

Committee for Risk Assessment
RAC

Opinion

proposing harmonised classification and labelling
at EU level of

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

OPINION OF THE COMMITTEE FOR RISK ASSESSMENT ON A DOSSIER PROPOSING HARMONISED CLASSIFICATION AND LABELLING AT EU LEVEL

In accordance with Article 37 (4) of Regulation (EC) No 1272/2008, the Classification, Labelling and Packaging (CLP) Regulation, the Committee for Risk Assessment (RAC) has adopted an opinion on the proposal for harmonised classification and labelling (CLH) of:

Chemical name:

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

EC Number: -

CAS Number: 1820573-27-0

The proposal was submitted by **Germany** and received by RAC on **30 November 2018**.

In this opinion, all classification and labelling elements are given in accordance with the CLP Regulation.

PROCESS FOR ADOPTION OF THE OPINION

Germany has submitted a CLH dossier containing a proposal together with the justification and background information documented in a CLH report. The CLH report was made publicly available in accordance with the requirements of the CLP Regulation at <http://echa.europa.eu/harmonised-classification-and-labelling-consultation/> on **18 March 2019**. Concerned parties and Member State Competent Authorities (MSCA) were invited to submit comments and contributions by **24 May 2019**.

ADOPTION OF THE OPINION OF RAC

Rapporteur, appointed by RAC: **Michal Martínek**

Co-Rapporteur, appointed by RAC: **Raili Moldov**

The opinion takes into account the comments provided by MSCAs and concerned parties in accordance with Article 37(4) of the CLP Regulation and the comments received are compiled in Annex 2.

The RAC opinion on the proposed harmonised classification and labelling was adopted on **4 May 2020** by **consensus**.

Classification and labelling in accordance with the CLP Regulation (Regulation (EC) 1272/2008)

	Index No	Chemical name	EC No	CAS No	Classification		Labelling			Specific Conc. Limits, M-factors and ATE	Notes
					Hazard Class and Category Code(s)	Hazard statement Code(s)	Pictogram, Signal Word Code(s)	Hazard statement Code(s)	Suppl. Hazard statement Code(s)		
Current Annex VI entry	607-254-00-7	α -cyano-4-fluoro-3-phenoxybenzyl-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylate ; beta-cyfluthrin	269-855-7	68359-37-5	Acute Tox. 2* Acute Tox. 2* Aquatic Acute 1 Aquatic Chronic 1	H330 H300 H400 H410	GHS06 GHS09 Dgr	H330 H300 H410			
Dossier submitters proposal	607-254-00-7	beta-cyfluthrin (ISO); reaction mass of <i>rel</i> -(R)-cyano(4-fluoro-3-phenoxyphenyl)methyl (1S,3S)-3-(2,2-dichloroethenyl)-2,2-dimethylcyclopropane-1-carboxylate and <i>rel</i> -(R)-cyano(4-fluoro-3-phenoxyphenyl)methyl (1S,3R)-3-(2,2-dichloroethenyl)-2,2-dimethylcyclopropane-1-carboxylate	-	1820573-27-0	Retain Aquatic Acute 1 Aquatic Chronic 1 Add Lact. STOT SE 3 Modify Acute Tox. 2 Acute Tox. 2	Retain H330 H300 H400 H410 Add H362 H335	Retain GHS06 GHS09 Dgr Add: GHS08	Retain H330 H300 H410 Add H362 H370 (nervous system)		Add oral: ATE = 14.3 mg/kg bw inhalation: ATE = 0.081 mg/L (dusts or mists) M = 1000000 M = 100000	
RAC opinion	607-254-00-7	beta-cyfluthrin (ISO); reaction mass of <i>rel</i> -(R)-cyano(4-fluoro-3-phenoxyphenyl)methyl (1S,3S)-3-(2,2-dichloroethenyl)-2,2-dimethylcyclopropane-1-carboxylate and <i>rel</i> -(R)-cyano(4-fluoro-3-phenoxyphenyl)methyl (1S,3R)-3-(2,2-dichloroethenyl)-2,2-dimethylcyclopropane-1-carboxylate	-	1820573-27-0	Retain Aquatic Acute 1 Aquatic Chronic 1 Add Lact. STOT SE 1 Modify Acute Tox. 2 Acute Tox. 2	Retain H330 H300 H400 H410 Add H362 H370 (nervous system)	Retain GHS06 GHS09 Dgr Add: GHS08	Retain H330 H300 H410 Add H362 H370 (nervous system)		Add inhalation: ATE = 0.081 mg/L (dusts or mists) oral: ATE = 11 mg/kg bw M = 1000000 M = 1000000	
Resulting Annex VI entry if agreed by COM	607-254-00-7	beta-cyfluthrin (ISO); reaction mass of <i>rel</i> -(R)-cyano(4-fluoro-3-phenoxyphenyl)methyl (1S,3S)-3-(2,2-dichloroethenyl)-2,2-dimethylcyclopropane-1-carboxylate and <i>rel</i> -(R)-cyano(4-fluoro-3-phenoxyphenyl)methyl (1S,3R)-3-(2,2-dichloroethenyl)-2,2-dimethylcyclopropane-1-carboxylate	-	1820573-27-0	Lact. Acute Tox. 2 Acute Tox. 2 STOT SE 1 Aquatic Acute 1 Aquatic Chronic 1	H362 H330 H300 H370 (nervous system) H400 H410	GHS06 GHS08 GHS09 Dgr	H362 H330 H300 H370 (nervous system) H410		inhalation: ATE = 0.081 mg/L (dusts or mists) oral: ATE = 11 mg/kg bw M = 1000000 M = 1000000	

GROUNDWORK FOR ADOPTION OF THE OPINION

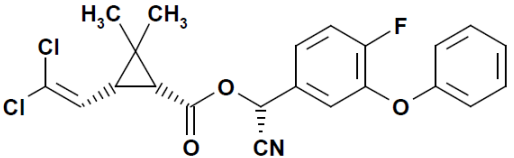
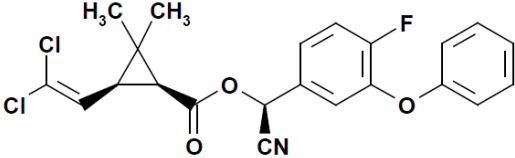
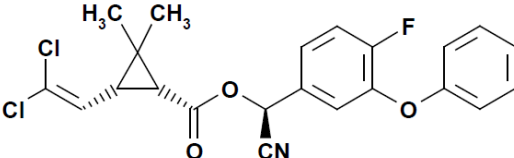
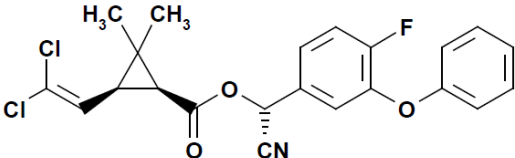
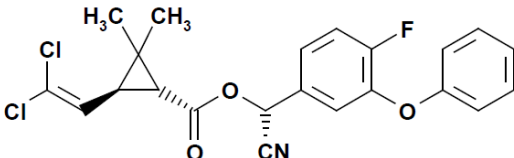
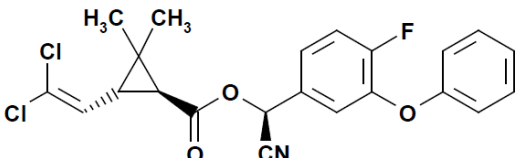
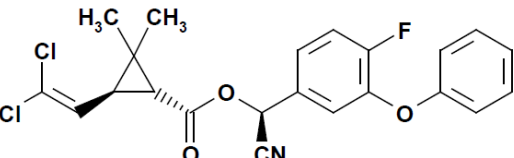
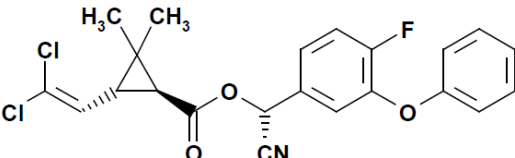
RAC general comment

Read-across for human health hazards

Cyfluthrin and beta-cyfluthrin are pyrethroid insecticides, belonging to the alpha-cyano, or Type II group of pyrethroids. Cyfluthrin is used in biocidal products and beta-cyfluthrin in plant protection products.

The dossier submitter (DS) proposed read-across between the two substances for all human health hazards evaluated and informed that read-across was generally accepted for the biocidal (cyfluthrin) and plant protection (beta-cyfluthrin) evaluation.

The molecule has 3 chiral centres, giving rise to 4 enantiomeric pairs denoted by the dossier submitter (DS) as diastereomer I to IV (see the table below). Cyfluthrin contains all four pairs in approximately equal amounts (ca. 20-35% each) while in beta-cyfluthrin pairs II and IV predominate (30-40% and 56-67% of pair II and pair IV respectively; sum of pairs I and III is below 5%).

I	 cyclopropane: 1R,3R (cis); cyano: R	 cyclopropane: 1S,3S (cis); cyano: S
II	 cyclopropane: 1R,3R (cis); cyano: S	 cyclopropane: 1S,3S (cis); cyano: R
III	 cyclopropane: 1R,3S (trans); cyano: R	 cyclopropane: 1S,3R (trans); cyano: S
IV	 cyclopropane: 1R,3S (trans); cyano: S	 cyclopropane: 1S,3R (trans); cyano: S

Biological activity (insecticidal activity and neurotoxicity to mammals) of pyrethroids significantly depends on stereochemistry. The molecule is probably active only as a whole (no molecular moiety could be identified as the toxophore) and not all stereoisomers fit equally well to the site of action (Soderlund *et al.*, 2002). Beta-cyfluthrin is a more potent insecticide than cyfluthrin.

A comparison of acute studies indicates that beta-cyfluthrin may be somewhat more potent than cyfluthrin also in mammals (see the table below).

Endpoint	Species, experimental conditions	Results (reference)	
		Cyfluthrin	Beta-cyfluthrin
Acute oral toxicity	Rat (Wistar), vehicle PEG 400	LD ₅₀ 590/1190 mg/kg bw (m/f; study 11)	LD ₅₀ 380/650 mg/kg bw (m/f; study 21)
	Rat (Wistar), vehicle acetone/peanut oil	LD ₅₀ 155/160 mg/kg bw (m/f; study 12)	LD ₅₀ 84/77 mg/kg bw (m/f; study 22)
	Rat (Wistar), vehicle aqueous Cremophor	LD ₅₀ 14-20 mg/kg bw (m; studies 1-8)	LD ₅₀ 11 mg/kg bw (m; Anonymous, 1986)
	Mouse, vehicle PEG 400	Strain: NMRI LD ₅₀ 290/610 mg/kg bw (m/f; study 14)	Strain: Bor:WISW LD ₅₀ 91/170 mg/kg bw (m/f; study 25)
Acute inhalation toxicity	Rat (Wistar), vehicle ethanol/PEG 400 (1:1), head-nose only	LC ₅₀ 0.41 mg/L (m+f; study 30)	LC ₅₀ 0.09/0.10 mg/L (m/f; study 35) LC ₅₀ 0.08 mg/L (m, f; study 36)

m=males; f=females

For repeated dose toxicity, a comparison of the available studies does not indicate a marked qualitative or quantitative difference in the toxicological profile (see for example the studies in the following table).

Endpoint	Species, experimental conditions	Results (reference)	
		Cyfluthrin	Beta-cyfluthrin
Repeat dose oral toxicity	Rat, dietary, 90-d	Strain: SD Abnormal gait and salivation at 1000 ppm; no significant effects at 300 ppm (study 59)	Strain: Wistar Abnormal gait and poor general condition at 500 ppm; no effects at 125 ppm (study 62)
	Beagle dog, dietary	1-y Abnormal gait and postural reaction deficits at 360 ppm; no effects at 100 ppm (study 60)	90-d Abnormal gait at 360 ppm; no effects at 60 ppm (study 63)
Repeat dose inhalation toxicity	Rat (Wistar), 4-w, vehicle ethanol/PEG 400 (1:1)	Ruffled coat, hyperactivity and bradypnoea at 47 mg/m ³ ; transient bradypnoea at 6.0 mg/m ³ (Anonymous, 1989)	Piloerection, increased activity and decreased respiratory rate at 24 mg/m ³ ; decreased respiratory rate at 2.7 mg/m ³ (study 67)

RAC agrees to consider the data for both substances together for all human health hazards except for acute toxicity. For acute oral and inhalation toxicity, the read-across is not applied as there is conclusive data for each substance and there appears to be a certain difference in potency.

RAC evaluation of physical hazards

Summary of the Dossier Submitter's proposal

Based on the following rationale, the DS concluded that beta-cyfluthrin should not be classified as flammable, oxidising or explosive.

Method	Results	Conclusion	Reference
EEC A.10 & EEC A.16	beta-cyfluthrin is not considered highly flammable and shows no signs of self-ignition.	Not classified as flammable.	Mix, 1995
EEC A.14	beta-cyfluthrin is not considered an explosive in accordance with EEC Method A.14.	Not classified as explosive.	Mix, 1995
EEC A.17	beta-cyfluthrin is not considered an oxidising substance.	Not classified as oxidising.	-

Comments received during public consultation

One MSCA commented that more recent tests are available in the AIR of beta-cyfluthrin.

Assessment and comparison with the classification criteria

RAC agrees with the proposal of the DS that no classification with regards to flammability, explosivity, or oxidising properties are warranted for beta-cyfluthrin, further based on the rationale below.

Flammability

The substance was not tested for flammable properties using UN test N.1. However, the negative result of study EEC A.10 is considered as conclusive for no classification; see ECHA guidance R.7.1.10.3.

Explosive

There are no chemical groups present in the chemical structure, which are associated with explosive properties, and hence, the classification procedure does not need to be applied. The negative result of study EEC A.14 is considered as supportive.

Oxidising properties

Beta-cyfluthrin contains fluorine, chlorine and oxygen atoms that are all chemically bound to carbon or hydrogen. Therefore, the classification procedure does not need to be applied.

The DS also proposed no classification by way of 'conclusive, but not sufficient for classification' for the hazard classes listed below. These are accompanied by rationale, which RAC derived from the information in the CLH dossier.

Self-reactive substances and mixtures

There are no chemical groups present in the molecule, which are associated with explosive or self-reactive properties, and hence, the classification procedure does not need to be applied.

Self-heating substances and mixtures

No classification is warranted because the substance is a solid having a melting point $\leq 160^{\circ}\text{C}$.

Substances and mixtures which in contact with water emit flammable gases

The classification procedure needs not to be applied because the organic substance does not contain metals or metalloids.

The DS did not specifically mention corrosivity to metals, even though this was open for PC as 'conclusive, but not sufficient for classification'. However, as the stated melting point is above 55°C , no classification is warranted.

The hazard classes listed below were opened for PC but were stated as having 'data lacking'.

Organic peroxides

RAC concludes that no classification is warranted as the substance does not fall under the definition of organic peroxides according to GHS and the relevant 'UN Manual of tests and criteria' (Seventh revised edition, 2019), and not due to 'data lacking'.

Pyrophoric solids

No data is available for beta-cyfluthrin and no read-across justification from cyfluthrin has been provided for physical properties. RAC notes that if a substance does not ignite upon contact with a very hot flame (as in an A.10 test) or upon heating, it will not ignite spontaneously at room temperature. Thus, beta-cyfluthrin does not meet the criteria for classification and no further information is needed.

RAC considers that there is sufficient information available to conclude on **no classification with regards of all physical hazards on beta-cyfluthrin**.

HUMAN HEALTH HAZARD EVALUATION

RAC evaluation of acute toxicity

Summary of the Dossier Submitter's proposal

Acute oral toxicity

The DS summarised data from six acute oral toxicity studies with beta-cyfluthrin and 20 with cyfluthrin. The lowest LD_{50} for beta-cyfluthrin of 77 mg/kg bw was found in a rat study using acetone/peanut oil as a vehicle (study 22). The DS noted that oral LD_{50} values of the two substances depend on the vehicle. Cremophor/water was found to be the vehicle leading to the lowest LD_{50} for cyfluthrin (out of the vehicles investigated), but the DS was not aware of any

acute oral toxicity study with beta-cyfluthrin using Cremophor. The DS proposed Acute Tox. 2 with an ATE of 14.3 mg/kg bw based on a rat study with cyfluthrin using aqueous Cremophor as a vehicle (study 5).

Acute dermal toxicity

Three acceptable acute dermal toxicity studies are available for beta-cyfluthrin, reporting LD₅₀ values of >2000 mg/kg bw or >5000 mg/kg bw. Acute dermal toxicity studies with cyfluthrin reported LD₅₀ values of >5000 mg/kg bw, but were considered supplementary due to insufficient reporting. The DS proposed no classification for acute dermal toxicity based on the studies with beta-cyfluthrin.

Acute inhalation toxicity

The DS summarised data from two acute inhalation toxicity studies with beta-cyfluthrin and eight studies with cyfluthrin. The DS proposed classification with Acute Tox. 2 based on an LC₅₀ of 0.081 mg/L (mist) from a rat study with beta-cyfluthrin (study 36).

Comments received during public consultation

Comments on acute toxicity of beta-cyfluthrin were received from two MSCAs and one manufacturer.

While both MSCAs supported the DS's proposal, the manufacturer disagreed with the DS's assessment of acute oral toxicity, arguing that Cremophor is not a suitable vehicle in this case. The relevant OECD TGs (401, 420 and 423) indicate that the use of an aqueous solution/suspension/emulsion should be considered first, followed in order of preference by a solution/suspension/emulsion in oil and then possibly solution in other vehicles. Cremophor is an emulsifier developed to enhance absorption of drugs and exaggerates the toxic potency of the test substance according to the manufacturer. Instead, they proposed to base the classification of both substances on the LD₅₀ of 77 mg/kg bw observed in female rats administered beta-cyfluthrin in acetone/peanut oil (study 22). The DS replied that according to the Guidance on the application of the CLP criteria (ECHA, 2017) the lowest valid value should be the basis for classification, and retained their original position.

Assessment and comparison with the classification criteria

Acute oral toxicity

Out of the vehicles tested, Cremophor yielded the lowest LD₅₀ values for both beta-cyfluthrin and cyfluthrin. The rat LD₅₀ for beta-cyfluthrin in Cremophor was 11 mg/kg bw compared to 77 mg/kg bw in acetone/peanut oil. Other vehicles (including PEG 400) led to higher values.

Beta-cyfluthrin is a strongly lipophilic substance (log K_{ow} ca. 6). RAC notes 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 PPPs containing pyrethroids. Thus, Cremophor cannot be dismissed as a vehicle for human hazard assessment. Therefore, RAC agrees to base the classification on studies where the substance was dissolved in aqueous Cremophor.

The lowest valid LD₅₀ in a relevant species should generally be used as a basis for classification. **RAC proposes to classify beta-cyfluthrin for Acute Tox. 2; H300 with an ATE of 11 mg/kg bw** based on a rat acute toxicity study with beta-cyfluthrin using aqueous Cremophor as a vehicle (Anonymous, 1986).

Acute dermal toxicity

Three acute dermal toxicity studies, all OECD test guideline- and GLP-compliant, are available for beta-cyfluthrin (studies 40, 41, 42; rat, vehicle PEG 400 or xylene). They reported LD₅₀ values of >2000 mg/kg bw or >5000 mg/kg bw.

As all available dermal LD₅₀ values are above 2000 mg/kg bw, RAC agrees with the DS that **no classification is warranted for acute dermal toxicity**.

Acute inhalation toxicity

The lowest LC₅₀ for beta-cyfluthrin was 0.081 mg/L (study 36; rat, head/nose only, vehicle ethanol/PEG 400; OECD TG 403, GLP). This LC₅₀ value corresponds to Category 2 (0.05 < ATE ≤ 0.5 mg/L). Thus, **RAC agrees with the DS's proposal to classify beta-cyfluthrin for Acute Tox. 2; H330 with and ATE of 0.081 mg/L (dusts or mists)**.

RAC evaluation of specific target organ toxicity – single exposure (STOT SE)

Summary of the Dossier Submitter's proposal

The DS discussed respiratory disturbances in rat inhalation studies and human data on respiratory irritation. They proposed STOT SE 3; H335 mainly based on evidence of respiratory irritation in humans exposed to cyfluthrin or other pyrethroids (asthma-like reactions, mild hyperaemia of nasal mucosa, moderate nasal irritation, mild irritation of throat, coughing, sneezing, watering eyes; studies 44, 45, 52, 53, 54). The DS acknowledged the possibility that these symptoms may be related to sensory irritation and thus out of the scope of STOT SE classification. However, the available data were not considered sufficient to differentiate between cytotoxic or sensory irritation. Therefore, the DS preferred to classify in order to make the user aware of the need for protection. The classification criteria for Categories 1 or 2 were not considered to be met since the symptoms were generally of short duration (lasting for up to 24 hours) and humans were assumed to be able to recover in a reasonable period of time without significant permanent alteration of structure or function.

Comments received during public consultation

Comments on the STOT SE classification of cyfluthrin and/or beta-cyfluthrin were received from four MSCAs and one manufacturer.

Three MSCAs supported the DS's proposal of STOT SE 3; H335. One of the MSCAs additionally proposed to consider classification for narcotic effects (STOT SE 3; H336) based on clinical signs such as tremors, ataxia and high-stepping gait in animal studies. The DS did not respond to this.

One MSCA proposed STOT SE 2 instead of STOT SE 3. In their opinion the symptoms observed in humans (asthma-like reactions, nasal irritation, irritation of the throat, coughing, sneezing, watering eyes) indicate cytotoxic reactions, the effects did not have a short duration after exposure and the symptoms could cause prolonged alteration.

The manufacturer presented a case against classification, arguing that there was no functional or histopathological evidence of cytotoxic irritation and/or inflammation in animal repeated exposure inhalation studies. The DS maintained that they did not find sufficient evidence to decide whether the symptoms observed in humans represented cytotoxic irritation or sensory irritation.

Assessment and comparison with the classification criteria

Respiratory tract irritation

Data on respiratory tract irritation are available from animal studies, a human volunteer study and occupationally exposed subjects.

Animal studies

Both acute and repeated exposure studies via inhalation in rats are available for cyfluthrin and beta-cyfluthrin.

The acute study 35 with beta-cyfluthrin reported hyperaemia of the visible nasal mucosa (as a clinical sign) from 11 mg/m³ (LC₅₀ ca. 90 mg/m³; head/nose only, vehicle PEG/ethanol). However, no hyperaemia and no histopathological findings in the respiratory tract were observed at 24 mg/m³ in a 4-w inhalation study with beta-cyfluthrin in the same strain (study 67; head/nose only, vehicle PEG/ethanol; the same author as of study 35). Decreased respiratory rate in study 67 was attributed to sensory irritation.

Human volunteer study (study 44)

Male volunteers were exposed to an insecticidal spray also containing cypermethrin (0.04%), piperonyl butoxide (0.22%), solvents (6.5%; acetone, kerosene), emulsifiers, fragrance, water and propellants. In the first experiment, only 2 out of 5 exposed subjects were able to tolerate exposure for 1 hour. Initial concentration of cyfluthrin in the first experiment was ca. 0.2 mg/m³. The findings included hyperaemia of nasal mucosa, running nose and coughing.

Human volunteer study, 1 st experiment; initial concentration of cyfluthrin ca. 0.2 mg/m ³			
Subject no.	Exposure duration (min)	Observations: subjective	Observations: objective
1	60	No symptoms	Hyperaemia of nasal mucosa
2	40	Nasal irritation	Hyperaemia of nasal mucosa
		Nose running clear mucous	Nose running clear mucous
		Irritation of the throat	Normal
3	3	Coughing	Chest clear
4	60	Nose running, sneezing	Normal
		Eyes watering	Normal
		Coughing - intermittent	
5	25 (initial conc. 0.09 mg/m ³)	Nose streaming	Nasal mucosa more injected than previously

The experiment was then repeated with another group at an initial concentration of ca. 0.1 mg/m³ of cyfluthrin. The subjects were pre-exposed to a placebo spray to alleviate anxiety. All five subjects tolerated the exposure for 1 hour as intended. A single volunteer had objective evidence of slight hyperaemia of the nasal mucosa.

Human volunteer study, 2 nd experiment; initial concentration of cyfluthrin ca. 0.1 mg/m ³		
Subject no.	Observations: subjective	Observations: objective
6	Slight nasal irritation	Slight hyperaemia
7	Nasal irritation	Normal
8	No effects	
9	Irritation at back of throat	Normal
	Nose running	Normal
10	Slight irritation at back of throat	Normal

RAC notes that the study was not designed as a double-blind placebo control study. Further, it is not clear to which extent other ingredients of the mixture (e.g. piperonyl butoxide) contributed to the observed irritation. Given that (beta-)cyfluthrin causes strong sensory irritation in animals and paresthesia in humans, it is plausible that the respiratory irritation in study 44 was caused mainly by cyfluthrin.

Reports from occupationally exposed subjects

The DS informed, with reference to studies 52-54, that people handling cyfluthrin (synthesis laboratory, manufacturing plant, formulation plant, toxicological laboratory) reported signs of irritation in the oro-pharyngeal cavity and the eyes besides skin effects. RAC, upon examination of these documents, found out that they report irritation of the eyes, skin, lips and genitals, but not of the respiratory tract.

Respiratory irritation from alpha-cyano pyrethroids can reportedly lead to asthma-like reactions (study 45). Unfortunately, no further details are available to RAC, which makes the information not possible to evaluate.

Additional information, not specifically on cyfluthrin but on pyrethrins and pyrethroids in general, can be found in the 'Agency for Toxic Substances and Disease Registry' (ATSDR) report (ATSDR, 2003). Some of the reported symptoms are indicative of irritation while severe asthmatic reactions from dermal and inhalation exposure to pyrethrins (*i.e.* constituents of natural pyrethrum extract) suggest a potential role of allergy.

According the CLP criteria, classification in Category 3 for respiratory tract irritation (CLP, Annex I, 3.8.2.2.1) is based primarily on symptoms of respiratory irritation in humans (e.g. redness, cough, pain, breathing difficulties). Subjective human observations could be supported by objective measurements (such as electrophysiological responses, biomarkers of inflammation). Ambiguous reports of simply 'irritation' shall be excluded as this term is commonly used to describe a wide range of sensations including smell, a tickling sensation or dryness, which are outside the scope of classification.

Animal data, such as relevant clinical signs of toxicity (e.g. dyspnea, rhinitis) and histopathological evidence of irritation (e.g. hyperaemia, oedema, minimal inflammation, thickened mucous layer), can be used as part of weight of evidence evaluation.

A STOT SE 3 classification for respiratory irritation can be applied only when more severe organ effects including in the respiratory system are not observed.

The Guidance on the application of the CLP criteria (CLP guidance, version 5.0, ECHA, 2017) further specifies that the generic term 'respiratory tract irritation' covers two different effects: 'sensory irritation' and 'local cytotoxic effects'. According to the CLP guidance, classification for

STOT SE Category 3 for respiratory tract irritation is generally limited to local cytotoxic effects. In the plenary discussion, some RAC members expressed a view that the CLP guidance is unclear and contradictory in this regard, and questioned whether the CLP guidance should be followed in this case. Still, RAC agreed that the currently applicable CLP guidance should be followed, and that where it can be established that sensory irritation is the sole mode of action (MoA), the substance should not be classified.

For cyfluthrin, cough, hyperaemia of nasal mucosa (objective) and irritation of the nasal cavity and throat (subjective) were reported in humans after a single exposure (<1 hour) to concentrations of 0.1-0.2 mg/m³ (study 44).

Clear evidence of respiratory tract irritation (bradypnoea) has been found in rat studies with (beta-)cyfluthrin at non-lethal concentrations. However, given the lack of histopathological findings in the respiratory tract up to 24 mg/m³ (4-w study 67), these effects are considered to represent sensory, not cytotoxic irritation.

In summary, there is clear evidence of respiratory tract irritation from (beta-)cyfluthrin exposure in animals and some evidence of respiratory tract irritation in humans. As no histopathological changes in the respiratory tract were observed in a rat subacute study (study 67) up to high concentrations, (beta-)cyfluthrin-related respiratory tract irritation is considered to represent sensory, not cytotoxic irritation. Therefore, **classification for respiratory tract irritation is not warranted**.

Neurotoxicity

The available information indicates that the cause of deaths in acute toxicity studies with pyrethroids is neurotoxicity (ATSDR, 2003). The neurotoxic effects (e.g. abnormal gait, salivation) in repeat dose studies are considered to represent a series of acute intoxications. Clinical signs of neurotoxicity typically lasted for several hours after administration and resolved before the next dose (Anonymous, 1983; study 63).

The proposed acute oral toxicity classification (Acute Tox. 2; ATE = 11 mg/kg bw) is based on a rat gavage study using aqueous Cremophor as a vehicle. With Cremophor, clinical signs of neurotoxicity started close to doses associated with mortality (studies 61, 76; Anonymous, 1997a, 1999).

In rat gavage studies using PEG 400 clinical signs began from about 40 mg/kg bw/d (study 72; Anonymous, 1983) and mortality from 100 mg/kg bw (study 21).

In rat dietary studies clinical signs of neurotoxicity started from ca. 60 mg/kg bw/d (study 59 – symptoms already after the 1st dose; study 70). Dogs were more sensitive with effects present already around 10 mg/kg bw/d (studies 60 and 63). Lethal doses via dietary route are not known.

Acute dermal toxicity studies reported no mortality up to 2000 mg/kg bw, a single mortality in a single study was observed at 5000 mg/kg bw (study 40). Clinical signs indicative of neurotoxicity (e.g. splayed gait) were observed from 1000 mg/kg bw (studies 40 and 41).

The proposed classification for acute inhalation toxicity is Acute Tox. 2 (ATE = 0.081 mg/L; vehicle ethanol/PEG 400). The information on the threshold for neurotoxicity in the acute studies available to RAC is limited. Increased activity after exposure was reported in subacute studies at 0.024 and 0.047 mg/L (study 67; Anonymous, 1989), which is relatively close to the ATE.

As to human data, signs of mild acute pyrethroid poisoning include dizziness, headache, and nausea, in addition to paresthesia. Higher levels of exposure to pyrethroids result in additional clinical signs such as lethargy, muscle twitches, and mild disturbance of consciousness. Even higher exposure levels may result in convulsive attacks and coma, and these severe effects may last for several weeks (ATSDR, 2003, p. 69).

Paresthesia observed in humans exposed to cyfluthrin (studies 52, 53, 54) and other pyrethroids (ATSDR, 2003), although not a severe effect by itself, is also a manifestation of neurotoxicity and may be viewed as additional support for a STOT SE classification.

Based on the available animal data on (beta-)cyfluthrin and human data on pyrethroids, RAC concludes that the interval between the threshold for neurotoxicity and lethal doses is sufficiently large at least for some routes of exposure to justify classification with STOT SE. In addition, no acute toxicity classification is proposed for the dermal route while neurotoxicity after dermal exposure was observed in rats.

As the clinical signs in animals occurred at or below 300 and 1000 mg/kg bw after oral and dermal exposure respectively, **classification in Category 1 is considered appropriate.** Classification in Category 1 is further supported by human data on pyrethroids.

RAC concludes that classification for STOT SE 1; H370 (nervous system) is justified based on clinical signs of neurotoxicity occurring in some cases significantly below lethal doses.

RAC evaluation of skin corrosion/irritation

Summary of the Dossier Submitter's proposal

The DS proposed no classification based on a negative skin irritation study in rabbits with beta-cyfluthrin where no evidence of skin irritation was observed (study 49). Human reports of paresthesia, typical for alpha-cyano pyrethroids, were considered to represent a direct effect on sensory nerve endings rather than a primary skin irritation.

Comments received during public consultation

Comments on the skin irritation classification of cyfluthrin and/or beta-cyfluthrin were received from three MSCAs, all in support of the DS's proposal.

Assessment and comparison with the classification criteria

One OECD test guideline- and GLP-compliant *in vivo* study is available for beta-cyfluthrin (study 49). The substance was applied as a powder moistened with water. All mean scores for erythema/eschar and oedema were 0.

Two *in vivo* studies are available for cyfluthrin. In study 47 the substance was applied undiluted as a viscous liquid for 24 h (OECD TG 404: 4 h), the applied amount was 0.1 mL (OECD TG 404: 0.5 mL). Slight erythema was noted in 1 out of 4 animals 24 h after patch removal and disappeared by the 72 h time point. The study is considered negative. The available information on study 48 is rather limited; the study was negative according to the CLH report.

RAC agrees with the DS that no classification for skin corrosion/irritation is warranted.

RAC evaluation of serious eye damage/irritation

Summary of the Dossier Submitter's proposal

The DS proposed no classification for serious eye damage/irritation based on two *in vivo* studies with beta-cyfluthrin (study 50 and 51) reporting mild eye irritation not meeting the classification criteria.

Comments received during public consultation

One MSCA supported the DS's proposal.

Assessment and comparison with the classification criteria

Two OECD test guideline- and GLP-compliant *in vivo* studies are available for beta-cyfluthrin (studies 50 and 51). The maximum mean scores for conjunctival redness or oedema were 1.3 and 1 in study 50 and 51 respectively (a mean score of ≥ 2 in 2 out of 3 animals triggers classification); the effects were reversible. No corneal opacity or iritis was present. The studies are considered negative.

Two pre-/non-guideline *in vivo* eye irritation studies are available for cyfluthrin (study 47 and 48), both reporting mild eye irritation. Study 47 is not suitable for classification purposes as it employed a different grading system from that recommended in the OECD TG 405. The pre-guideline study 48 can be considered negative provided the grading system was comparable to that used under CLP.

RAC agrees with the DS that no classification for eye damage/irritation is warranted.

RAC evaluation of skin sensitisation

Summary of the Dossier Submitter's proposal

The DS proposed no classification based on a negative Guinea Pig Maximisation Test (GPMT) with cyfluthrin (study 57) and a negative Buehler test with beta-cyfluthrin (study 58). However, they pointed out several supposed deficiencies:

- Lack of justification why higher concentrations (than 50% in the GPMT and 66% in the Buehler assay) were not tested;
- The Buehler test was conducted with three applications instead of nine;
- Occlusive conditions were not claimed nor documented for the main experiment in the Buehler test;
- Stability and homogeneity was documented for 40% but not 66% test item in the Buehler test, analytical method was not described.

Comments received during public consultation

One MSCA commented on beta-cyfluthrin and considered both studies (57 and 58) inadequate due to the deficiencies mentioned by the DS. No comments were received on cyfluthrin.

Assessment and comparison with the classification criteria

GPMT with cyfluthrin (study 57)

The study was conducted under GLP and according to OECD TG 406. The test substance group comprised 20 males. Two negative control groups consisted of 10 males each. There was no concurrent positive control group; reliability was periodically checked using 2-mercaptobenzothiazole.

The test substance, described as thick brown oil, was dissolved immediately prior to treatment in PEG 400 at 70°C to yield a solution. Stability was analytically verified. A concentration of 5% was used for intradermal induction, 50% for topical induction (1 week later) and 50% and 25% for challenge (21 days after the first induction). No pre-test on irritant effects was performed. One day before topical induction animals were treated with 10% sodium lauryl sulphate in vaseline.

No skin reaction was seen in any animal in the control group. No skin reaction was seen in any animal of the test group at 48 h. At 72 h, one animal (out of 20) showed slight skin reddening at the challenge concentration of 50%.

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.

Buehler test with beta-cyfluthrin (study 58)

The study was conducted under GLP and according to the OECD TG 406. The test substance group consisted of 20 animals, and 10 animals were used as negative controls. Reliability of the method was confirmed with alpha hexyl cinnamic aldehyde (25% and 45% of the animals exhibited dermal reactions after the first and second challenge, respectively).

The test substance, being a solid, was applied as a paste in Cremophor EL/saline (500 mg of test item mixed with 0.25 mL of the vehicle, *i.e.* ca. 66%). Three inductions took place at approximately weekly intervals. The challenge was performed 13 days after the last induction.

The substance did not induce any skin effect upon challenge in the test item group or in the control group (all scores 0).

RAC has not identified any critical deficiencies compromising validity of the study. 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.

RAC concludes that no classification for skin sensitisation is warranted.

RAC evaluation of specific target organ toxicity – repeated exposure (STOT RE)

Summary of the Dossier Submitter's proposal

Repeat dose toxicity studies with cyfluthrin or beta-cyfluthrin are available for the rat (dietary, gavage, inhalation and dermal exposure), dog (dietary exposure), mouse (dietary exposure) and rabbit (dermal exposure).

Mortality and clinical signs of neurotoxicity (e.g. abnormal gait) were observed below the guidance values for classification in several studies. However, these effects were considered to represent acute toxic/neurotoxic effects, already covered by the proposed classification with Acute Tox. 2. Due to intensive metabolism and rapid excretion of cyfluthrin and beta-cyfluthrin, daily administrations of the substances were considered to represent a sequence of acute intoxications. Therefore, the DS proposed no classification for STOT RE.

Comments received during public consultation

Comments on the STOT RE classification of cyfluthrin and/or beta-cyfluthrin were received from 2 MSCAs. One MSCA supported the DS's proposal of no classification while the other one proposed classification with STOT RE 2 (nervous system), pointing out that effects occurred significantly below the LD₅₀ values in some repeat dose studies. They also mentioned histopathological findings in the nervous system in study 59. In their response the DS reiterated that the clinical signs were acute effects addressed by the proposed acute toxicity and STOT SE 3 classifications.

Assessment and comparison with the classification criteria

No other effects potentially relevant for a STOT RE classification apart from neurotoxicity were observed in the available studies.

Clinical signs of neurotoxicity such as gait abnormalities were observed in many single dose and repeat dose studies with cyfluthrin and beta-cyfluthrin. Based on the information available to RAC, the neurotoxic effects in the repeat dose studies seem to represent a series of acute intoxications. For example, in a 90-d rat dietary study with cyfluthrin (study 59), straddle gait appeared in 13 out of 40 animals on day 1, in 25 animals on day 3 and the incidence started to decrease from week 4 at a dose of 61/68 mg/kg bw/d (m/f).

Slight axonal degeneration of single nerve fibres in the sciatic nerve was observed in 8 out of 40 animals in a 90-d rat dietary study with cyfluthrin (study 59) at 61/68 mg/kg bw/d (m/f), which could potentially support a STOT RE classification. However, minimal single fibre degeneration in the sciatic nerve was observed in 6 out of 8 rats (vs. none in controls) 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 do not necessarily represent a repeat dose effect.

Taking into account the temporal pattern of the neurotoxic findings, classification for acute toxicity and STOT SE is considered more appropriate than a STOT RE classification. **RAC agrees with the DS that no classification is warranted for STOT RE.**

RAC evaluation of reproductive toxicity

Summary of the Dossier Submitter's proposal

The DS presented a two-generation study in rats with cyfluthrin, several pre-natal developmental toxicity (PNDT) studies with cyfluthrin (oral and inhalation studies in the rat, oral studies in the rabbit), a rat oral PNDT study with beta-cyfluthrin and a developmental neurotoxicity (DNT) study in rats with beta-cyfluthrin.

Fertility

The DS proposed no classification based on lack of effects on fertility in the two-generation study with cyfluthrin (study 70).

Development

The DS discussed increased incidence of microphthalmia and other developmental effects in the rat inhalation PNDT studies with cyfluthrin (study 77 and 78). They considered the findings as secondary to the hypoxic condition of the dams (hypoxia due to decreased respiratory rate resulting from sensory irritation) since oxygen supplementation reduced the incidences and no treatment-related malformations were observed in oral studies.

Increased post-implantation loss was observed in one of the rabbit studies with cyfluthrin (study 75) but the DS did not consider this finding sufficient for classification. Retarded ossification and reduced foetal weight were observed in the rat PNDT study with beta-cyfluthrin (study 76) in the presence of maternal toxicity. No other effects related to developmental toxicity were found in the available studies.

Overall, the DS proposed no classification for effects on development.

Lactation

The DS proposed classification with Lact.; H362 based on increased incidence of coarse tremors in pups (from postnatal day (PND) 5 to 18) and decreased pup weights during lactation in the two-generation study with cyfluthrin (study 70). The tremors in pups were observed not only at the top dose of 400 ppm associated with neurotoxicity in dams (splaying of the hind limbs) but also at the mid-dose of 125 ppm without maternal toxicity. Transfer of the substance from the dams to the pups via milk was confirmed by detection of beta-cyfluthrin in pup brains on PND 4 in the DNT study (study 80). The DS also pointed out that cyfluthrin residues were detected in human breast milk samples.

Comments received during public consultation

Comments on the reproductive toxicity classification of cyfluthrin and/or beta-cyfluthrin were received from five MSCAs and two industry commenters (one manufacturer and one downstream user).

The DS proposal for no classification for fertility was supported by two MSCAs.

As to the development, two MSCAs proposed classification in Category 2 mainly based on microphthalmia in the rat inhalation PNDT studies. They did not consider the proposed MoA sufficiently demonstrated as oxygen supplementation did not reduce the incidence of microphthalmia down to the control levels. One of the MSCAs suggested that the absence of microphthalmia in the oral PNDT studies could be a consequence of first pass effect.

One MSCA and the industry commenters supported the DS's proposal of no classification for development. The manufacturer summarised the available toxicokinetic data indicating that plasma concentrations of cyfluthrin or beta-cyfluthrin (parent substances) in the negative rat PNDT studies via gavage were much higher than those measured in the inhalation studies where eye malformations were observed. Industry also referred to a recent publication reviewing the regulatory and mechanistic inhalation studies with cyfluthrin and beta-cyfluthrin (Pauluhn, 2018).

Classification with Lact.; H362 was supported by four MSCAs. The manufacturer put forward arguments against classification. They argued that the tremors in the neonates are transient and characteristic of acute neurotoxicity associated with Type II pyrethroids, when threshold concentrations of the parent compound reach the brain. Neonatal rats are more sensitive than adults to acute toxicity of Type II pyrethroids most likely due to limited metabolic capacity (as indicated e.g. by a study with deltamethrin where the LD₅₀ values differed 7-fold between weanlings and adults but the brain concentrations at the LD₅₀ were approximately the same; Sheets, 1994). Industry mentioned an ongoing research on metabolism of pyrethroids. According to their interpretation of the available data, pyrethroids are metabolised primarily by P450 enzymes in rats and carboxylesterases in humans, with carboxylesterases developing rapidly after birth in humans. Based on this information the manufacturer proposed that human infants are not more sensitive than the mothers to the neurotoxicity of Type II pyrethroids. Further, industry presented a risk-based argument to support their case against classification: humans, including lactating females, would never be exposed to the high concentrations of cyfluthrin or beta-cyfluthrin required to overwhelm the metabolising capacity of the sensitive neonate rat. The DS replied that the argumentation via metabolic capacity of carboxylesterases is based on a lot of speculation, which cannot be used to exclude a hazard for human health.

Assessment and comparison with the classification criteria

Adverse effects on fertility and sexual function

A two-generation study in rats conducted according to OECD TG 416 (1983) is available for cyfluthrin (study 70; GLP; started in 1993; top dose 400 ppm). RAC notes that the study did not investigate some of the parameters added into the test guideline in 2001 (e.g. sperm parameters, puberty onset).

In addition, a follow-up two-generation study (study 71; top dose 50 ppm) was conducted to clarify whether 50 ppm in the previous study was a no-observed-adverse-effect level (NOAEL) for effects in the offspring. No treatment-related effects were observed in this study. It was concluded that the transient pup body weight reductions seen in the first study were not treatment-related, and hence the 50 ppm NOAEL was confirmed.

Information related to fertility and sexual function can also be obtained from a DNT study in rats with beta-cyfluthrin (study 80; OECD TG 426, GLP; top dose 200 ppm).

Two-generation study in rats with cyfluthrin (study 70)

Cyfluthrin was administered to Sprague-Dawley rats at dietary concentrations of 0, 50, 125 and 400 ppm, corresponding to 0, 3/4, 9/10 and 29/33 mg/kg bw/d (m/f), respectively, except for females during lactation when the test substance intake approximately doubled (to 0, 7, 19 and 59 mg/kg bw/d). Top dose females of both generations displayed clinical signs of neurotoxicity (splaying of the hind limbs; incidence 15/29 and 9/25 in F0 and F1 respectively) during lactation only, probably due to increased test substance intake during this period. Sucklings were found to be more sensitive than dams, with coarse tremors starting already from 125 ppm; the tremors in pups are discussed under lactation.

There were no effects on reproductive parameters (oestrus cycle staging; pre-coital interval; mating, fertility and gestation indices; gestation length; number of implantation sites; birth index). No treatment-related gross or histopathological lesions were observed in the reproductive organs.

Developmental neurotoxicity study in rats with beta-cyfluthrin (study 80)

Beta-cyfluthrin was administered to female Wistar rats via diet from gestation day (GD) 0 to lactation day (LD) 21. The top dose of 200 ppm (18 mg/kg bw/d during gestation and 41 mg/kg bw/d during lactation) caused body weight reduction in pups (none at birth, by ca. 10% on PND 11, no further decrease compared to controls). Maternal body weight gain and food consumption during gestation were not affected.

There was no effect on reproduction parameters and no effect on puberty onset in this study.

No effects on reproductive parameters or reproductive organs were observed in the available studies with cyfluthrin and beta-cyfluthrin. **No classification is warranted for adverse effects on fertility and sexual function.**

Adverse effects on development

Several types of studies are available to provide information on developmental toxicity of cyfluthrin and beta-cyfluthrin: rat PNDD studies via gavage, rabbit PNDD studies via gavage, rat PNDD studies via inhalation, a rat dietary DNT study and a rat dietary two-generation study. Developmental findings potentially relevant for classification were observed in one of the rabbit PNDD studies (increased post-implantation loss in study 75) and in the rat PNDD studies via inhalation (increased incidence of microphthalmia in studies 77 and 78).

Rat PNDD studies via gavage with cyfluthrin and beta-cyfluthrin (studies 72, 73 and 76)

In study 72 cyfluthrin was administered to BAY:FB rats in PEG 400 from GD 6 to 15. The top dose of 30 mg/kg bw/d induced clinical signs of neurotoxicity (high-stepping gait, ataxia) in several dams. No developmental toxicity was observed.

In study 76 beta-cyfluthrin was administered to Wistar rats in aqueous Cremophor from GD 6 to 15. Maternal toxicity at the top dose of 40 mg/kg bw/d included mortality (3 out of 26 animals), clinical signs (hypoactivity, locomotor incoordination, salivation; all or almost all animals, depending on the effect) and reduced body weight gain (net body weight gain reduced by 14 g). Developmental toxicity at the top dose was limited to reduced foetal weight (by 9%) and delayed ossification. The top dose is considered to exceed the maximum tolerated dose (MTD). The mid-dose of 10 mg/kg bw/d caused slight maternal toxicity (reduced body weight gain) and no developmental toxicity.

In study 73 cyfluthrin was administered to Wistar rats in aqueous Cremophor from GD 6 to 15. No developmental or maternal toxicity was observed up to the top dose of 10 mg/kg bw/d. Lack of maternal toxicity at the top dose is considered a significant limitation of this study.

In summary, no effects warranting classification were observed in the available rat PNDD studies via gavage.

Rabbit PNDD studies via gavage with cyfluthrin (studies 74 and 75)

In study 74, cyfluthrin was administered to Himalayan rabbits in aqueous Cremophor from GD 6 to 18. Two dams aborted on GD 25 and 28 and one dam completely resorbed her three implants at the top dose of 45 mg/kg bw/d. Reporting of the study in the brief study report available to RAC is rather limited and individual data for most parameters are not provided. It is thus not clear whether two abortions and one complete resorption in this study represent maternal or developmental toxicity. Post-implantation loss was 6%, 14%, 17% and 20% at 0, 5, 15 and 45

mg/kg bw/d respectively (the two abortions at the top dose excluded, the dam with total litter loss included). No treatment-related malformations were observed.

In study 75 cyfluthrin was administered to Chinchilla rabbits in corn oil from GD 6 to 18 at 0, 20, 60 and 180 mg/kg bw/d. Maternal food consumption during the treatment period was significantly reduced by 41% and 27% at the high and mid-dose respectively. Corrected weight gain was not affected as the dams were able to compensate for the initially impaired weight gain by the end of the study (dosing until GD 18, sacrifice on GD 28). Post-implantation loss was increased approx. 3-fold at the top dose, above the historical control range (only foetus-based historical control data (HCD) available: mean 8%, SD 5%, range 2-20%; current study 11%, 11%, 20%, 29% at 0, 20, 60, 180 mg/kg bw/d respectively; HCD comprise 13 studies within 3 years before the current study). There was no strong correlation between food consumption during the treatment period and post-implantation loss at the level of individual data (see 'Supplemental information in the Background document'). Still, this does not exclude some contribution of maternal toxicity to the observed effect on embryonic/foetal viability. No treatment-related increase in malformations or variations was observed in this study. Foetal weights were not decreased.

Rabbit PNDT study 75				
Dose (mg/kg bw/d)	0	20	60	180
Total no. of females	16	16	16	16
Pregnant	16	13	16	16
Total litter loss	0	0	0	1
Food consumption GD 6-19 (g/animal/day)	131	121	96*	77*
Post-implantation loss ^a (%; \pm SD)	10 (\pm 11)	14 (\pm 21)	19 (\pm 15)	31/26 ^b (\pm 29/23)
Embryonic resorptions ^a (%; \pm SD)	4 (\pm 7)	10 (\pm 21)	12 (\pm 15)	22/17 ^b (\pm 30/22)
Implantation sites (mean/dam)	12.1	9.8	11.4	12.4/12.2 ^b
Live foetuses (mean/dam)	10.8	8.8	9.2	8.9/8.3 ^b

^a The study report provides only foetus-based values; litter-based values (i.e. mean of % losses in the individual litters) have been calculated by RAC. As to statistical evaluation, post-implantation loss is not significant (at $p=0.05$) in Kruskal-Wallis and significant in parametric ANOVA, embryonic resorptions not significant in Kruskal-Wallis nor parametric ANOVA (top dose dam with total litter loss included)

^b Including/excluding the dam with total litter loss

* Stat. significant, $p \leq 0.05$; stat. analysis of food consumption conducted by RAC (ANOVA followed by Dunnett's test)

Two-generation study with cyfluthrin and DNT study with beta-cyfluthrin (studies 70 and 80)

No developmental toxicity was observed in these two dietary studies. Marked pup body weight reductions observed in the two-generation study (study 70) from PND 4 are discussed under lactation.

Rat PNDT studies via inhalation with cyfluthrin (studies 77 and 78)

Study 77 comprised two experiments that served as pilot studies to the main study, study 78.

In the first experiment of study 77, Wistar rats (Bor:WISW) were exposed to cyfluthrin in ethanol/PEG 400 head-nose only from GD 6 to 15 for 6 hours per day at concentrations of 0 (vehicle), 1.1, 4.7 and 23.7 mg/m³. Clinical signs (dyspnea, reduced motility, piloerection, ruffled/unkempt fur, irritation of the visible eye mucous membranes) were observed from 4.7 mg/m³. Body weight gain of the dams was reduced at all concentrations; part of the reduction is due to lower foetal weights (foetal weights were reduced by up to 29%). Post-implantation loss

was increased at the top concentration in the presence of maternal toxicity. Incidence of microphthalmia was increased at the top concentration; all cases were unilateral. According to HCD (studies within two years before the current study), microphthalmia occurred in controls of 5 out of 23 studies (incidences per group: 1, 1, 4, 1, 1).

Rat inhalation PNDT study 77, 1st experiment				
Concentration (mg/m³)	0 (vehicle)	1.1	4.7	23.7
Pregnant rats	25	29	29	28
Incidence of dyspnea	0	0	5	20
Incidence of piloerection	0	0	25	28
Bw gain ¹ during pregnancy (g)	76	67*	57**	46**
Number of implantations per dam	11.5	12.2	11.7	11.6
Number of live fetuses per dam	10.8	11.3	10.1	9.3
Post-implantation loss (absolute; mean ± SD)	0.7 (±1.0)	0.9 (±1.2)	1.6 (±3.1)	2.3* (±2.5)
Total number of fetuses	271	329	292	261
Foetal weight (g)	3.40	3.16*	2.89**	2.43**
No. of fetuses for skeletal examination (mean)	7.5	7.9	7.6	6.6
Skeletal variations (absolute; mean ± SD)	1.8 (±1.7)	2.6 (±1.6)	3.9* (±2.5)	5.3** (±2.7)
Microphthalmia, foetal (litter) incidence	1 (1)	2 (2)	2 (2)	8 (5)
All malformations, foetal (litter) incidence	1 (1)	2 (2)	4 (3)	9 (5)
All malformations (mean ± SD)	0.04 (±0.20)	0.07 (±0.26)	0.15 (±0.46)	0.29 (±0.71)

Statistically significant difference from control: *, p<0.05; **, p<0.01

¹ body weight not corrected for gravid uterine weight

The second experiment of study 77 used concentrations of 0 (vehicle), 0.09, 0.25, 0.59 and 4.16 mg/m³. The test atmosphere at the top concentration of 4.16 mg/m³ was enriched in oxygen (30% v/v instead of 21% v/v). The purpose of oxygen enrichment was to investigate whether the developmental effects at 4.7 mg/m³ in the first experiment could be related to foetal hypoxia. The clinical signs at 4.16 mg/m³ + O₂ were less pronounced than those at 4.7 mg/m³ in the first experiment, as was foetal toxicity (foetal weight reduction 5% instead of 15%, no increase in skeletal variations vs. a two-fold increase). No increase in microphthalmia was observed at 4.16 or 4.7 mg/m³ in either experiment.

Rat inhalation PNDT study 77, 2nd experiment					
Concentration (mg/m³)	0 (vehicle)	0.09	0.25	0.59	4.16+O₂
Pregnant rats	23	29	25	29	22
Incidence of dyspnea	0	0	0	0	0
Incidence of piloerection	0	0	0	0	11
Bw gain during pregnancy (g)	58	63	60	59	56

Number of implantations per dam	10.7	11.4	11.2	11.0	11.2
Number of live foetuses per dam	9.0	9.6	8.8	9.2	9.5
Post-implantation loss (absolute; mean \pm SD)	1.7 (± 2.0)	1.8 (± 2.4)	2.4 (± 2.4)	1.8 (± 1.6)	1.7 (± 2.2)
Total number of foetuses	206	278	221	268	209
Foetal weight (g)	3.48	3.51	3.53	3.47	3.29*
No. of foetuses for skeletal examination (mean)	6.3	6.7	6.2	6.4	6.6
Skeletal variations (absolute; mean \pm SD)	2.5 (± 2.2)	2.5 (± 1.9)	1.6 (± 1.4)	1.9 (± 1.8)	2.8 (± 1.3)
Microphthalmia, foetal (litter) incidence	1 (1)	1 (1)	2 (2)	1 (1)	1 (1)
All malformations, foetal (litter) incidence	1 (1)	3 (3)	5 (3)	1 (1)	1 (1)
All malformations (mean \pm SD)	0.04 (± 0.21)	0.10 (± 0.31)	0.20 (± 0.65)	0.03 (± 1.19)	0.05 (± 0.21)

Statistically significant difference from control: *, $p < 0.05$; **, $p < 0.01$

The main study (study 78), conducted seven years after the pilot studies, employed concentrations of 0 (air), 0 (vehicle), 0.46, 2.55, 11.9 mg/mg³ and 12.8 mg/m³ + O₂ (39% v/v). Since repeat dose and mechanistic inhalation studies performed prior to study 78 revealed strong effects on respiration and body temperature, measurements of lung function (in a plethysmograph, GD 6) and rectal temperature (GD 6 and 13) were also included in study 78. However, as these measurements could induce stress-related effects difficult to quantify, lung function and body temperature were only measured in satellite animals (5/group, exposure GD 6-13) not subject to foetal examination. These satellite animals were also used for determination of plasma levels of cyfluthrin (immediately after exposure on GD 13).

Clinical signs (e.g. ruffled fur, retarded breathing) were present mainly at the top concentrations (11.9 and 12.8 mg/m³). Respiratory volume at the top concentrations was reduced ca. 2.5-fold compared to controls. Body temperature was reduced by ca. 4°C after the first exposure at the top concentrations irrespective of oxygen supplementation; the difference on GD 13 was smaller, approx. 3°C and 2°C without and with oxygen supplementation, respectively. Foetal weight was significantly reduced from 2.55 mg/m³. At the top concentrations, foetal weight reduction, delayed ossification (phalanges, metacarpals, metatarsals, sternebrae, vertebrae, pelvis, skull) and increased incidence of microphthalmia were observed both without and with oxygen supplementation, but effects in the oxygen-supplemented group were weaker (foetal weight reduction 17% vs. 27%, lower incidence of reduced ossification, lower incidence of eye malformations). The incidence of microphthalmia was not clearly related to the occurrence of clinical signs at the level of individual data (which is not surprising given that clinical signs occurred in most animals at the top concentrations). Respiratory rate and rectal temperature were only measured in satellite animals. According to the HCD (1988-1992, *i.e.* within five years before the current study, the same strain), microphthalmia occurred in 9 out of 25 studies, maximum incidence per study was altogether three foetuses, distributed in two litters.

Rat inhalation PNDT study 78						
Concentration (mg/m³)	0 (a.)	0 (v.)	0.46	2.55	11.9	12.8+O₂
Dams with implantations	21	22	24	24	23	23
Dams with viable fetuses	21	22	23	23	23	23
Incidence of retarded breathing	0	0	0	0	17	10
Incidence of ruffled fur	0	0	0	1	19	21
Food intake, pregnancy (g/day)	20	20	19**	19**	18**	17**
Bw gain during pregnancy (g)	84	89	77*	75**	59**	62**
Corrected bw gain (g)	20	23	20	19*	14**	13**
Respiratory rate (breath/min), satellite animals	143	148	115	107	111	89
Respiratory minute volume (mL/min/kg), satellite animals	1520	1680	1200	1100	710	650
Rectal temperature after first exposure (°C), satellite animals	37.6	37.0	36.0*	34.4	32.9**	32.6**
Rectal temperature after exposure on GD 13 (°C), satellite animals	37.6	38.5**	38.0	37.2	34.7*	36.1
Number of implantations per dam	12.3	12.8	11.3	11.4	11.3	11.3
Number of live fetuses per dam	11.6	12.0	10.7	10.9	10.4*	10.4*
Post-implantation loss per dam (absolute)	0.8	0.8	0.7	0.5	0.9	0.8
Foetal weight (g)	3.41	3.50	3.48	3.13**	2.48**	2.83**
Distal phalanx (forelimb) unossified, 1 st right (%)	4.8	3.6	1.6	7.5	45.2**	10.3
Metacarpal incompletely ossified, 2 nd right (%)	0.8	0.0	0.8	3.0	41.1**	15.1**
Sternum unossified, 2 nd segment (%)	0.0	0.0	0.0	0.8	19.4**	7.9**
Microphthalmia; fetuses (litters)	1 (1)	2 (2)	1 (1)	3 (2)	13 (8)	7 (5)

Anophthalmia; fetuses (litters)	0	0	0	0	1 (1)	1 (1)
Eye malformations; fetuses (litters)	1 (1)	2 (2)	1 (1)	3 (2)	14 (9)	7 (5)
Fetuses per group	243	263	245	251	239	240
All malformations, foetal (litter) incidence	3 (2)	3 (3)	2 (2)	8 (4)	21 (10)	10 (7)

Statistically significant difference from control: *, $p < 0.05$; **, $p < 0.01$

An increase in microphthalmia was observed only at concentrations apparently causing strong sensory irritation to which the maternal animals responded with pronounced physiological changes. Pauluhn (2018) proposed a MoA for the developmental effects observed in the inhalation PNDT studies with cyfluthrin, which can be briefly summarised as follows: Stimulation of sensory neurons mediating pain reception in the airways triggers escape or homeostatic adaptation. Rats are able to adapt to environmental changes by reducing their energetic needs through a reversible state of suppressed metabolic demand and reduced body temperature ('hibernation-like state'). Under such conditions, the delivery of oxygen to the tissues is reduced and this reduction is counterbalanced by decreased tissue oxygen demand at lower temperatures. However, when this occurs in pregnant rats, the altered oxygen delivery to the (rapidly growing) foetus may have developmental consequences. A more detailed description of this MoA can be found in the publication by Pauluhn (2018).

The foetal hypoxia in the current study could have been at least partly compensated by the two-fold increase in partial pressure of oxygen in the oxygen-supplemented group. The reduced incidence of eye malformations in the oxygen-supplemented group (from 14 to 7 fetuses, from 9 to 5 litters) indicates that foetal hypoxia did play a role in their aetiology. On the other hand, the incidence of malformations did not drop to control levels. Nevertheless, it is noted that oxygen supplementation did not fully counteract the altered metabolic status of maternal animals; at least hypothermia was still present also in the oxygen-supplemented group.

RAC further notes that microphthalmia was always present in concurrent controls and that no increase in microphthalmia was observed in oral PNDT studies up to maternally toxic doses associated with plasma levels markedly (at least 10-fold) higher than in the inhalation studies (for details see 'Supplemental information in the Background document').

Taking into account all available information, RAC considers maternal adaptive mechanisms triggered by sensory irritation as a plausible MoA behind the increased incidence of microphthalmia in studies 77 and 78, although there are some remaining uncertainties (e.g. the fact that oxygen supplementation did not completely prevent an increase in microphthalmia).

Based on the available evidence, RAC considers plausible that the increased incidence of microphthalmia in the rat inhalation studies 77 and 78 resulted from maternal adaptive mechanisms ('hibernation-like state' involving bradypnoea and hypothermia) triggered by sensory irritation. As this strong physiological response observed in rats is not likely to be tolerated by humans exposed to (beta-)cyfluthrin, the increase in eye malformations is considered of low human relevance.

Increased post-implantation loss in one of the rabbit studies (study 75) could be considered borderline for classification in Category 2. However, taking into account the magnitude of the increase, and concomitant maternal toxicity, RAC concluded that this effect is not sufficient to trigger classification.

Overall, **RAC agrees with the DS's proposal of no classification for developmental toxicity.**

Adverse effects on or via lactation

Findings in the offspring attributable to effects on or via lactation were observed in two studies: in the two-generation study with cyfluthrin (study 70; tremors, reduced pup body weight by up to 25%) and in the DNT study with beta-cyfluthrin (study 80; reduced pup body weight by ca. 10%). The magnitude of pup weight reduction in the DNT study is not considered sufficient for classification. Therefore, the assessment will be focused on the two-generation study.

Two-generation study in rats with cyfluthrin (study 70)

Cyfluthrin was administered at dietary concentrations of 0, 50, 125 and 400 ppm. Coarse tremors were observed in mid-and high dose pups from PND 5 to 18. Pup body weight reduction on PND 7 reached 25% at the top dose; the effect at the mid-dose was weaker (11%). Findings at the top dose are considered less relevant for classification due to concurrent maternal neurotoxicity (splayed hind limbs). However, the incidence of coarse tremors at the mid-dose without maternal toxicity is still rather high especially in the F2 generation.

Two-generation study in rats (study 70): effects during lactation				
Dose (ppm)	0	50	125	400
Dose (mg/kg bw/d) during lactation	0	7	19	59
F0/F1				
Incidence of splayed hind limbs in dams	0/30	0/27	0/26	15/29*
Litter incidence of coarse tremors in pups; [day of onset - day of last occurrence]	0/30	0/27	4/25 [PND 7–15]	15/28* [PND 5–17]
Pup bw on PND 1, males + females (g)	6.6	6.6	6.4	6.6
Pup bw on PND 4 post-culling (g)	10.0	10.3	9.7	9.2* (-8%)
Pup bw on PND 7 (g)	16.2	16.4	15.0* (-7%)	13.7* (-15%)
Pup bw on PND 14 (g)	31.4	31.5	29.5* (-6%)	25.2* (-20%)
Pup bw on PND 21 (g)	49.0	50.1	46.1	39.4* (-20%)
F1/F2				
Incidence of splayed hind limbs in dams	0/25	0/27	0/27	9/25*
Litter incidence of coarse tremors in pups; [day of onset - day of last occurrence]	0/25	0/26	19/26* [PND 7–16]	9/25* [PND 7–13]
Pup bw on PND1 (g)	6.7	6.4*	6.4	6.3* (-6%)
Pup bw on PND 4 post-culling (g)	10.3	9.3*	9.5	8.2* (-20%)
Pup bw on PND 7 (g)	16.1	14.7*	14.4* (-11%)	12.0* (-25%)
Pup bw on PND 14 (g)	30.3	28.8	25.8* (-15%)	23.0* (-24%)
Pup bw on PND 21 (g)	45.4	42.8	39.0* (-14%)	33.6* (-26%)

* Statistically significant difference from control, $p \leq 0.05$

Although cyfluthrin levels in milk were not measured in this study, occurrence of neurotoxicity in pups as early as PND 5 (*i.e.* before pups start feeding on maternal diet) strongly indicates transfer

via milk. The DNT study with beta-cyfluthrin (study 80) reported a concentration-dependent increase in test substance concentration in foetal brains already on PND 4, which again indicates a transfer of the substance via milk. No neurotoxic symptoms were observed in the DNT study up to 200 ppm.

Transfer of the substance into milk was confirmed in lactating cows and goats. The parent substance was the major residue in cow and goat milk (EFSA, 2018). Cyfluthrin was also detected in human breast milk samples in several studies (e.g. Bouwman *et al.*, 2006; Feo *et al.*, 2012).

According to CLP, classification for effects on or via lactation can be assigned based on results of one- or two-generation studies in animals which provide clear evidence of adverse effect in the offspring due to transfer in the milk or adverse effect on the quality of the milk.

Coarse tremors in pups in the two-generation study with cyfluthrin, although transient, are considered an adverse effect. At 125 ppm the tremors occurred in the absence of maternal toxicity. The weight of evidence (high lipophilicity, tremors began before the pups started to feed on maternal diet, substance was detected in pup brains on PND 4 in the DNT study, transfer via milk documented for cows, goats and humans) is sufficient to establish that the tremors are a consequence of transfer in the milk.

Industry proposed no classification based on lack of human relevance, assuming that breastfed babies would not be more susceptible to neurotoxicity of (beta-)cyfluthrin than their mothers. While RAC agrees that lower metabolic capacity of neonatal rats compared to adult animals is a plausible explanation of their increased susceptibility, the available data do not indicate that the situation in humans should be different from that in rats at least for infants under three weeks of age (see 'Supplemental information in the Background document').

Industry further argued that humans (including lactating females) would never be exposed to the high concentrations of (beta-)cyfluthrin required to overwhelm the metabolising capacity of the sensitive neonate rat. Nevertheless, risk-based arguments cannot be taken into account in hazard assessment.

Thus, **RAC agrees with the DS's proposal to classify for Lact.; H362** mainly based on coarse tremors in pups of the two-generation study (study 70) attributable to transfer of the test substance via milk and occurring in the absence of maternal toxicity.

ENVIRONMENTAL HAZARD EVALUATION

RAC evaluation of aquatic hazards (acute and chronic)

Summary of the Dossier Submitter's proposal

Current entry in Annex VI, CLP Regulation: Aquatic Acute 1 (H400), Aquatic Chronic 1 (H410).

DS proposal: Aquatic Acute 1 (H400), M-factor=1 000 000, Aquatic Chronic 1 (H410), M-factor=100 000

Degradation

Abiotic degradation

Hydrolysis of beta-cyfluthrin was studied as a function of pH on mixtures of four different diastereomers of identical composition forming mixtures during the hydrolysis. The hydrolysis half-lives were calculated for temperatures 20 °C and 25 °C (by extrapolation).

Beta-cyfluthrin is found to be stable at pH 4 (> 1 year), as well as relatively stable at pH 7 (DT₅₀ 61 - 281 days). The hydrolysis rates increase at pH 9 (DT₅₀ < 2 days). These half-lives were recalculated without experiment showing same results.

Direct photodegradation half-lives were calculated based on a mean quantum yield of 0.001149 and the molar extinction coefficients. Half-lives between 4.97 days (summer 30-50° latitude) and 93.5 days (winter 60° latitude) were estimated, dependent on degree of latitude and seasonal conditions; half-lives ranged from 5.2 to 56 days. Weak potential for direct photolytic interactions of beta-cyfluthrin with sunlight in the environment is shown. Moderate photodegradation of beta-cyfluthrin in aqueous solution in a range of 19 to 21% was measured by HPLC after a maximum irradiation period of 500 minutes.

Biodegradation

No data is available for ready biodegradation.

The dissipation of beta-cyfluthrin was studied in two different water-sediment systems and later evaluated according to FOCUS 2006 where beta-cyfluthrin was shown not rapidly degradable with a DT₅₀ of 14.4 – 53 days (total system) and DT₅₀ of 14.3 – 81.5 days (sediment).

Beta-cyfluthrin is hydrolytically stable under acidic and neutral conditions. Aquatic photolysis is not considered an important transformation route for beta-cyfluthrin in the environment with DT₅₀ of 5 - 56 days.

The metabolism/degradation pathway of beta-cyfluthrin is expected via cleavage of the ester or diphenyl ether bond hydroxylation at the phenoxy ring and hydrolysis of the cyano group. Further degradation mainly resulted in generation of CO₂ and bound residues.

The DS gave no information on the hazards presented to the aquatic environment by the metabolites.

Metabolites of beta-cyfluthrin:

Environmental compartment	Metabolites
<i>Biodegradation</i>	
Water sediment	1. FPB-acid (4-fluoro-3-phenoxybenzoic acid, FCR 3191, CAS-no.: 77279-89-1) Water: 29 % of applied radioactivity 2. FPB-ald Sediment: 16 % of applied radioactivity

The DS concluded that based on the available information, beta-cyfluthrin does not fulfil the criteria to be considered as rapidly degradable in the aquatic environment. This is based on data for beta-cyfluthrin.

Bioaccumulation

Beta-cyfluthrin consists mainly of two diastereoisomers II and IV, with log K_{ow} values of 5.91 for diastereoisomer IV and 5.94 for diastereoisomer II. An approximate estimation of the bioconcentration factor BCF_{fish} has been performed for the diastereoisomers using the standard equation in the EU Technical Guidance Document (TGD) on Risk Assessment (2003), Part II, 3.8.3.2. The calculated BCF is ranging between 22336 L/kg_{wet} in fish, for diastereoisomer II, and 21062 L/kg_{wet} in fish, for diastereoisomer IV.

Results of a bioaccumulation study with Bluegill sunfish at an average exposure concentration of 0.12 µg eq/L are given for beta-cyfluthrin. The plateau level, determined as the average concentration in the fish of the last two time intervals of the uptake phase, was 0.155 µg/g. Due to a malfunction in the flow system, no reliable steady state in uptake phase was reached and the BCF_{ss} is not reliable. The lipid and growth-normalised kinetic BCF [L kg⁻¹] BCF_{KLg} is 1822 for beta-cyfluthrin related to total radioactive residues and this whole fish value is above the CLP criterion of 500.

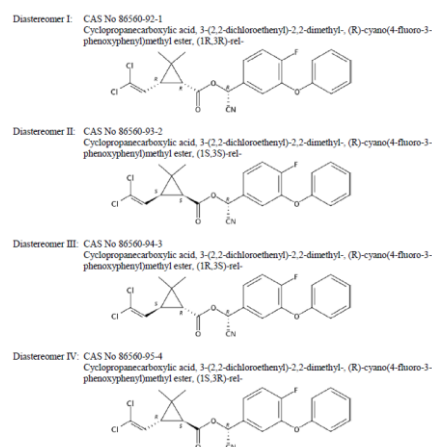
The DS considers beta-cyfluthrin as having a high potential for bioaccumulation based on reliable data for diastereomers and beta-cyfluthrin.

Justification of read-across of data from cyfluthrin to beta-cyfluthrin for aquatic toxicity

Beta-cyfluthrin and cyfluthrin are mixtures of eight isomers four of the isomers are considered active. The proportion of diastereoisomer pairs and their structures in beta-cyfluthrin and cyfluthrin are shown in figures below:

Diastereomer	Cyfluthrin	Beta-Cyfluthrin
I (1R,3R-R+1S,3S-S = 1:1; cis) CAS: 86560-92-1	23-27 %	< 2 %
II (1R,3R-S + 1S,3S-R = 1:1; cis) CAS: 86560-93-2	17-21 % (mean 19 %)	30-40 % (mean 35 %)
III (1R,3R-R + 1S,3R-S = 1:1; trans) CAS: 86560-93-2	32-36 %	< 3%
IV (1R,3S-S + 1S,3R-R = 1:1; trans) CAS: CAS: 86560-95-4	21-25 % (mean 22%)	57-67 % (mean 62 %)
Sum of active diastereoisomers	~ 41 %	~ 97 %
Relation of II/IV	0.86	0.56

Active diastereoisomers are written in bold.



Beta-cyfluthrin represent a major constituent of cyfluthrin. Beta-cyfluthrin and cyfluthrin share the same chemical structure, consisting of three asymmetric carbon atoms. These lead to four diastereomers, each consisting of an enantiomer pair. While cyfluthrin consists of all four diastereomers (referred to as diastereomer I, II (1R,3R, αS + 1S,3S, αR = 1:1; cis), III and IV (1R,3S, αS + 1S,3R αR =1:1; trans)), beta-cyfluthrin mainly consists of the two most active diastereomers II and IV (II: 30.0 – 40.0 %, IV: 57.0 – 67.0 % of the sum of the four diastereoisomers). Due to the common structure of the diastereomers it can be assumed that all diastereomers show a similar chemical and biological activity and share the same insecticidal mode of action. It was generally accepted for the biocidal (cyfluthrin, ECHA 2018) and plant protection evaluation (beta-cyfluthrin, EFSA 2002) that both substances share a similar toxicological profile.

There are indications from the scientific literature (Leicht, 1996) that diastereomers I and III could be regarded as around one order of magnitude less active than isomers II and IV. If only diastereomers II and IV would be biologically active, beta-cyfluthrin would be approximately 2.4 times more toxic as cyfluthrin (cyfluthrin consists of 40% diastereomers II + IV). However, it has been assumed that diastereomers I and III also show significant biological activity and a significant degree of isomerisation between the diastereomers in the environment or in organisms. Furthermore, it has been shown that isomer III can synergise the activity of isomer IV. Consequently, an activity ratio of 1.3 between cyfluthrin and beta-cyfluthrin has been postulated, instead of the expected value of 2.4 based on the 40% beta-cyfluthrin content of cyfluthrin (Leicht, 1996).

Generally, it can be expected that beta-cyfluthrin is at least equally toxic as cyfluthrin to aquatic organisms. Therefore, equivalent level of relevance of data for both substances can be concluded and effect studies with cyfluthrin are considered for aquatic toxicity in the hazard assessment of beta-cyfluthrin.

Aquatic toxicity

Summary of relevant information on aquatic toxicity of beta-cyfluthrin

Test details	Test species	Result µg/L	Reference
Fish			
beta-cyfluthrin OECD TG 203 flow-through, 96 h	<i>Oncorhynchus mykiss</i>	LC ₅₀ = 0.089 based on mean measured concentrations	Anonymous-F1,1988a (Rep. No. FF-207)
beta-cyfluthrin OECD TG 203 flow-through, 96 h	<i>Oncorhynchus mykiss</i>	LC ₅₀ = 0.068 based on mean measured concentrations	Anonymous-F2, 1994a (Rep. No 103231)
beta-cyfluthrin OECD TG 203 flow-through, 96 h	<i>Lepomis macrochirus</i>	LC ₅₀ = 0.28 based on mean measured concentrations	Anonymous-F3, 1994b (Rep. No 103232)
beta-cyfluthrin OECD TG 203 flow-through, 96 h	<i>Leuciscus idus melanotus</i>	LC ₅₀ = 0.33 based on mean measured concentrations	Anonymous-F4, 1988b (Rep. No. FO-1011)
cyfluthrin (purity 96%) Test laboratory's internal method, equivalent to EPA - FIFRA § 72-4 and OECD TG 210 flow-through, 58 d	<i>Oncorhynchus mykiss</i>	NOEC = 0.01 based on mean measured concentrations	Anonymous-F5, 1985 (Rep. No. 683)
¹⁴ C-cyfluthrin (purity 99%) US-EPA FIFRA § 72-4 guideline, 40 CFR, Section 158.145 flow-through, 307 d	<i>Pimephales promelas</i>	NOEC = 0.14 based on mean measured concentrations	Anonymous-F6, 1990 (Rep. No. 100097)
Invertebrates			
beta-cyfluthrin OECD TG 202 semi-static, 48h	<i>Daphnia magna</i>	LC ₅₀ = 0.105 based on mean measured concentrations	Kimmel, 2014a (Rep. No. D58707)
beta-cyfluthrin EPA-FIFRA §72-3 flow-through, 96 h	<i>Americamysis bahia</i>	LC ₅₀ = 0.0022 based on mean measured concentrations	Machado, 1994 (Rep. No. 106797)
cyfluthrin (purity 95.8%) OCSPP draft 850.1020 flow-through, 96 h	<i>Hyalella azteca</i>	LC₅₀ = 0.00055 based on mean measured concentrations	Bradley, 2013 (Rep. No. 13656.6168)
beta-cyfluthrin OECD TG 211 semi-static, 21 d	<i>Daphnia magna</i>	NOEC = 0.025 (offspring production, parental body length) based on mean measured concentrations	Kimmel, 2014b (Rep. No. D58718)
beta-cyfluthrin (purity 99.2%) OCSPP draft 850.1350 flow-through, 28 d	<i>Americamysis bahia</i>	NOEC = 0.00041 based on mean measured concentrations	Schwader, 2013 (Rep. No. 13798.6307)
Algae and other aquatic organisms			

beta-cyfluthrin (purity 98.0%) OECD TG 201 static, 96 h	<i>Scenedesmus subspicatus</i>	EC ₅₀ > 0.01 mg/L based on nominal test concentrations	Heimbach, 1987 (Rep. No HBF/AL 40)
beta-cyfluthrin OECD TG 219 static, spiked water, 28 d	<i>Chironomus riparius</i>	NOEC = 0.4 based on nominal concentrations	Kimmel, 2014c (Rep. No. D58720)

Acute Aquatic Toxicity

Acute toxicity of beta-cyfluthrin to fish was investigated in studies, which can be considered valid and equivalent to OECD TG 203. Three different fish species (Rainbow trout, Bluegill sunfish and Golden orfe) were exposed under flow-through conditions for 96 h. The LC₅₀ values ranged from 0.068 µg/L to 0.33 µg/L. The lowest no observed effect level out of the four acute fish toxicity tests was 0.068 µg/L. The results are based on mean measured concentrations.

Two acute invertebrate tests are given for beta-cyfluthrin with *Daphnia* and mysid shrimp based on mean measured concentrations and considered valid. The 48-h EC₅₀ for *Daphnia magna* exposed to beta-cyfluthrin was 0.105 µg/L. No effect on immobilisation was reported up to 0.05 µg/L. The *A. bahia* 96-h LC₅₀ was 0.0022 µg/L and NOEC of 0.0013 µg/L. The lowest value for invertebrates is based on cyfluthrin with *H. azteca*, the 96-h study, based on mortality, a **LC₅₀ = 0.00055 µg/L** was derived.

Chronic Aquatic Toxicity

The chronic toxicity information for beta-cyfluthrin is based on cyfluthrin data in two fish species: Rainbow trout and Fathead minnow. Toxicity was investigated according to a flow-through test procedure, which can be considered equivalent to EPA-FIFRA G. 72-4 and OECD TG 210. The NOEC values were determined to be 0.01 µg/L and 0.14 µg/L based on mean measured concentrations.

The presented valid *Daphnia* chronic study was conducted in accordance with OECD TG 211. The 21-day NOEC value without effects after exposure period was 0.025 µg/L based on mean measured concentrations for *Daphnia magna*. The chronic study with beta-cyfluthrin in *A. bahia* covers 28 days under flow-through conditions and has been performed with five test concentrations of nominally 0.25, 0.50, 0.99, 2.0 and 4.0 ng/L (corresponding to mean measured concentrations of 0.11, 0.23, 0.41, 0.83 and 1.5 ng/L) using seawater. The study is considered as valid and reliable. Based on female body length and reproduction (mean number of offspring), a **NOEC of 0.00041 µg/L** beta-cyfluthrin (mean measured) was derived.

Toxicity in Algae

The overall 28-d NOEC of beta-cyfluthrin for *C. riparius* in this water-sediment study was determined to be 0.4 µg/L. For green algae, no effects were seen, giving a NOEC ≥ 0.01 mg/L for biomass and the growth rate.

Comments received during public consultation

Three MSCAs supported the proposed environmental classification Aquatic acute 1 (H400), M = 1000000 and Aquatic Chronic 1 (H410), M = 100000 based on the available data for the most sensitive species (Invertebrates: *H. Azteca*; 96-h LC₅₀= 0.55 ng/L as a read-across from cyfluthrin; and *A. bahia* 28-d NOEC=0.41 ng/L beta-cyfluthrin, respectively).

However, one of the MSCAs stated that chronic classification could be based on acute *H. azteca* data with cyfluthrin as no chronic data is available for this species and the surrogate would result in a more stringent chronic classification (Aquatic Chronic 1, M = 1000000).

Two MSCAs pointed out the difference in the composition of beta-cyfluthrin and cyfluthrin as well as the importance to take into account the different biological activity and therefore the sensitivity of the biologically active isomers towards different species (algae, fish, and invertebrates). The DS responded that this had been taken into account in their assessment in the CLH report.

Assessment and comparison with the classification criteria

Taking into account the grounds for read-across of aquatic toxicity data from cyfluthrin to beta-cyfluthrin based on beta-cyfluthrin consisting of up to 97% of the sum of active diastereomers (II + IV) and sharing the same chemical structure with cyfluthrin, RAC agrees to the use of data read-across from cyfluthrin for aquatic toxicity endpoints.

RAC agrees with the DS submitter that based on data for beta-cyfluthrin, there is no evidence that beta-cyfluthrin degrades to a degree greater than 70% over 28 days. Therefore, RAC agrees with the DS to consider beta-cyfluthrin as not rapidly degradable.

RAC also agrees that the available information indicates that the experimentally determined BCF for beta-cyfluthrin exceeds the trigger value of 500, which is supported by the available Log K_{ow} values for the diastereomers. Consequently, RAC agrees with the DS that beta-cyfluthrin is bioaccumulative in the aquatic environment.

There is reliable experimental data on acute toxicity on fish, invertebrates, and algae available with the lowest value being for beta-cyfluthrin with *A. bahia* 96-h LC_{50} = 0.0022 µg/L and a 96-h LC_{50} for *H. azteca* of 0.00055 µg/L as read-across from cyfluthrin. RAC notes that the reliability given to the algae study with *S. subspicatus* is questionable as no analytical monitoring was reported, while the substance has a high adsorption potential. However, RAC accepts the study is suitable for CLP and that its inclusion does not affect the classification outcome.

RAC agrees with the DS that based on the content of the biologically active isomers, beta-cyfluthrin is possibly up to 2.4 or 1.3 times more toxic than cyfluthrin and notes that the possible effects on the most sensitive species *H. azteca* need to be considered with regards to aquatic hazard classification.

There is no chronic data available for beta-cyfluthrin in fish. There are reliable experimental data on chronic toxicity for fish based on cyfluthrin and, following the acceptance of the read-across, these data are used to complete the data set. Reliable beta-cyfluthrin data is available for invertebrates and algae.

The lowest value is a 28-d NOEC for *A. bahia* 0.00041 µg/L based on a study with beta-cyfluthrin resulting in classification of beta-cyfluthrin as Aquatic Chronic 1, H410 with M-factor 100 000. However, classification based on beta-cyfluthrin chronic data as proposed by the DS may underestimate the chronic effects of beta-cyfluthrin on the most sensitive species (*H. Azteca*) as well as its possible toxic potency. Even though the available chronic data does not indicate which species is in fact more sensitive for beta-cyfluthrin (*A. bahia* or *H. azteca*), using the surrogate approach based on the acute data, read-across from cyfluthrin would result in a more stringent chronic classification. All data RAC considers for comparison with the CLP criteria are summarised in the table below.

Table: Summary of data for classification of beta-cyfluthrin

Results	Test substance	Remarks
Fish		
96-h LC ₅₀ = 0.000068 mg/L <i>Onchorhynchus mykiss</i>	beta-cyfluthrin	
58-d NOEC = 0.000010 mg/L <i>Oncorhynchus mykiss</i>	cyfluthrin	growth, read-across from cyfluthrin
Invertebrates		
96-h LC ₅₀ = 0.00000055 mg/L <i>Hyalella azteca</i>	cyfluthrin	read-across from cyfluthrin
28-d NOEC = 0.00000041 mg/L <i>Americamysis bahia</i>	beta-cyfluthrin	reproduction, parental body length
Algae/Aquatic plants		
ErC ₅₀ = > 10 µg/L NOEC = 10 µg/L <i>Scenedesmus subspicatus</i>	beta-cyfluthrin	

In conclusion, RAC agrees with the DS that considering the available acute data for beta-cyfluthrin (which would result in an aquatic acute classification of Aquatic Acute 1, M=100000), the classification should be based on read-across from cyfluthrin. Based on this data, beta-cyfluthrin warrants classification as **Aquatic Acute 1 (H400), M=1000000** (96-h LC₅₀ for *H. azteca* of 0.00055 µg/L as read-across from cyfluthrin).

For chronic aquatic hazards, RAC disagrees with the DS's proposal and proposes to classify beta-cyfluthrin as **Aquatic Chronic 1 (H410), M=1000000** based on the surrogate approach using acute data (96-h LC₅₀ for *H. azteca* of 0.00055 µg/L) read-across from cyfluthrin.

RAC notes that if data becomes available for beta-cyfluthrin with *H. Azteca*, the classification of beta-cyfluthrin could be reconsidered.

Additional references

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ANNEXES:

- Annex 1 The Background Document (BD) gives the detailed scientific grounds for the opinion. The BD is based on the CLH report prepared by the Dossier Submitter; the evaluation performed by RAC is contained in 'RAC boxes'.
- Annex 2 Comments received on the CLH report, response to comments provided by the Dossier Submitter and RAC (excluding confidential information).