 100 proposed in the CLH report. From the EFSA journal, the following classification is proposed for cypermethrin : Category Acute 1 | Endpoint: 0.0053 µg a.s./L [48h EC50 Hyalella azteca] H400 (M-factor = 100000) Category Chronic 1 | Endpoint: 0.03 µg a.s./L [Chronic NOEC Pimephales promelas] H410 (M-factor = 1000) - Beside the new endpoint available for Hyalella azteca, new chronic endpoints are also available in the EFSA journal for Daphnia magna and Chironomus riparius. It is FR opinion that for completeness, these endpoints should appear in the list of available data in the CLH report.				
Dossier Submitter's Response				
Thank you for your comment. It is not clear why the List of endpoint published by EFSA in 2018 (EFSA Journal 2018;16(8):5402) for cyfluthrin is cited. The public consultation for cyfluthrin is in progress at the same time. Actually for beta-cyfluthrin there is also a List of endpoint (2018) available. From the List of endpoint published by EFSA in 2018 (EFSA Journal 2018;16(9):5405), the following classification is proposed for beta-cyfluthrin : Category Acute 1 | Endpoint: 0.00225 µg a.s./L [96h EC50 Americamysis bahia] H400 (M-factor = 100000) Category Chronic 1 | Endpoint: 0.00041 µg a.s./L [28 d NOEC Americamysis bahia] H410 (M-factor = 100000) It should be noted that proposals for classification made in the context of the evaluation procedure under regulation (EC) No. 1107/2009 are not formal proposals.				
RAC's response				
Thank you for your comment. Please also see reponse to comments No. 1.				

OTHER HAZARDS AND ENDPOINTS – Physical Hazards

Date	Country	Organisation	Type of Organisation	Comment number
17.05.2019	France		MemberState	26
Comment received				
FR: p17 and 20 More recent tests are available in the AIR of the active substance beta-cyfluthrin: the substance has no self-ignition up to 440°C according to EC A 16 (study Smeykal (2013) and the substance is not flammable according to EC A10 (study Smeykal (2013).				

A test has been provided in the AIR of the active substance beta-cyfluthrin. The substance has no oxidizing properties according to the EC A 17 (study Smeykal (2013).
Dossier Submitter's Response
Thank you for your support.
RAC's response
Thank you for your comment. It is noted.

PUBLIC ATTACHMENTS
1. M-635090-01-2_Expert statement reprotox_sanitized.pdf [Please refer to comment No. 2]
2. CLH commenting_sanitized.zip [Please refer to comment No. 3, 10, 19]

CONFIDENTIAL ATTACHMENTS
1. M-635090-01-1_Expert statement reprotox.pdf [Please refer to comment No. 2]
2. CLH commenting.zip [Please refer to comment No. 3, 10, 19]