COMMENTS AND RESPONSE TO COMMENTS ON CLH: PROPOSAL AND JUSTIFICATION

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

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Last data extracted on 03.06.2019

Substance name: cyfluthrin (ISO); α-cyano-4-fluoro-3-phenoxybenzyl-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylate
CAS number: 68359-37-5
EC number: 269-855-7
Dossier submitter: Germany

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
17.05.2019	France		MemberState	1
Comment received				
Page 13: According to the CAR of the active substance the enantiomeric ratio is 1:1 within each diasteroisomer pair. Page 17: According to the CAR of the active substance, for explosive properties, the purity of the tested compound is 94,3% w/w (Mixture of 4 Diastereoisomers).				

TOXICITY TO REPRODUCTION

Date	Country	Organisation	Type of Organisation	Comment number
03.05.2019	Sweden		MemberState	2
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).

Date	Country	Organisation	Type of Organisation	Comment number
17.05.2019	France	Bayer SAS	Company-Manufacturer	3

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 (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	France	Bayer SAS	Company-Manufacturer	4

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.

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Date	Country	Organisation	Type of Organisation	Comment number
17.05.2019	Finland		MemberState	5

Comment received

Cyfluthrin has lipophilic properties and it can accumulate in the lipid-rich tissues of the breast. The studies indicate that cyfluthrin and/or its metabolites transfer into breast milk in humans and animals. Cyfluthrin through the milk is considered to be a main determinant of offspring neurotoxicity in the 2-generation toxicity study in rats. Based on

available information and the classification criteria FI CA supports classification of cyfluthrin as a reproductive toxicant via lactation; H362.

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 in rats with cyfluthrin, 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 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.				

OTHER HAZARDS AND ENDPOINTS – Acute Toxicity

Date	Country	Organisation	Type of Organisation	Comment number
17.05.2019	France	Bayer SAS	Company-Manufacturer	7
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.

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Date	Country	Organisation	Type of Organisation	Comment number
17.05.2019	Finland		MemberState	8
Comment received				
Hazard class - Acute Toxicity: oral Several studies indicate that the experimental oral LD50 values of cyfluthrin (ISO) have a broad range. DE CA's conclusion that this may be due to different polarity leading to modified absorption in the gastrointestinal track is reasonable. FI CA considers that classification according to the lowest value (study 5) is justified based on CLP regulation as generally the lowest valid value would be the basis for classification. The FI CA supports the classification proposal Acute Tox. 2; H300. Hazard class – Acute Toxicity: inhalation The lowest LC50 values for cyfluthrin determined in inhalation studies after 4h expo-sure to dust were 0.141 mg/L air (cyfluthrin in ethanol/PEG 400, 4h-exposure, head-nose only; study 33). The FI CA supports the classification proposal Acute Tox. 2; H330.				

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. Therefore, a classification as Acute Tox 2, H300 – Fatal if swallowed is warranted. Inhalation The LC50 values of cyfluthrin and beta-cyfluthrin were determined in rodents after exposure to dust. The lowest LC50 value for cyfluthrin was 0.141 mg/L air (cyfluthrin in ethanol/PEG 400, 4h-exposure, head-nose only) and 0.047 mg/L air (cyfluthrin in ethanol/PEG 400, 5x6 h-exposure, nose only). 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/L air beta-cyfluthrin in ethanol/PEG 400 as mist (4h-exposure, head-nose only). The lowest rat LC50 value after dust exposure was 0.532				

mg/L air beta-cyfluthrin (4h-exposure, head-nose only). Therefore, a classification as Acute Tox 2, H330 - Fatal if inhaled is warranted

OTHER HAZARDS AND ENDPOINTS – Skin Hazard

Date	Country	Organisation	Type of Organisation	Comment number
26.04.2019	Spain		MemberState	10
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 skin irritation classification.				

Date	Country	Organisation	Type of Organisation	Comment number
03.05.2019	Sweden		MemberState	11
Comment received				
Although clear symptoms of irritation of skin are observed after contact with cyfluthrin, and it appears acknowledged that personal protective equipment is needed when handling the substance, 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.				

OTHER HAZARDS AND ENDPOINTS – Eye Hazard

Date	Country	Organisation	Type of Organisation	Comment number
03.05.2019	Sweden		MemberState	12
Comment received				
Although clear symptoms of irritation of eyes are observed after contact with cyfluthrin, and it appears acknowledged that personal protective equipment is needed when handling the substance, 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 – Specific Target Organ Toxicity Single Exposure

Date	Country	Organisation	Type of Organisation	Comment number
03.05.2019	Sweden		MemberState	13
Comment received				
The Swedish Chemicals Agency support the proposal for STOT SE 3, H335 ("May cause respiratory irritation") based on the human and animal data provided. In addition, 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 SE 3, H336 ("May cause drowsiness or dizziness") may be warranted.				

Date	Country	Organisation	Type of Organisation	Comment number
17.05.2019	France	Bayer SAS	Company-Manufacturer	14
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" (Pauluhn, 2017, 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" (Pauluhn, Tox Letters 282 (2018) 8-24; M-658738-01-1). 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				

Date	Country	Organisation	Type of Organisation	Comment number
17.05.2019	Finland		MemberState	15
Comment received				
Both animal studies and human data showed respiratory disturbances. FI CA con-siders that the severity of the human effects is a borderline case and cyfluthrin could even be classified as STOT-SE category 2 as the weight of human evidence in-dicates cytotoxic reactions as asthma-like reactions, moderate nasal irritation, irri-tation of the throat, coughing, sneezing and watering eyes. Based on the results FI CA considers that the				

effects do not have a short duration after exposure and the symptoms can cause prolonged alteration. Consequently, based on the reported data and classification criteria, FI CA considers that the substance should be classi-fied STOT SE category 2; H335

Date	Country	Organisation	Type of Organisation	Comment number
26.04.2019	Spain		MemberState	16
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.				

OTHER HAZARDS AND ENDPOINTS – Specific Target Organ Toxicity Repeated Exposure

Date	Country	Organisation	Type of Organisation	Comment number
03.05.2019	Sweden		MemberState	17
Comment received				
The Swedish Chemicals Agency is of the opinion that classification of 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 RE 2-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	Belgium		MemberState	18
Comment received				

BE CA supports the proposed environmental classification with Aquatic acute 1, H400 and Aquatic Chronic 1, H410.
Based on the available data for the most sensitive species (Invertebrates : Hyalella Azteca; 96hLC50= 0.55ng/L Americamysis bahia 28dNOEC=0.41ng/L) a M-factor for acute toxicity of 1 000 000 and for chronic toxicity of 100 000 is warranted.

Date	Country	Organisation	Type of Organisation	Comment number
17.05.2019	France		MemberState	19
Comment received				
FR agrees with the Aquatic Acute 1 (H400 ; M-factor=1.000.000) and Aquatic Chronic 1 (H410; M-factor=100.000) classification proposal. □				

Date	Country	Organisation	Type of Organisation	Comment number
17.05.2019	United Kingdom		MemberState	20
Comment received				
Cyfluthrin (EC: 269-855-7; CAS: 68359-37-5) 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 (P. subcapitata): We agree that algae are likely to not the most sensitive species for hazard assessment. We do not agree that the presented study is suitable for definitive hazard classification as the study controls were not valid indicating the study is not reliable.				

PUBLIC ATTACHMENTS
1. M-635090-01-2_Expert statement reprotox_sanitized.pdf [Please refer to comment No. 3]
2. CLH commenting_sanitized.zip [Please refer to comment No. 4, 7, 14]

CONFIDENTIAL ATTACHMENTS
1. M-635090-01-1_Expert statement reprotox.pdf [Please refer to comment No. 3]
2. CLH commenting.zip [Please refer to comment No. 4, 7, 14]