

## COMMENTS AND RESPONSE TO COMMENTS ON CLH: PROPOSAL AND JUSTIFICATION

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**Last data extracted on 03.06.2019**

**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**  
**CAS number: 1820573-27-0**  
**EC number: -**  
**Dossier submitter: Germany**

### GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
13.05.2019	Netherlands		MemberState	1
Comment received				
<p>Agreed with minor comments</p> <p>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.</p> <p>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.</p> <p>The read-across does not affect the acute aquatic toxicity classification, as the lowest value is obtained for <i>Hyaella azteca</i> that was exposed to cyfluthrin yielding a LC50 of 0.55 ng/L (mean measured). <i>H. azteca</i> is a factor 290 more sensitive than <i>Daphnia magna</i> (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 <i>Americamysis bahia</i> following exposure to beta-cyfluthrin for 28 days. <i>A. bahia</i> is a factor 50 more sensitive than <i>Daphnia magna</i> (NOEC of 20 ng/L conducted with cyfluthrin). These data suggest that if beta-cyfluthrin is indeed more toxic than cyfluthrin, <i>A. bahia</i> is considerably less sensitive than <i>H. azteca</i>. That said, as there is no chronic ecotoxicity data for the most sensitive acute species <i>H. azteca</i> the NL CA considers it appropriate to base the chronic</p>				

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).

## 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/m<sup>3</sup>, 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

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 II 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.

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

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 microphthalmia 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 microphthalmia 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 strain 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).

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.

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.

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).

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/m<sup>3</sup>. 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/m<sup>3</sup>, 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.

## OTHER HAZARDS AND ENDPOINTS – Acute Toxicity

Date	Country	Organisation	Type of Organisation	Comment number
26.04.2019	Spain		MemberState	9
Comment received				
<p>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.</p> <p>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.</p>				

Date	Country	Organisation	Type of Organisation	Comment number
17.05.2019	Germany	Bayer AG	Company-Manufacturer	10
Comment received				
<p>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)</p> <p>Documents mentioned are either referenced in the CLH Report or enclosed as attachments.</p> <p>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</p>				

Date	Country	Organisation	Type of Organisation	Comment number
17.05.2019	France		MemberState	11
Comment received				
FR: Acute toxicity				
<p>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.</p> <p>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.</p>				

#### **OTHER HAZARDS AND ENDPOINTS – Skin Hazard**

Date	Country	Organisation	Type of Organisation	Comment number
03.05.2019	Sweden		MemberState	12
Comment received				
<p>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.</p>				

Date	Country	Organisation	Type of Organisation	Comment number
26.04.2019	Spain		MemberState	13
Comment received				
<p>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.</p>				

Date	Country	Organisation	Type of Organisation	Comment number
17.05.2019	France		MemberState	14
Comment received				
<p>FR: Skin corrosion / irritation</p> <p>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</p>				

sensory nerve endings and do not result from a primary skin irritation. Therefore, classification is not 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.				

#### **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.				

#### **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.				

Date	Country	Organisation	Type of Organisation	Comment number
26.04.2019	Spain		MemberState	18
Comment received				
<p>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.</p> <p>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.</p>				

Date	Country	Organisation	Type of Organisation	Comment number
17.05.2019	Germany	Bayer AG	Company-Manufacturer	19
Comment received				
<p>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:</p> <ol style="list-style-type: none"> <li>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</li> <li>2) those symptoms are rapidly reversible and</li> <li>3) no evidence of 'cytotoxic irritation'.</li> </ol> <p>The following Expert Statement and recent publication, which support the above reasoning against the proposed classification, are available for submission:</p> <ul style="list-style-type: none"> <li>- Expert Statement entitled "Cyfluthrin-Induced Sensory Irritation in Rats and Humans" (M-546404-01-1)</li> <li>- Publication entitled "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" (M-658738-01-1).</li> </ul> <p>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.</p> <p>Documents mentioned are either referenced in the CLH Report or enclosed as attachments.</p> <p>ECHA note – An attachment was submitted with the comment above. Refer to public attachment CLH commenting_sanitized.zip</p>				

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

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.				

### **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.				

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.				

### **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 sensitivities?

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 success 75%.

Was there an analytical determination of beta-cyfluthrin concentration in the *Scenedesmus subspicatus* study (Heimbach, 1987)?

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.

#### **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				
<p>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)).</p> <p>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)).</p>				

#### **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]