Committee for Risk Assessment

RAC

Annex 1

Background document

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

cyfluthrin (ISO); α-cyano-4-fluoro-3-phenoxybenzyl-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylate

EC Number: 269-855-7
CAS Number: 68359-37-5

CLH-O-0000006802-74-01/F

The background document is a compilation of information considered relevant by the dossier submitter or by RAC for the proposed classification. It includes the proposal of the dossier submitter and the conclusion of RAC. It is based on the official CLH report submitted to public consultation. RAC has not changed the text of this CLH report but inserted text which is specifically marked as 'RAC evaluation'. Only the RAC text reflects the view of RAC.

Adopted

4 May 2020

CLH report

Proposal for Harmonised Classification and Labelling

**Based on Regulation (EC) No 1272/2008 (CLP Regulation),
Annex VI, Part 2**

Substance Name:

α-cyano-4-fluoro-3-phenoxybenzyl-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylate;

Cyfluthrin

EC Number: **269-855-7**

CAS Number: **68359-37-5**

Index Number: **607-253-00-1**

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Version number: **3.0**

Date: **November 2018**

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Part A.

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Part A.

1 PROPOSAL FOR HARMONISED CLASSIFICATION AND LABELLING

1.1 Substance

Table 1: Substance identity

Substance name:	***Cyfluthrin;*** ***α-cyano-4-fluoro-3-phenoxybenzyl-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylate***
EC number:	***269-855-7***
CAS number:	***68359-37-5 (unstated stereochemistry)***
Annex VI Index number:	***607-253-00-1***
Degree of purity:	***≥ 95.5 % (w/w)***
Impurities:	***No relevant impurities were identified.***

1.2 Harmonised classification and labelling proposal

Table 2: The current Annex VI entry and the proposed harmonised classification

	CLP Regulation
Current entry in Annex VI, CLP Regulation	Acute Tox. 2 *, H300 Acute Tox. 3 *, H331 Aquatic Acute 1, H400 Aquatic Chronic 1, H410 M = 1 000
Current proposal for consideration by RAC	**Add**: STOT SE 3, H335 Lact. H362 Aquatic Acute 1, H400 M = 1 000 000 **Modify**: Acute Tox. 2, H300 Acute Tox. 2, H330 Aquatic Chronic 1, H410 M = 100 000
Resulting harmonised classification (future entry in Annex VI, CLP Regulation)	Acute Tox. 2, H300 oral: ATE = 14.3 mg/kg Acute Tox. 2, H330 inhalation: ATE = 0.081 mg/L (dusts or mists) Lact. H362 STOT SE 3, H335 Aquatic Acute 1, H400 M = 1 000 000 Aquatic Chronic 1, H410 M = 100 000

1.3 Proposed harmonised classification and labelling based on CLP Regulation

Table 3: Proposed classification according to the CLP Regulation

CLP Annex I ref	Hazard class	Proposed classification	Proposed SCLs and/or M-factors	Current classification [1)]	Reason for no classification [2)]
2.1.	Explosives	None	-	None	Conclusive but not sufficient for classification
2.2.	Flammable gases	-			Conclusive but not sufficient for classification
2.3.	Flammable aerosols	-			Conclusive but not sufficient for classification
2.4.	Oxidising gases	-			Conclusive but not sufficient for classification
2.5.	Gases under pressure	-			Conclusive but not sufficient for classification
2.6.	Flammable liquids	None	-	None	Conclusive but not sufficient for classification
2.7.	Flammable solids	None	-	None	Conclusive but not sufficient for classification
2.8.	Self-reactive substances and mixtures	None	-	None	Conclusive but not sufficient for classification
2.9.	Pyrophoric liquids	None	-	None	Conclusive but not sufficient for classification
2.10.	Pyrophoric solids	None	-	None	Conclusive but not sufficient for classification
2.11.	Self-heating substances and mixtures	None	-	None	Conclusive but not sufficient for classification
2.12.	Substances and mixtures which in contact with water emit flammable gases	None	-	None	Conclusive but not sufficient for classification
2.13.	Oxidising liquids	None	-	None	Conclusive but not sufficient for classification
2.14.	Oxidising solids	None	-	None	Conclusive but not sufficient for classification
2.15.	Organic peroxides	None	-	None	Conclusive but not sufficient for classification
2.16.	Substance and mixtures corrosive to metals	None	-	None	Conclusive but not sufficient for classification

3.1.	Acute toxicity - oral	Acute Tox. 2, H300		Acute Tox. 2*, H300	
	Acute toxicity - dermal	None		None	Conclusive but not sufficient for classification.
	Acute toxicity - inhalation	Acute Tox. 2, H330		Acute Tox. 3*, H331	
3.2.	Skin corrosion / irritation	None		None	Conclusive but not sufficient for classification.
3.3.	Serious eye damage / eye irritation	None		None	Conclusive but not sufficient for classification.
3.4.	Respiratory sensitisation				Data lacking
3.4.	Skin sensitisation	None		None	Conclusive but not sufficient for classification.
3.5.	Germ cell mutagenicity	None		None	Conclusive but not sufficient for classification.
3.6.	Carcinogenicity	None		None	Conclusive but not sufficient for classification.
3.7.	Reproductive toxicity	Lact. H362		None	
3.8.	Specific target organ toxicity –single exposure	STOT-SE 3, H335		None	
3.9.	Specific target organ toxicity – repeated exposure	None		None	Conclusive but not sufficient for classification.
3.10.	Aspiration hazard				Data lacking
4.1.	Hazardous to the aquatic environment	Aquatic Acute 1, H400 Aquatic Chronic 1, H410	M = 1 000 000 M = 100 000	Aquatic Acute 1, H400 Aquatic Chronic 1, H410 M = 1 000	
5.1.	Hazardous to the ozone layer	Not applicable			

[1)] Including specific concentration limits (SCLs) and M-factors
[2)] Data lacking, inconclusive, or conclusive but not sufficient for classification

Table 4: Proposed labelling based according to the CLP Regulation

	Labelling	Wording
Pictograms		GHS06 GHS09
Signal Word	Danger	Dgr
Hazard statements	H300 H330 H362 H335 H410	Fatal if swallowed Fatal if inhaled May cause harm to breast-fed children May cause respiratory irritation Very toxic to aquatic life with long lasting effects
Suppl. Hazard statements		

Proposed notes assigned to an entry: -

2 BACKGROUND TO THE CLH PROPOSAL

No active REACH registrations available on 9 May 2017

2.1 History of the previous classification and labelling

The harmonised environmental classification of cyfluthrin as R50/51 was initially established based on classification criteria in accordance with directive 67/548/EEC. In the CLP-Regulation (EC) No 1272/2008 cyfluthrin was introduced as Aquatic Acute 1, H400 and Aquatic Chronic 1, H410 and with Regulation (EC) No 790/2009 (1. ATP) an M factor = 1 000 was established.
Regarding health hazards, cyfluthrin (CAS-No. 68359-37-5) has a legal classification (regulation (EC) No 1272/2008) for the toxicological endpoints acute oral and acute inhalative toxicity (Acute Tox. 2*, H300 Fatal if swallowed; Acute Tox. 3*, H331 Toxic if inhaled).

2.2 Short summary of the scientific justification for the CLH proposal

During the evaluation process/approval procedure of the biocidal active substance cyfluthrin in the frame of the Biocides Directive 98/8/EC and the renewal procedure for beta-cyfluthrin under Regulation (EC) No 1107/2009, it was noted that this current legal classification should be amended to include a classification for:

- reproductive toxicity (Lact. H362), based on the evidence of coarse tremors in the offspring due to cyfluthrin exposure via breast milk during lactation and
- specific target organ toxicity after single exposure (STOT-SE 3, H335), based on signs of respiratory irritation observed in humans in a volunteer study, in humans during handling of

the active substance and in appropriate animal teratogenicity studies with inhalative exposure of cyfluthrin.

The increased frequency of microphthalmia observed in developmental toxicity studies with inhalation exposure was regarded to be not relevant by the dossier submitter. However, during the renewal procedure for beta-cyfluthrin under Regulation (EC) No 1107/2009 it was noted that these findings may trigger classification as Repro2 H361d .

The increased frequency of microphthalmia was discussed during the Pesticides Peer Review Meeting 172. A proposal for classification as developmental toxicant cat 2 (H361 d "Suspected of damaging the unborn child" was agreed by majority of experts. However, the dossier submitter maintains the proposed classifications as presented in Table 2.

The existing classification for the acute oral endpoint and the non-classification regarding the remaining toxicological endpoints was considered appropriate (see Table 3). Therefore, the toxicological data relevant for the inhalation route and the toxicological data relevant for the evaluation of the newly proposed hazards are reported in this CLH dossier.

Since the last update of the classification as hazardous to the aquatic environment with Regulation (EC) No 790/2009 new classification criteria for the assessment of long-term aquatic hazards have been introduced (Regulation (EC) No 286/2011) and new data on aquatic ecotoxicity is available. Hence, an update of the current classification (mainly the M factors) is necessary. Acute toxicity for crustacea (EC_{50} = 0.55 ng/L for *H. azteca*) and the prolonged toxicity for crustaceae (NOEC = 0.41 ng β-Cyfluthrin/L for *A. bahia*) justify the classification as Aquatic Acute 1, H400 with an acute M factor = 1 000 000 and Aquatic Chronic 1, H410 with an chronic M factor = 100 000.

2.3 Current harmonised classification and labelling

cyfluthrin (CAS-No. 68359-37-5, Index No. 607-253-00-1)

Acute Tox. 2 *	H300
Acute Tox. 3 *	H331
Aquatic Acute 1	H400
Aquatic Chronic 1	H410
M = 1 000	

2.4 Current self-classification and labelling

Table 5: C&L notifications for cyfluthrin and beta-cyfluthrin (November 2018, www.echa.eu)

Classification		Labelling			
Hazard Class and Category Code(s)	**Hazard Statement Code(s)**	**Hazard Statement Code(s)**	**Supplementary Hazard Statement Code(s)**	**Pictograms, Signal Word Code(s)**	**Specific Concentration limits, M-Factors**
Acute Tox. 2	H300	H300		GHS09	M=1000
Acute Tox. 3	H331	H331		GHS06	
Aquatic Acute 1	H400			Dgr	
Aquatic Chronic 1	H410	H410			
Acute Tox. 2	H300	H300		GHS09	
Acute Tox. 2	H330	H330		GHS06	
Aquatic Acute 1	H400	H400		Dgr	

Aquatic Chronic 1	H410	H410		
Acute Tox. 2	H300	H300+H330	GHS09	M(Chronic)=1000
Acute Tox. 2	H330		GHS06	M=1000
Aquatic Acute 1	H400		Dgr	
Aquatic Chronic 1	H410	H410		
Acute Tox. 2	H300	H300	GHS09	
Acute Tox. 3	H331	H331	GHS06	
Aquatic Acute 1	H400		Dgr	
Aquatic Chronic 1	H410	H410		
Acute Tox. 2	H300	H300 (H300)	GHS09	
Acute Tox. 2	H330	H331 (H331)	GHS06	
Aquatic Acute 1	H400		Dgr	
Aquatic Chronic 1	H410	H410 (H410)		
Acute Tox. 2	H300	H300	GHS09	
Acute Tox. 3	H331	H331	GHS06	
Aquatic Acute 1	H400	H400	Dgr	
Aquatic Chronic 1	H410	H410		
Acute Tox. 2	H300	H300	GHS09	
Acute Tox. 2	H330	H330	GHS06	
Aquatic Acute 1	H400		Dgr	
Aquatic Chronic 1	H410	H410		

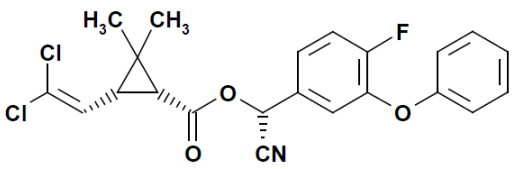
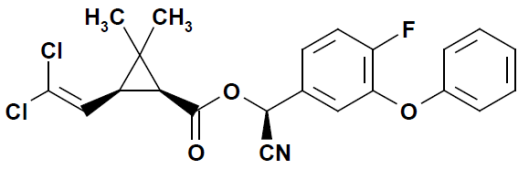
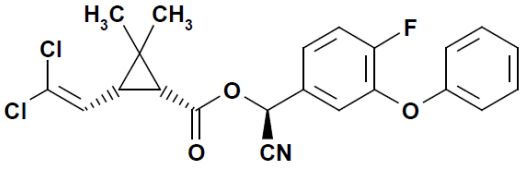
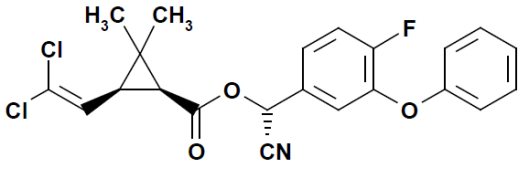
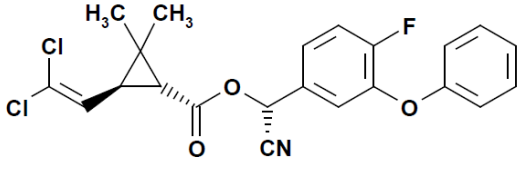
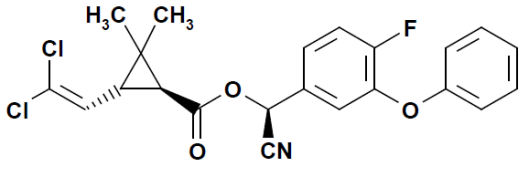
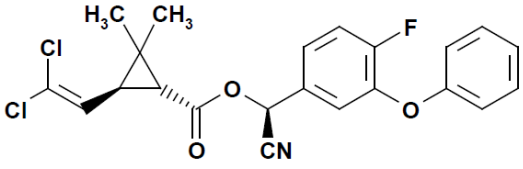
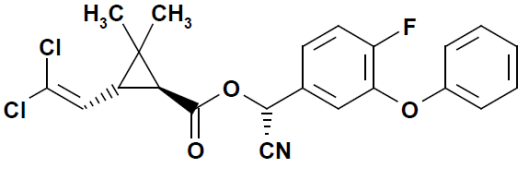
RAC general comment

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 between the two substances (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.

3 JUSTIFICATION THAT ACTION IS NEEDED AT COMMUNITY LEVEL

Cyfluthrin is an active substance in the meaning of Regulation (EU) No. 528/2012 and therefore subject to harmonised classification and labelling (Regulation EC 1272/2008).

Part B.

SCIENTIFIC EVALUATION OF THE DATA

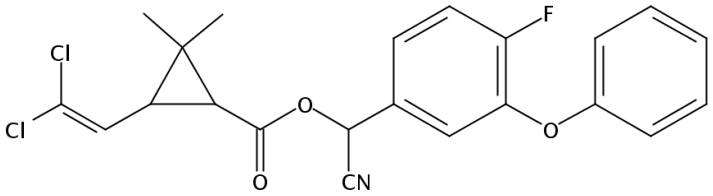
1 IDENTITY OF THE SUBSTANCE

1.1 Name and other identifiers of the substance

Table 6: Substance identity

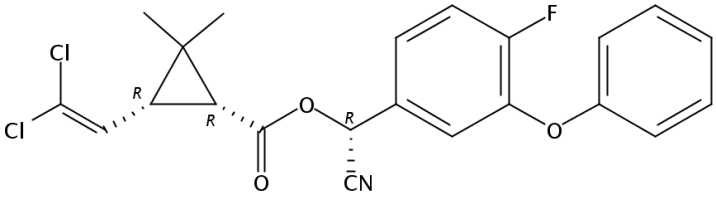
EC number:	269-855-7
EC name:	α-cyano-4-fluoro-3-phenoxybenzyl 3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylate
CAS number (EC inventory):	68359-37-5
CAS number:	68359-37-5
CAS name:	Cyclopropanecarboxylic acid, 3-(2,2-dichloroethenyl)-2,2-dimethyl-, cyano(4-fluoro-3-phenoxyphenyl) methyl ester
IUPAC name:	(RS)-α-Cyano-4-fluoro-3-phenoxybenzyl (1RS,3RS;1RS,3SR)-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylate
CLP Annex VI Index number:	607-253-00-1
Molecular formula:	$C_{22}H_{18}Cl_2FNO_3$
Molecular weight range:	434.3 g/mol

Structural formula:

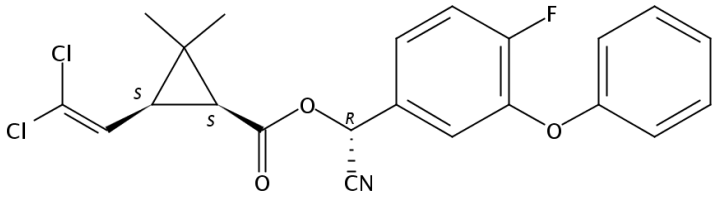


Cyfluthrin is a mixture of stereoisomers and consists mainly of four diastereomers:

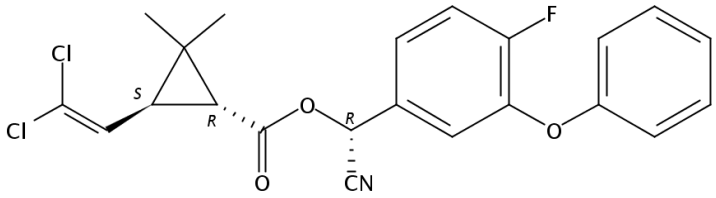
Diastereomer I: CAS No 86560-92-1
Cyclopropanecarboxylic acid, 3-(2,2-dichloroethenyl)-2,2-dimethyl-, (R)-cyano(4-fluoro-3-phenoxyphenyl)methyl ester, (1R,3R)-rel-



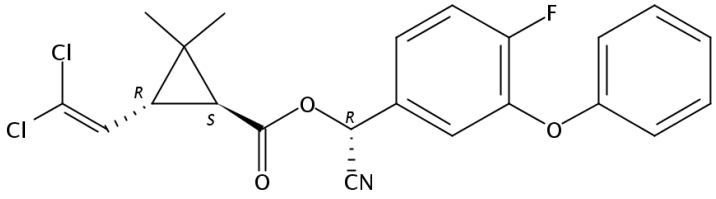
Diastereomer II: CAS No 86560-93-2
Cyclopropanecarboxylic acid, 3-(2,2-dichloroethenyl)-2,2-dimethyl-, (R)-cyano(4-fluoro-3-phenoxyphenyl)methyl ester, (1S,3S)-rel-



Diastereomer III: CAS No 86560-94-3
Cyclopropanecarboxylic acid, 3-(2,2-dichloroethenyl)-2,2-dimethyl-, (R)-cyano(4-fluoro-3-phenoxyphenyl)methyl ester, (1R,3S)-rel-



Diastereomer IV: CAS No 86560-95-4
Cyclopropanecarboxylic acid, 3-(2,2-dichloroethenyl)-2,2-dimethyl-, (R)-cyano(4-fluoro-3-phenoxyphenyl)methyl ester, (1S,3R)-rel-



1.2 Composition of the substance

Table 7: Constituents (non-confidential information)

Constituent	Typical concentration	Concentration range	Remarks
Diastereomer I: CAS No 86560-92-1		23- 27 % (w/w)	*For further information: please refer to the IUCLID file.*
Diastereomer II: CAS No 86560-93-2		17- 21 % (w/w)	*For further information: please refer to the IUCLID file.*
Diastereomer III: CAS No 86560-94-3		32-36 % (w/w)	*For further information: please refer to the IUCLID file.*
Diastereomer IV: CAS No 86560-95-4		21-25 % (w/w)	*For further information: please refer to the IUCLID file.*

Table 8: Impurities (non-confidential information)

Impurity	Typical concentration	Concentration range	Remarks

For further information: please refer to the IUCLID file.

1.3 Physico-chemical properties

Table 9:Summary of physico - chemical properties

Property	**Value**	**Reference**	**Comment (e.g. measured or estimated)**
State of the substance at 20 °C and 101,3 kPa	brown viscous mass with crystalline parts (> 92 %)	CA report for a.s. Cyfluthrin	visual assessment
Melting/freezing point	Diastereomer I: 64.40 °C Diastereomer II: 80.71 °C Diastereomer III: 64.04 °C Diastereomer IV: 106.19 °C	CA report for a.s. Cyfluthrin	experimental result (method: 92/69/EEC, A.1 (DSC))
Boiling point	not applicable (decomposition above 250 °C)	CA report for a.s. Cyfluthrin	experimental result (method: 92/69/EEC, A.2 (DTA))
Relative density	1.26	CA report for a.s. Cyfluthrin	experimental result (method: 92/69/EEC, A.3 (pycnometer))
Vapour pressure	Isomer I: 9.6×10^{-7} Pa at 20 °C 2.1×10^{-6} Pa at 25 °C Isomer II: 1.4×10^{-8} Pa at 20 °C 3.4×10^{-7} Pa at 25 °C Isomer III: 2.1×10^{-8} Pa at 20° 4.7×10^{-7} Pa at 25 °C Isomer IV: 8.5×10^{-8} Pa at 20 °C 2.0×10^{-7} Pa at 25 °C	CA report for a.s. Cyfluthrin	experimental result (method: 92/69/EEC, A.4 (vapour pressure balance))
Surface tension	-	-	not applicable (solubility less than 1 mg/L)
Water solubility	pH 7: Isomer I = 2.2 µg/L Isomer II = 1.9 µg/L Isomer III = 2.2 µg/L Isomer IV = 2.9 µg/L pH 3: Isomer I = 2.5 µg/L Isomer II = 2.1 µg/L Isomer III = 3.2 µg/L Isomer IV = 4.3 µg/L	CA report for a.s. Cyfluthrin	experimental result (method: 92/69/EEC, A.6 (column elution method))
Partition coefficient n-octanol/water	Log Pow (Isomer I) = 6.0 Log Pow (Isomer II) = 5.9 Log Pow (Isomer III) = 6.0 Log Pow (Isomer IV) = 5.9 (Log Pow at 20ºC; pH not declared)	CA report for a.s. Cyfluthrin	experimental result (method: 92/69/EEC, A.8 (shake flask method))
Flash point	131 °C, c.c. (94,3 % w/w, Mixture of 4 diastereoisomers)	Smeykal, H (2005) Report No.: 20051029.02	EEC Method A.9 (DIN EN ISO 2719)

Flammability	not a highly flammable solid The substance has no pyrophoric properties and does not liberate flammable gases on contact with water.	Smeykal, H (2005) Report No.: 20051029.03 expert judgement	EEC Method A.10
Explosive properties	non explosive	Smeykal, H (2005) Report No.: 20051029.04	EEC Method A.14
Self-ignition temperature	375 °C (94,3 % w/w, Mixture of 4 diastereoisomers)	Smeykal, H (2005) Report No.: 20051029.05	EEC Method A.15 (IEC 79-4, DIN 51794)
Oxidising properties	no oxidising properties (94,3 % w/w, Mixture of 4 diastereoisomers)	Heins, U (2005) Report No.: 05/00009	EEC Method A.21
Granulometry	-	-	no data available
Solubility in organic solvents	at 20 °C: Toluene: ▫ > 200 g/L (Isomers I, II, III); ▫ 100-200 g/L (Isomer IV) n-Hexane: ▫ 10 - 20 g/L (Isomers I, II, III); ▫ 1-2 g/L (Isomer IV) 2-Propanol: ▫ 20 - 50 g/L (Isomer I) ▫ 5 -10 g/L (Isomer II) ▫ 10 -20 g/L (Isomer III) ▫ 2 - 5 g/L (Isomer IV) Dichloromethane: ▫ > 200 g/L (Isomers I, II, III, IV)	CA report for a.s. Cyfluthrin	experimental result (method: in-house method)
Dissociation constant	-	-	Not applicable. The substance does not have acid or alkaline properties.
Viscosity	-	-	Not determined (oily viscous mass with crystalline particles).

Data waiving

Information requirement: Flammable gases (including chemically unstable gases)
Reason: study technically not feasible
Justification: The study does not need to be conducted because the substance is not a gas.

Information requirement: Aerosols
Reason: study technically not feasible
Justification: The study does not need to be conducted because the substance is no aerosol.

Information requirement: Oxidising gases
Reason: study technically not feasible
Justification: The study does not need to be conducted because the substance is not a gas.

Information requirement: Gases under pressure
Reason: study technically not feasible
Justification: The study does not need to be conducted because the substance is not a gas.

Information requirement: Self-reactive substances and mixtures
Reason: study scientifically not necessary
Justification: The study does not need to be conducted because 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.

Information requirement: Pyrophoric liquids
Reason: study scientifically not necessary
Justification: The study does not need to be conducted because the substance is known to be stable in contact with air at room temperature for prolonged periods of time (days) and hence, the classification procedure does not need to be applied.

Information requirement: Pyrophoric solids
Reason: study scientifically not necessary
Justification: The study does not need to be conducted because the substance is known to be stable in contact with air at room temperature for prolonged periods of time (days) and hence, the classification procedure does not need to be applied.

Information requirement: Self-heating substances and mixtures
Reason: study technically not feasible / study scientifically not necessary
Justification: The study does not need to be conducted because the substance is a liquid.
The study does not need to be conducted because the substance is a solid having a melting point <= 160 °C.

Information requirement: Substances and mixtures which in contact with water emit flammable gases
Reason: study scientifically not necessary
Justification: The classification procedure needs not to be applied because the organic substance does not contain metals or metalloids.

Information requirement: Oxidising liquids
Reason: study scientifically not necessary
Justification: The study does not need to be conducted because the organic substance contains oxygen atoms which are chemically bonded only to carbon or hydrogen and hence, the classification procedure does not need to be applied.

Information requirement: Oxidising solids
Reason: study technically not necessary
Justification: The study does not need to be conducted because the organic substance contains oxygen atoms which are chemically bonded only to carbon or hydrogen and hence, the classification procedure does not need to be applied.

Information requirement: Organic peroxides
Reason: study scientifically not necessary

Justification: The study does not need to be conducted because the substance does not fall under the definition of organic peroxides according to GHS and the relevant UN Manual of tests and criteria.

2 MANUFACTURE AND USES

2.1 Manufacture

2.2 Identified uses

Cyfluthrin is a biocidal active substance for Product Type 18 (Insecticide).

3 CLASSIFICATION FOR PHYSICO-CHEMICAL PROPERTIES

Table 10: Summary table for relevant physico-chemical studies

Method	Results	Remarks	Reference
refer to Table 9			

3.1 *Physico-chemical properties*

3.1.1 Summary and discussion

A flash point of 131 °C was determined according to the standard DIN EN ISO 2719 (67/548/EEC, Annex V, A.9).

Experience in handling and use indicates Cyfluthrin technical grade is not pyrophoric and does not react with water to liberate flammable gases.

Further, it was also tested in a standard auto-ignition temperature study (EEC Method A.15) and spontaneous ignition was found at 375 °C.

Cyfluthrin has no oxidizing properties in the sense of EEC Method A.21 and no explosive properties in sense of EEC Method A.14.

3.1.2 Comparison with criteria

Cyfluthrin technical grade does not have to be classified as flammable, oxidizing or explosive.

3.1.3 Conclusions on classification and labelling

No classification and labelling with regard to the physical hazards are proposed.

RAC evaluation of physical hazards

Summary of the Dossier Submitter's proposal

A flash point of 131°C was determined according to the standard DIN EN ISO 2719 (Council Directive 67/548/EEC, Annex V, A.9).

Experience in handling and use indicates cyfluthrin is not pyrophoric and does not react with water to liberate flammable gases.

Furthermore, it was also tested in a standard auto-ignition temperature study (EEC Method A.15) and spontaneous ignition was found at 375°C.

Cyfluthrin has no oxidising properties according to EEC Method A.21 and no explosive properties according to of EEC Method A.14.

The DS also proposed no classification for the physical hazard classes listed below with the accompanied rationale:

Self-reactive substances and mixtures/explosive

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

Pyrophoric solids

Cyfluthrin is known to be stable in contact with air at room temperature for prolonged periods of time (days) 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 ≤ 160°C.

Substances and mixtures which in contact with water emit flammable gases

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

Oxidising solids

No classification is warranted because the organic substance contains oxygen, chlorine, and fluorine atoms that are chemically bonded only to carbon or hydrogen and hence, the classification procedure does not need to be applied.

Organic peroxides

No classification is warranted because 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).

The DS concluded that cyfluthrin should not be classified as flammable, oxidising or explosive or for any other physical hazard classes.

Comments received during public consultation

No comments received during public consultation.

Assessment and comparison with the classification criteria

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 and the chemical structure does not raise a concern about corrosive properties (no dissociation etc.), no classification is warranted.

RAC agrees with the rationale of the DS that **no classification with regards to the physical hazards is warranted for cyfluthrin**.

4 HUMAN HEALTH HAZARD ASSESSMENT

Beta-cyfluthrin (FCR 4545) and cyfluthrin (FCR 1272) have the same chemical structure (see figure below). The common molecular structure shows 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, III and IV), beta-cyfluthrin consists of the two most active diastereomers II and IV (diastereomer II: 30.0 – 40.0 %, diastereomer IV: 57.0 – 67.0 % of the sum of the four diastereoisomers; see Table 11).

Read-across of beta-cyfluthrin and cyfluthrin properties is considered scientifically appropriate and was generally accepted for the biocidal (cyfluthrin) and plant protection evaluation (beta-cyfluthrin) due to the very similar toxicological profile of both substances. Also because beta-cyfluthrin contains the biologically most active diastereomers at about 40 % also contained in cyfluthrin, the lowest dose of adverse effects for each study endpoint was taken into account. Specifically the read-across applies for systemic and/or local toxicity and all routes of exposure for both substances. Hence, it is concluded that studies with beta-cyfluthrin can be applied to cyfluthrin risk assessment, and vice versa. Consequently, the entire acceptable data set of beta-cyfluthrin and cyfluthrin is considered in this dossier.

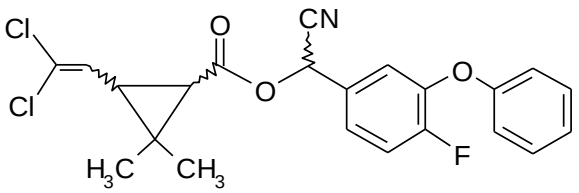


Figure 1: Structural formula of Cyfluthrin

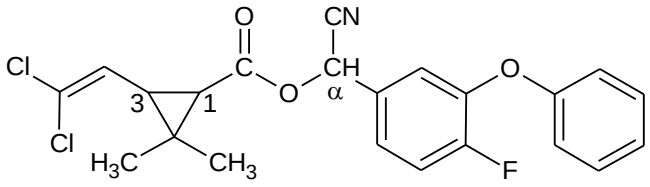


Figure 2: Diastereoisomeric pairs of beta-cyfluthrin

Table 11: Isomer compositions of cyfluthrin and beta-cyfluthrin

Diastereomer		Cyfluthrin	Beta-Cyfluthrin (FCR 4545)
I.	**1R - 3R - αR** **1S - 3S - αS**	23-27 %	≤2 %
II.	**1R - 3R - αS** **1S - 3S - αR**	17-21 %	30-40 %
III.	**1R - 3S - αR** **1S - 3R - αS**	32-36 %	≤3 %
IV.	**1R - 3S - αS** **1S - 3R - αR**	21-25 %	57-67 %

4.1 Absorption, distribution, metabolism and excretion in mammals (ADME)

No significant differences in toxicokinetic behaviour between cyfluthrin and beta-cyfluthrin were observed. Thus, the toxicokinetic data on cyfluthrin are considered representative for beta-cyfluthrin and vice versa, further supporting a read across of toxicological data for systemic and/or local toxicity and all routes of exposure.

Study 86 investigated the metabolic fate of the cyclopropyl-moiety of the molecule ([cyclopropane-1-^{14}C] beta-cyfluthrin), using PEG 300 as a vehicle. This moiety was not investigated in the older dataset on cyfluthrin (see Table 13) and is thus considered to complete the assessment of the metabolic fate of beta-cyfluthrin.

To address an additional point in the new data requirements of Regulation 283/2013, a comparative *in vitro* metabolism study in rat/human liver microsomes has been included (study 83, Table 12). Species differences in the intrinsic clearance and the enzymes involved in the metabolism of pyrethroid pesticides were examined in rat and human hepatic microsomes. Different pyrethroids including beta-cyfluthrin were incubated in rat and human hepatic microsomes in the presence or absence of NADPH. Metabolism was measured using a parent depletion approach. The intrinsic clearance of the majority of pyrethroids was 5 to 15-fold greater in rat relative to human microsomes. The metabolism of beta-cyfluthrin in microsomes from both species was metabolized by both oxidative and hydrolytic pathways. Rat cytochrome P450 isoforms that showed activity toward several pyrethroids included CYP1A1, CYP1A2, CYP2C6, CYP2C11, CYP3A1, and CYP3A2. Human P450 isoforms that showed activity toward multiple pyrethroids were CYP2C8, CYP2C9, CYP2C19, and CYP3A4. Species-specific differences in metabolism may result in variable detoxification of pyrethroids, which may in turn result in divergent neurotoxic outcomes. These species differences and isomer interactions in metabolism of pyrethroids should be considered when assessing the potential adverse health effects of pyrethroid pesticides. This publication supports the results in study 84 that showed that after incubation of [fluorophenyl-UL-^{14}C]-beta-cyfluthrin with active rat liver microsomes in the presence of NADPH regeneration system the test item was extensively metabolised.

Absorption:

The previously evaluated studies with cyfluthrin on rats (Table 13) showed a high degree of absorption (approximately 90 %: 50 % urinary, 12 % faecal, 33 % biliary, a fraction of the total amount via the bile was subject to an enterohepatic circulation) of the radioactivity. The biliary value is based on the experiments with bile duct cannulated animals. Unfortunately, from the toxicokinetic studies with beta-cyfluthrin (study 85,86,87; Table 12) information about radioactivity present in bile was not provided since the animals were not bile duct cannulated. Therefore, it cannot be assumed that the proportion recovered in faeces represents material which had undergone systemic absorption. Therefore, for beta-cyfluthrin a minimum absorption of 60 % can be derived from these studies (single oral low and high dose: 0.5 and 10 mg/kg bw).

The extent of absorption depends largely on the polarity of the formulation vehicle. Cyfluthrin in Cremophor EL/distilled water is absorbed faster (maximum 1 hour) and more intensively than cyfluthrin in polyethylene glycol 400 (maximum 6 hours). Accordingly, rats receiving cyfluthrin in Cremophor EL/distilled water showed signs of toxicity (i.e. hypersalivation, piloerection, diarrhea) whereas rats receiving cyfluthrin in polyethylene glycol 400 had no symptoms (study 88).

Approximately one third of the retrieved radioactivity was excreted via bile fluid during the first 2 hours and more than 90 % within the first 6 hours post application. Relating these results to the faecal excretion of intact rats following both routes of administration, it can be stated that at least one half of the faecally excreted radioactivity is due to an absorbed and biliary eliminated amount. A part of the biliary radioactivity is subject to entero-hepatic circulation (study 89).

Distribution:

The radioactivity is slowly distributed into the tissues and the distribution of radioactivity from the intravascular space into the tissues is low (study 89,90, Table 13). The highest values were found in fatty tissue, adrenals, kidney and liver in each case. At the end of the studies (up to 10 days after administration) very low levels were found in the brain, spleen, testes, erythrocytes and plasma. Maximum relative plasma concentrations were reached 2 hours after oral administration of the low dose or the high dose. The plasma concentrations were around 1.2 times higher in the females than those measured in the males (study 89,85,86,87)

After oral administration of 10 mg/kg bw cyfluthrin, at the time of maximum plasma level (1.5 hours after administration) values in the liver and in the kidneys were markedly higher in comparison to other organs/tissues. Parallel to the onset of excretion in urine and bile, a slow redistribution of radioactivity into the fatty tissue occurs (study 90).

Metabolism:

The new studies submitted for renewal were conducted with beta-cyfluthrin. The test substance was either radiolabelled in the fluorophenyl- (study 87) or in the cyclopropyl-moiety (study 86), of the molecule.

The investigation of the metabolite pattern in urine and faeces revealed that beta-cyfluthrin was extensively metabolized independent of dose and sex (Table 12). When radiolabelled in the cyclopropyl-moiety urinary metabolite pattern consisted of at least 6 metabolite fractions. The main metabolites in urine are a glucuronide conjugate of 3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropane-carboxylic acid (DCVA acyl glucuronide, 26.3-39.1 % of recovered radioactivity) and cis/trans DCVA (25.7-48.8 %). All other fractions were $\leq$ 3 % of dose. No unchanged parent was detected in urine whereas it was the major test-related material found in faeces.

The faecal metabolite pattern revealed at least 9 metabolite fractions. The metabolite pattern was dominated by three major fractions: cis/trans DCVA accounted for 7.9 and 8.4 % in males for the high and low dose respectively, and for 4.6 and 4.7 % in females for the high and low dose, respectively. Unchanged beta-cyfluthrin was found from 14.9-7.7 % in males for the high and low dose, respectively, and from 26.5-7.6 % in females for the high and low dose, respectively. The proposed metabolic pathway is the following: beta-cyfluthrin → DCVA → DCVA glucuronide conjugate (study 86).

When radiolabelled in the fluorophenyl-moiety the main metabolites in urine after 48 h are a sulphate conjugate of OH-FPB (46.7 % of recovered radioactivity), its free form (2 %) and FPB-acid (14.6 %). Only 0.5 % unchanged parent compound was detected in the urine while the parent compound was the major test substance related material detected in faeces (20.03 %) (study 87).

In metabolism studies with cyfluthrin (Table 13), 65-72 % of the recovered radioactivity in the dose groups A and B (both single low dose) and approximately 82 % in the dose groups C (multiple low dose groups) and D (single high dose) which were eliminated via the urine and faeces could be identified. The main metabolites were a conjugate of 4'-hydroxy-4-fluoro-3-phenoxybenzoic acid (OH-FPB acid; 51-52 % of recovered radioactivity), its free form ("FCR 3145", 3.0-5.0 % of recovered radioactivity) and 4-fluoro-3-phenoxybenzoic acid (FPB-acid, approx. 10 % of recovered radioactivity). The unchanged parent compound FCR1272 accounted for approximately half of the faecally eliminated portion (study 91).
The first step in the process of biotransformation is the cleavage of the ester bond and oxidation to FPB-acid, which then undergoes further hydroxylation and conjugation or is bound to glycine with formation of the appropriate hippuric acids. Depending upon the dose groups, unchanged parent compound and metabolites account for 65-82 % of the recovered radioactivity and 4-8 % of the radioactivity was unextractable. The metabolism is slightly dose-dependent, with the proportion of the OH-FPB acid conjugate decreasing with dose and the proportion of FPB-acid increasing with dose.

A common metabolic scheme for cyfluthrin in rats, hens and cows has been established and is depicted in Figure 3.

As demonstrated in the bile cannulation study with cyfluthrin, the parent found in faeces was absorbed and subject to enterohepatic circulation. Like with cyfluthrin, the first step in the process of biotransformation is the cleavage of the ester bond and oxidation to FPB-acid, which then undergoes further hydroxylation and conjugation. Unchanged parent compound and metabolites account for 25.46 % after 48 hours of the recovered radioactivity and 1.13 % of the radioactivity was unextractable. A metabolic scheme for beta-cyfluthrin in rats has been established and is depicted in Figure 3.

Moreover, a comparative *in vitro* metabolism study of [fluorophenyl-UL-^{14}C] beta-cyfluthrin (study 84, Table 12) revealed that after adding to liver microsomes [^{14}C] beta-cyfluthrin was rapidly and more extensively metabolised in rat than in human liver microsomes. All metabolites observed with human material have also been observed in rat material. It is thus concluded that the available safety dataset in the rat is relevant and there is no unique human metabolite that would deserve further attention in risk assessment.

Elimination:

Beta-cyfluthrin and cyfluthrin are eliminated fast from the body. Thus, > 97 % of the orally and intravenously administered dose had been eliminated from the body after two days.

Beta-cyfluthrin and cyfluthrin were predominantly excreted via urine and faeces (renal/faecal: approx. 2:1). Excretion via expired gases is small, 48 hours after the oral administration of 10 mg/kg

bw cyfluthrin, less than 0.001 % of the administered dose is expired (study 90). The amount of radioactivity excreted is proportional to the dose levels tested and independent of the sex of the animals.

Accumulation:

The kinetics of excretion of beta-cyfluthrin and cyfluthrin and, as well as the concentration curves in the individual tissues and organs, indicate that these substances do not accumulate, but are continuously eliminated.

Table 12: ADME studies with beta-cyfluthrin

Study Type	Test substance Dosing regime	Scope of study	Reference
Absorption, Distribution and Excretion of [fluorophenyl-UL-^{14}C] beta-cyfluthrin in Male Rats After Single Oral Administration at One Dose Level (GLP: yes; OECD TG 417)	Beta-cyfluthrin, fluorophenyl-UL-^{14}C, radiochemical purity 99.3 % 10 mg/kg bw (single oral) Wistar rats , 4 males /group Vehicle: Cremophor EL	Absorption, tissue distribution, excretion pattern und kinetics. No metabolism.	study 85 †
Absorption, Distribution, Excretion and Metabolism of [fluorophenyl-UL-^{14}C] Beta-Cyfluthrin in Male Rats After Single Oral Administration at One Dose Level. (GLP: yes; OECD TG 417)	Beta-cyfluthrin, fluorophenyl-UL-^{14}C, radiochemical purity 99.3 % 10 mg/kg bw (single oral) Wistar rats , 4 males /group Vehicle: PEG400	Absorption, tissue distribution, metabolism, excretion pattern und kinetics	study 87 †
Absorption, Distribution, Excretion and Metabolism of [cyclopropane-1-^{14}C] Beta-Cyfluthrin in Male and Female Rats After Single Oral Administration at Two Dose Levels. (GLP: yes; OECD TG 417)	Beta-cyfluthrin, cyclopropane-1-^{14}C, radiochemical purity 99.3 % 0.5, 10 mg/kg bw (single oral) Wistar rats , 4 males and 4 females /groupVehicle: PEG400	Absorption, tissue distribution, metabolism, excretion pattern und kinetics	study 86 †
Comparative *in vitro* Metabolism of [fluoro-phenyl-UL-^{14}C] beta-cyfluthrin in Rat and Human Liver Microsomes. (GLP: yes, Guideline: no)	Beta-cyfluthrin, fluorophenyl-UL-^{14}C, radiochemical purity 99.3 % 10 µM	*In vitro* comparison of metabolism in rat and human liver microsomes	study 84 †
In vitro metabolism of pyrethroid pesticides by rat and human hepatic microsomes and cytochrome P450 isoforms (GLP and guideline not applicable)	Beta-cyfluthrin and other pyrethroid pesticides purity >98 %, different vehicles	*In vitro metabolism in rat and human microsomes*	study 83

†Key study

Table 13: ADME studies with cyfluthrin

Study Type	Test substance Dosing regime	Scope of study	Reference
Comparative study of rats on absorption of FCR 1272 after single oral administration in polyethylene glycol 400 or Cremophor EL/water as formulation vehicle. (GLP: no; guideline: no, supplemental)	Cyfluthrin, isomer ratio: I 26.6 %; II 19.1 %; III 33.7 %; IV 20.6 %; purity not reported. 10 mg/kg bw (one single oral dose, ♂ only) Different Vehicles: Polyethylene glycol 400 and Cremophor EL/distilled water	Provides comparative data on oral uptake from different vehicles (PEG400 and Cremophor/water): The higher toxicity of cyfluthrin in Cremophor EL/distilled water is caused by faster and higher absorption.	study 88
Fluorophenyl-UL-14C cyfluthrin (FCR 1272) biokinetic study in rats.	Cyfluthrin, cis/trans ratio of 42/58, purity: 97.5 %	Information on accumulation, absorption, excretion, and	study 90 †

Study Type	Test substance Dosing regime	Scope of study	Reference
(GLP: no; guideline, partly OECD TG 417)	a) 0.5 mg/kg bw (single i.v. or intraduodenal, ♂), b) 0.5 mg/kg bw (single oral, ♂), c) 10 mg/kg bw (single oral, ♂) d) 0.5 mg/kg bw (single oral, ♀)	distribution over 10 days	
Biokinetic part of the general metabolism studies in the rat. (GLP: no; guideline according to EPA specifications compatible to Directive 87/302/EEC, Part B)	Cyfluthrin, cis/trans ratio of 42/58, purity: 97.5 % Vehicle: Cremophor/saline Administration (♂ only): a) 0.5 mg/kg bw (single i.v. or intraduodenal) b) 0.5 mg/kg bw (single oral) c) 0.5 mg/kg bw/day (oral: 14 nonradioactive doses + single radioactive dose) d) 10 mg/kg bw (single oral) Rat, Mura: SPRA (SPF 68 Han) *Intraduodenal/bile cannulated:* 5 males *Single oral low dose group:* 9 males + 9 females *other groups:* 5 males + 5 females	Provides mass balance and distribution of radiolabel in excreta and carcass following different routes of administration.	study 89 †
[Fluorobenzene-UL-^{14}C]cyfluthrin: Metabolism part of the general metabolism studies in the rat. (GLP: no; guideline according to EPA specifications compatible to Directive 87/302/EEC, Part B)	Cyfluthrin, cis/trans ratio of 42/58, radiochemical purity: 98 % Vehicle: Cremophor/saline Administration (♂ only): a) 0.5 mg/kg bw (single i.v.) b) 0.5 mg/kg bw (single oral) c) 0.5 mg/kg bw/day (oral: 14 nonradioactive doses + single radioactive dose) d) 10 mg/kg bw (single oral) Rat, Sprague Dawley (4 males and 4 females)	Identification of metabolites in excreta	study 91 †
Thiocyanate excretion in rats' urine after intraperitoneal administration of FCR 1272 and decamethrin in comparable doses and after exposure to defined FCR 1272 concentrations in the inhalation air. (GLP: no, Guideline: no, supplemental)	Cyfluthrin, isomer ratio: I 24.9 %; II 17.9 %; III 30.0 %; IV 22.2 %; purity: 95 %; Decamethrin purity: 99.2 % 0, 1, 5, 10, 15 mg/kg bw i.p. (♂ only); 0, 59, 93, 180 mg/m³ exposure via inhalativetion (♂+♀)	Focus on thiocyanate excretion in urine following i.p. and exposure via inhalation of cyfluthrin and decamethrin	study 92
Biotransformation of [F-phenyl-UL-14C]cyfluthrin; characterisation and preliminary identification of the metabolites. (GLP: no, Guideline: no)	Cyfluthrin, cis/trans ratio of 42/58, radiochemical purity: 98 % 10 mg/kg bw oral (only ♂); vehicle not reported	Preliminary study for identification of urinary metabolites	study 93

†Key study

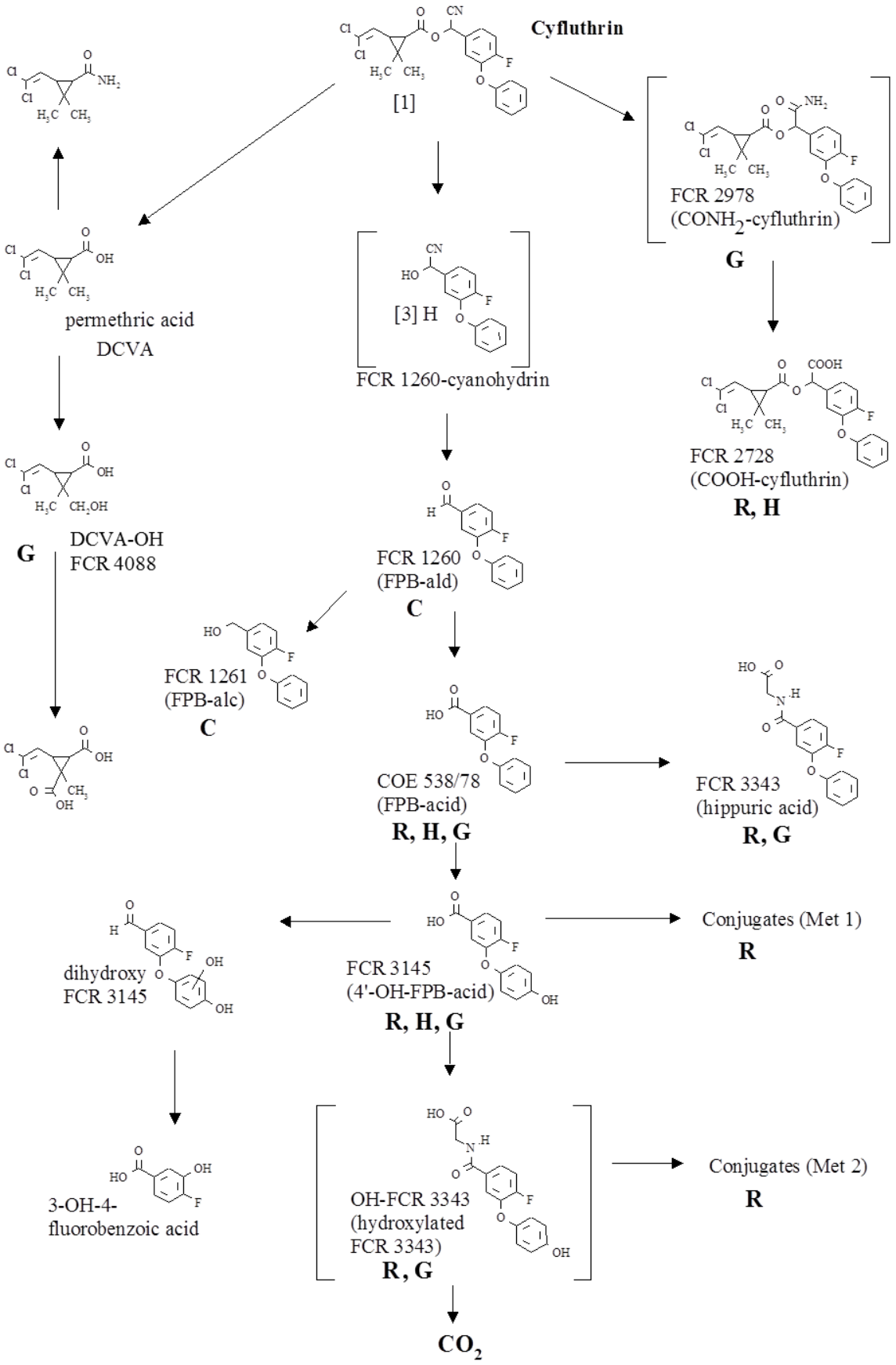


Figure 3: Proposed metabolic pathway for cyfluthrin in rats (R) , laying hens (H), cows (C) and goats (G)

Table 14: Toxicokinetics and metabolism in rats - Excretion of total radioactivity and radioactive residues in the rat 48 hours after application of [fluorophenyl-UL-14C] cyfluthrin (values are given in % of recovered radioactivity)

Report	Administration	Dose [mg/kg bw]	Sex	CO_2	Bile	Urine	Faeces	Total excreted	Ratio Urine/ Faeces	Body without GIT	GIT	Recovery (% of applied)
sudy 89	intraduodenal	0.5	m	-	33	54	12	99	4.5	0.5	0.15	103
	oral[1)]	10	m	<0.001	-	67	31	98	2.2	1.3	0.27	106
	intravenous	0.5	m	-	-	69	24	93	2.9	5.6	0.74	94
	oral	0.5	m	-	-	74	25	99	3.0	1.1	0.22	93
	pretreat. oral	0.5	m	-	-	73	26	99	2.8	1.2	0.24	91
	oral	10	m	-	-	66	33	99	2.0	1.4	0.23	99
	oral	10	f	<0.001	-	67	31	98	2.2	2.1	0.42	98
	intravenous	0.5	f	-	-	65	28	93	2.3	6.5	0.78	93
	oral	0.5	f	-	-	61	37	98	1.6	1.6	0.59	101
	pretreat. oral	0.5	fw	-	-	63	36	99	1.8	1.2	0.32	96
	oral	10	f	-	-	52	45	97	1.2	1.6	0.45	101
study 90	intraduodenal	0.5	m	-	33.5	54.2	11.6	99.3	4.7	0.5	0.15	103.1
	oral[1)]	10	m	<0.001	-	59.1	39.3	98.4	1.5	1.4	0.30	95.0
	intravenous	0.5	m	-	-	69.5	24.1	93.6	2.9	5.7	0.75	93.5
	oral	0.5	m	-	-	74.2	24.5	98.7	3.0	1.1	0.21	93.8
	oral	0.5	f	-	-	61.7	36.7	97.4	1.7	1.6	0.60	99.3
	oral	10	m	-	-	65.9	32.4	98.3	2.0	1.4	0.25	99.4
study 91	intravenous	0.5	m	-	-	67.0	26.6	93.6	2.5	6.4		90.0
	intravenous	0.5	f	-	-	65.2	25.3	90.5	2.6	9.5		87.6
	oral	0.5	m	-	-	73.0	25.7	98.7	2.8	1.3		97.1
	oral	0.5	f	-	-	61.4	36.5	97.9	1.7	2.1		94.0
	pretreat. oral	0.5	m	-	-	71.8	26.7	98.5	2.7	1.5		87.4
	pretreat. oral	0.5	f	-	-	62.2	35.4	97.6	1.8	2.4		93.6
	oral	10	m	-	-	65.0	33.4	98.4	1.9	1.6		94.8
	oral	10	f	-	-	59.6	37.8	97.4	1.6	2.6		96.9

GIT: gastrointestinal tract;

[1)] Preliminary study to assess the volatility of cyfluthrin.

Table 15: Toxicokinetics and metabolism in rats - Relative concentration of radioactivity (P) in individual parts of the body of rats after application of [fluorophenyl-UL-14C] cyfluthrin (all values are multiplied with the factor 100)

Report	Admini-stration	Dose (mg/kg bw)	Sex	Time (h)	Body without GIT	Plas-ma	Ery-thro-cytes	Testes or Ovaries	Femur	Brain	Skin	Heart	Spleen	Liver	Kidney	Renal fat	Adre-nal
study 89	intra-venous	0.5	m	48	6	17	4,5	1,2	2.0	0.6	6.2	3.4	13	14	5.4	53	16
	oral	0,5	m	48	1.1	0.94	0.2	0.16	0.38	0.065	1.3	0.26	0.54	2.0	1.1	16	1.4
	pretreat.oral	0.5	m	48	1.3	1.1	0.31	0.18	0.23	0.057	1.8	0.27	0.36	2.1	1.3	9	2.3
	oral	10	m	48	1.6	0.86	0.44	0.21	0.42	0.07	1.8	0.29	0.27	2.5	1.3	18	1.6
	intra-venous	0.5	f	48	6.6	18	4.7	2.7	2.8	0.57	9.7	3.9	16	15	7.4	33	24
	oral	0.5	f	48	1.8	3.2	0.56	3.2	0.54	0.13	2.2	0.67	0.48	3.4	3.2	12	3.9
	pretreat.oral	0.5	fw	48	1.3	2.4	0.47	1.6	0.39	0.077	1.8	0.51	0.24	2.3	2.0	5.3	1.5
	oral	10	f	48	1.8	2.6	0.52	3.0	0.43	0.12	2.5	0.8	0.36	3.0	2.7	11	2.4
study 90	oral	10	m	1.5	44	220	48	16	15	-	35	-	22	170	130	36	73
	oral	10	m	4	33	130	30	16	10	-	29	-	14	100	85	60	32
	oral	10	m	8	21	65	12	11	5.5	-	18	-	5.8	51	46	42	10
	oral	10	m	24	4.7	12	2.6	2.2	1.6	-	5.0	-	1.6	8.3	7.0	24	5.3
	oral	10	m	48	2.0	1.6	0.51	0.35	0.72	-	1.9	-	0.61	2.8	1.5	22	10
	oral	10	m	72	1.1	0.49	0.18	0.1	0.52	-	1.1	-	0.14	1.8	0.7	17	0.89
	oral	10	m	144	0.5	0.24	0.064	0.061	0.39	-	0.29	-	0.059	0.9	~0.35	8.4	0.79
	oral	10	m	240	0.26	0.061	0.037	0.017	0.14	-	~0.13	-	0.016	~0.43	0.13	6.1	~0.19

P= measured activity / g tissue or plasma administered activity / g bw

Table 16: Toxicokinetics and metabolism in rats - Distribution of metabolites in the excreta of rats 48 hours after administration of [fluorophenyl-UL-14C]cyfluthrin. For codes of the metabolites Figure 3 (values are given in % of the recovered radioactivity)

Report	Administration	Dose (mg/kg)	Excretion	Sex	Met.1 ❶	FCR 3145	Met. 2 ❷	FCR 3343	COE 538/78	FCR 1272	un-known	unex-tractable	Total
study 91	intravenous	0.5	Urine	m	47.0	2.9	1.5	2.4	12.1	-	1.1	-	67.0
	intravenous	0.5	Faeces	m	0.1	1.9	0.1	-	-	0.4	24.1	8.0	26.6
			∑		47.1	4.8	1.6	2.4	12.1	0.4	25.2	8.0	93.6
	intravenous	0.5	Urin	f	44.4	4.4	1.5	2.3	10.8	-	1.8	-	65.2
	intravenous	0.5	Faeces	f	0.2	4.9	-	-	0.3	0.5	12.1	7.3	25.3
			∑		44.6	9.3	1.5	2.3	11.1	0.5	13.9	7.3	90.5
	oral	0.5	Urine	m	52.0	3.8	2.1	3.6	10.1	-	1.4	-	73.0
	oral	0.5	Faeces	m	-	1.1	0.1	-	-	0.1	19.5	4.9	25.7
			∑		52.0	4.9	2.2	3.6	10.1	0.1	20.9	4.9	98.7
	oral	0.5	Urine	f	41.1	3.9	2.6	2.4	9.9	-	1.5	-	61.4
	oral	0.5	Faeces	f	-	4.6	0.4	0.2	0.3	0.1	23.9	7.0	36.5
			∑		41.1	8.5	3.0	2.6	10.2	0.1	25.4	7.0	97.9
	pretr.oral	0.5	Urine	m	47.4	3.2	3.0	6.7	10.5	-	1.0	-	71.8
	pretr.oral	0.5	Faeces	m	-	0.8	0.1	-	0.1	11.6	8.9	5.2	26.7
			∑		47.4	4.0	3.1	6.7	10.6	11.6	9.9	5.2	98.5
	pretr.oral	0.5	Urine	fw	41.8	4.4	2.9	2.7	8.3	-	2.1	-	62.2
	pretr.oral	0.5	Faeces	f	-	6.4	-	0.3	-	16.2	8.9	3.6	35.4
			∑		41.8	11.0	2.9	3.0	8.3	16.2	11.0	3.6	97.6
	oral	10	Urine	m	35.9	1.8	0.8	0.5	24.1	-	1.9	-	65.0
	oral	10	Faeces	m	-	1.2	-	0.4	-	16.6	10.2	5.0	33.4
			∑		35.9	3.0	0.8	0.9	24.1	16.6	12.1	5.0	98.4
	oral	10	Urine	f	35.2	4.5	2.1	17.3		-	0.5	-	59.6
	oral	10	Faeces	fw	-	4.3	-	-		19.0	9.5	5.0	37.8
			∑		35.2	8.8	2.1	17.3		19.0	10.0	5.0	97.4

❶: Conjugate of FCR 3145 ❷: Probably conjugate of hydroxylated FCR 3343.

4.2 Acute toxicity

4.2.1 Non-human information

4.2.1.1 Acute toxicity: oral

The experimental oral LD_{50} values of cyfluthrin and beta-cyfluthrin are covering a broad range. This finding could be evoked by different factors:

The acute oral toxicity of cyfluthrin and beta-cyfluthrin seems to be dependent on the vehicle used (see Table 17 and Table 18). This may be due to different polarity leading to modified absorption in the gastrointestinal tract. Furthermore, beta-cyfluthrin generally possesses, vehicle-dependently, a higher acute oral toxicity than cyfluthrin. The lowest LD_{50} values determined in acceptable studies with beta-cyfluthrin were 77 mg/kg bw (acetone/peanut oil; study 22 in rats and 91 mg/kg bw (PEG 400; study 25) in mice. The lowest LD_{50} values determined in acceptable studies with cyfluthrin were 14.3 mg/kg bw (Cremophor/water; study 5) in rats and 291 mg/kg bw (PEG 400; study 14) in mice. A further study evaluated as supplementary indicated a LD_{50} value < 100 mg/kg bw (Cremophor/water) for cyfluthrin in mice (study 13). As laid down in the actual CLP regulation, […] "generally the lowest valid value would be the basis for classification […] if there are different LD_{50} values from tests using different vehicles" (page 265). For this reason, the classification for acute oral toxicity for cyfluthrin was based on study 5 (solvent: Chemophor/water).

Table 17: Summary table of relevant acute oral toxicity studies with cyfluthrin*

Parameter	Species	Sex	Vehicle	Result	Comment	Reference
acute oral LD_{50} (GLP: no, similar to OECD 401)	Rat (Wistar)	male male male male (5-20/ group)	cremophor/water acetone/oil dimethylsuphoxide *N*-methylpyrrolidone (cyfluthrin batch no. 816170019, purity 95 %)	16.2 mg/kg bw 254 mg/kg bw 396 mg/kg bw 500-1000 mg/kg bw	(fasted) -preliminary LD_{50} determination -no detailed information given (e.g. doses, group size)	study 1
acute oral LD_{50} (GLP: no, similar to OECD 401)	Rat (Wistar)	5 male/ group	cremophor/water (cyfluthrin batch no.: 816270011, purity: 93.7 %)	20 mg/kg bw	-combination study -LD_{50} (cyfluthrin + propoxur) = 57 mg/kg bw -no necropsy	study 2
acute oral LD_{50} (GLP: no, similar to OECD 401)	Rat (Wistar)	5 male/ group	cremophor/water (cyfluthrin batch no.: 816270011, purity: 93.7 %)	20 mg/kg bw	-combination study -LD_{50} (cyfluthrin + dichlorvos) = 70 mg/kg bw -no necropsy	study 3
acute oral LD_{50} (GLP: no, similar to	Rat (Wistar)	5 male/ group	cremophor/water (cyfluthrin batch no. 816270011, purity 93.7 %)	20 mg/kg bw[3]	-combination study -LD_{50} (cyfluthrin +	study 4

Parameter	Species	Sex	Vehicle	Result	Comment	Reference
OECD 401)					fenfluthrin) = 67 mg/kg bw -no necropsy	
acute oral LD_{50} (GLP: no, similar to OECD 401)	Rat (Wistar)	10 male	cremophor/water (cyfluthrin batch no. 816170019, purity 95 %)	14.3 mg/kg bw	(fasted)	study 5 †
acute oral LD_{50} (GLP: no, similar to OECD 401)	Rat (Wistar)	5-10 male/ group	cremophor/water (cyfluthrin batch no.: 816170019, purity: 94.9 %)	18 mg/kg bw	-combination study -LD_{50} (cyfluthrin + methamidphos) = 26 mg/kg bw	study 6
acute oral LD_{50} (GLP: yes, similar to OECD 401)	Rat (Wistar)	5 male/ group	cremophor/water (cyfluthrin batch no.: 238005176, purity: 95.1 %)	15 mg/kg bw[2]	-combination study -only two doses tested -LD_{50} (cyfluthrin + imidacloprid) = 414 mg/kg bw	study 7
acute oral LD_{50} (GLP: no, similar to OECD 401)	Rat (Wistar)	5-20 male/group	cremophor/water (cyfluthrin batch no.: 816170019, 816270030, purity: 94.9 %, 94.7 %)	19.6 mg/kg bw	-study for antidote effect -no necropsy	study 8
acute oral LD_{50} (GLP: no, similar to OECD 401)	Rat (Wistar)	5 male/ group	PEG 400 (cyfluthrin batch no.: 233690489, purity: 95.7 %)	500 mg/kg bw	-combination study -LD_{50} (cyfluthrin + omethoate) = 218 mg/kg bw	study 9
acute oral LD_{50} (GLP: no, unpublished)	Rat (Wistar)	15 male 15 female	PEG 400 (cyfluthrin batch no. 16001/79, purity: 83.6 %)	869 mg/kg bw[1,2,3] 1271 mg/kg bw[1,2,3]	(animals not fasted)	study 10
acute oral LD_{50} (GLP: no, unpublished)	Rat (Wistar)	15 male 15 female	PEG 400 (cyfluthrin batch no. 16001/79, purity: 83.6 %)	590 mg/kg bw[3] 1189 mg/kg bw[3]	(fasted)	study 11
acute oral LD_{50} (GLP: yes, OECD 401)	Rat (Wistar)	5-10 male and 5-10 female/ group	acetone/peanut oil (cyfluthrin batch no. 23490583, purity: 93 %)	155 mg/kg bw[3] 160 mg/kg bw[3]	(fasted)	study 12
acute oral LD_{50} (GLP: no, similar to OECD 401)	Mouse (NMRI)	female	cremophor/water (cyfluthrin batch no. 816170019, purity 95 %)	<100 mg/kg bw[2,3]	-preliminary LD_{50} determination -no detailed information	study 13

Parameter	Species	Sex	Vehicle	Result	Comment	Reference
					given (e.g. doses, group size)	
acute oral LD_{50} (GLP: no, unpublished)	Mouse (NMRI)	15 male 15 female	PEG 400 (cyfluthrin batch no. 16001/79, purity: 83.6 %)	291 mg/kg bw[3] 609 mg/kg bw[3]		study 14 †
acute oral LD_{50} (GLP: no, unpublished)	Rabbit (White New Zeland)	3 male	PEG 400 (cyfluthrin batch no. 16001/79, purity: 83.6 %)	>1000 mg/kg bw[2,3]	-only three animals per dose -no necropsy	study 15
acute oral LD_{50} (GLP: no, unpublished)	Dog (Beagle)	2 male	PEG 400 (cyfluthrin batch no. 16001/79, purity: 83.6 %)	>100 mg/kg bw[2,3]	-vomiting at 50 mg/kg bw and above -only two animals per dose -no necropsy	study 16
acute oral LD_{50} (GLP: no, unpublished)	Dog (Beagle)	1 male 1 female	cremophor/water (cyfluthrin batch no. 816170019, purity 95 %)	>100 mg/kg bw[1,2,3]	-vomiting observed -animals not fasted -only two animals per dose (1 per sex) -only two doses -no necropsy	study 17
acute oral LD_{50} (GLP: yes, OECD 401)	Chicken (White Leghorn Hens)	5 female/ group	cremophor/water (cyfluthrin batch no. 233590478, purity 93.5 %)	>5000 mg/kg bw[1,2,3]	-animals not fasted -only two doses tested	study 18
acute oral LD_{50} (GLP: no, similar OECD 418 and 419)	Chicken (White Leghorn Hens)	10 female/ group	PEG 400 (cyfluthrin batch no.: 16001/79, purity: 85.3 %)	~5000 mg/kg bw[1,2]	-animals not fasted	study 19
acute oral LD_{50} (GLP: yes, OECD 401)	Chicken (White Leghorn Hens)	5 female/ group	PEG 400 (cyfluthrin batch no.: 233590478, purity: 93.5 %)	~4500 mg/kg bw[1,2,3]	-animals not fasted -only two doses tested	study 20

[*] Not-acceptable studies were not included.
[1] Animals not fasted.
[2] These studies are considered supplementary.
[3] These studies were not submitted by the applicant (but available to the RMS e.g. from other applications).
†Key study

Table 18: Summary table of relevant acute oral toxicity studies with beta-cyfluthrin*

Parameter	Species	Sex	Vehicle	Result	Reference
acute oral LD_{50} (GLP: yes; OECD 401)	Rat (Wistar)	male female male female (5 male and 5 female/group)	PEG 400 (beta-cyfluthrin batch no.: 16002/84, purity: 99.1 %)	655 mg/kg bw[1,2] 1369 mg/kg bw[1,2] 380 mg/kg bw 651 mg/kg bw	
acute oral LD_{50} (GLP: yes; OECD 401)	Rat (Wistar)	male female male female (5 male and 5 female/group)	acetone/ peanut oil (beta-cyfluthrin batch no.: 16002/84, purity: 99.1 %)	141 mg/kg bw[1,2] 108 mg/kg bw[1,2] 84 mg/kg bw 77 mg/kg bw	Study 22 †
acute oral LD_{50} (GLP: yes; OECD 401)	Rat (Wistar)	male female male female (5 male and 5 female/group)	xylene (beta-cyfluthrin batch no.: 16002/84, purity: 99.1 %)	307 mg/kg bw[1,2] 343 mg/kg bw[1,2] 211 mg/kg bw 336 mg/kg bw	Study 23
acute oral LD_{50} (GLP: yes; OECD 423)	Rat (Wistar)	female (3 /group)	acetone/corn oil (beta-cyfluthrin batch no.: FFEBCTQ043, purity: 99.2 %)	200 mg/kg bw	Study 24
acute oral LD_{50} (GLP: yes; OECD 401)	Mice (Bor:WISW (SPF-Han)	male female (5 male and 5 female/group)	PEG 400 (beta-cyfluthrin batch no.: 16002/84, purity: 99.1 %)	91 mg/kg bw 165 mg/kg bw	Study 25 †
acute oral LD_{50} (GLP: no, unpublished)	Chicken (White Leghorn Hens)	5 female	cremophor/water (beta-cyfluthrin (batch no.: 16002/84, purity: 99.1 %)	>5000 mg/kg bw[1,2,3]	Study 26

* Not-acceptable studies were not included.
[1] Animals not fasted.
[2] These studies are considered supplementary.
[3] These studies were not submitted by the applicant (but available to RMS e.g. from literature search in database or other applications).
†Key study

4.2.1.2 Acute toxicity: inhalation

The LC_{50} values of cyfluthrin and beta-cyfluthrin were determined in rodents after exposure to dust (see Table 19 and Table 20). Based on the worst-case LC_{50} value determined in an acceptable inhalation study, the LC_{50} value in rats used for classification was 0.081 mg/L air (81 mg beta-cyfluthrin in ethanol/PEG 400/m³ air as mist, 4h-exposure, head-nose only; study 36). The lowest rat LC_{50} value after dust exposure was 0.532 mg/L air (532 mg beta-cyfluthrin /m³ air as dust, 4h-exposure, head-nose only; study 36). It is mentioned that the terms “dust” and “mist” and “aerosol” used by the authors of the acute inhalation studies all refer to the hazard category “dust and mists”.

Table 19: Summary table of relevant acute inhalation toxicity studies with cyfluthrin*

Parameter	Species	Sex	Vehicle	Result	Comment	Reference
acute inhal. LC_{50} (1 h, nose only) (GLP: no, unpublished)	Rat (Wistar)	10 male +10 female (group)	ethanol/PEG 400 (1:1) (mist aerosol) (cyfluthrin batch no. 16001/79, purity: 83.6 %)	>1089 mg/m³ air³ (male + female)	-inhalation particle content not given -no vehicle control	Study 27
acute inhal. LC_{50} (4 h, nose only) (GLP: no, unpublished)	Rat (Wistar)	10 male +10 female (group)	ethanol/PEG 400 (1:1) (mist aerosol) (cyfluthrin batch no. 16001/79, purity: 83.6 %)	469-592 mg/m³ air³ (male + female)	-inhalation particle content not given -no vehicle control	Study 28
acute inhal. LC_{50} (4 h, head/nose only assumed) (GLP: no, unpublished)	Rat (Crj: CD)	male + female	ethanol/PEG 400 ethanol/PEG 400 (1:1) (mist aerosol) (cyfluthrin lot no. Eg 3/81, purity 95 %)	1010 /1020 mg/m³ air³ (male/female)	-inhalation particle content not given - number of animals used not indicated.	Study 29
acute inhal. LC_{50} (4 h, head/nose only) (GLP: yes, OECD 403)	Rat (Wistar)	5 male + 5 female (group)	ethanol/PEG 400 (1:1) (mist aerosol) (cyfluthrin batch no. 233490583, purity: 93 %)	405 mg/m³ air³ (male/female)	-no vehicle control	Study 30
acute inhal. LC_{50} (4 h, head/nose only) (GLP: no, unpublished)	Rat (Wistar)	male + female male + female (10 male and 10 females / group)	1) water 2) DMSO (mist aerosol) (cyfluthrin batch no.816170019, purity: 95 %)	1) >735 /200-735 m³ air³ (male/female) 2) 575 /490 mg/m³ air³ (male/female)	-inhalation particle content not given -no vehicle control	Study 31
acute inhal. LC_{50} (5 x 6 h, nose only) (GLP: no, unpublished)	Rat (Wistar)	10 male +10 female (group)	ethanol/PEG 400 (1:1) (mist aerosol) (cyfluthrin batch no. 16001/79, purity: 83.6 %)	47-196 mg/m³ air[2,3] (range for male/female)	-inhalation particle content not given -no vehicle control -no different time points	Study 32
acute inhal. LC_{50} (4 h, head/nose only) (GLP: yes, OECD 403)	Mouse (NMRI)	5 male + 5 female (group)	ethanol/PEG 400 (1:1) (mist aerosol) (cyfluthrin batch no. 233782017, purity: 93.9 %)	~141 mg/m³ air³ (male/female)		Study 33
acute inhal. LC_{50} (4 h, whole body) (GLP: no, similar to OECD 403 and 412)	Chicken (White Leghorn Hens)	10 female/group	ethanol/PEG 400 or water/cremophor (mist aerosol) (cyfluthrin batch number: 816 170 019; purity 95.0 %)	>596 mg/m³ air[2]	-inhalation particle content not given -different solvents -no vehicle control	Study 34

* Not-acceptable studies were not included.
[1] Animals not fasted.
[2] These studies are considered supplementary.
[3] These studies were not submitted by the applicant (but available to the RMS e.g. from other procedures).

Table 20: Summary table of relevant acute inhalation toxicity studies with beta-cyfluthrin*

Parameter	Species	Sex	Vehicle	Result	Reference
acute inhal. LC_{50} (4 h, head-nose) (GLP: yes OECD 403)	Rat (Wistar)	5 male + 5 female (group)	ethanol/PEG 400 (mist aerosol) (beta-cyfluthrin batch no: 16002/84, purity: 98.5 %)	~90 /~ 100 mg/m³ air (male/female) ~967 /~ 695 mg/m³ air (male/female)	Study 35
acute inhal. LC_{50} (4 h, head-nose) (GLP: yes OECD 403)	Rat (Wistar)	5 male + 5 female (group)	ethanol/PEG 400 (mist) ethanol/PEG 400 (mist) dust (beta-cyfluthrin batch no: 16001/87, purity: 97.9 %)	~82 /81 mg/m³ air (male/female) 532 mg/m³ air (male + female)	Study 36 †

* Not-acceptable studies were not included.

† Key study

4.2.1.3 Acute toxicity: dermal

The dermal toxicity of cyfluthrin and beta-cyfluthrin is very low (see Table 21 and Table 22). The lowest dermal LD_{50} value in rats determined in an acceptable study with beta-cyfluthrin was used for non-classification decision (>2000 mg/kg bw, solvent: PEG 400; study 24).

Table 21: Summary table of relevant acute dermal toxicity studies with cyfluthrin*

Parameter	Species	Sex	Vehicle	Result	Comment	Reference
acute dermal LD_{50} (GLP: no, similar to OECD 401)	Rat (Wistar) (24 h contact)	male + female (5-10 male and 5-10 female)	cremophor/water (cyfluthrin batch no.: 816170019, 816270030, purity: 94.9 %, 94.7 %)	>5000 mg/kg bw[2,3]	-only two doses tested (limit test not sufficient) -unclear which sex was used at lower concentration -no necropsy	Study 37
acute dermal LD_{50} (GLP: no, similar to OECD 401)	Rat (Wistar) (24 h contact)	male + female (5-10 male and 5-10 female)	PEG 400 (cyfluthrin batch no.: 816170019, 816270030, purity: 94.9 %, 94.7 %)	>5000 mg/kg bw[2,3]	-no neropsy -no detailed information given	Study 38
acute dermal LD_{50} (GLP: no, similar to OECD 401)	Rat (Wistar) (24 h contact)	male + female (5-10 male and 5-10 female)	NaCl solution (cyfluthrin batch no.: 816170019, 816270030, purity: 94.9 %, 94.7 %)	>5000 mg/kg bw[2,3]	-only two doses tested (limit test not sufficient) -unclear which sex was used at lower concentration -no necropsy	Study 39

* Not-acceptable studies were not included.
[2] These studies are considered supplementary.
[3] These studies were not submitted by the applicant (but available to the RMS e.g. from other procedures).

Table 22: Summary table of relevant acute dermal toxicity studies with beta-cyfluthrin*

Parameter	Species	Sex	Vehicle	Result	Reference
acute dermal LD_{50} (GLP: yes OECD 402)	Rat (Wistar)	male + female (5 males and 5 females)	PEG 400 (beta-cyfluthrin batch no.: 16002/84, purity: 99.1 %)	>5000 mg/kg bw	Study 40
acute dermal LD_{50} (GLP: yes OECD 402)	Rat (Wistar)	male + female (5 males and 5 females)	Xylene (beta-cyfluthrin batch no.: 16002/84, purity: 99.1 %)	>5000 mg/kg bw	Study 41
acute dermal LD_{50} (GLP: yes OECD 402)	Rat (Wistar)	male + female (5 males and 5 females)	PEG 400 (beta-cyfluthrin batch no.: FFEBCTQ043, purity: 99.2 %)	>2000 mg/kg bw	Study 42 †

* Not-acceptable studies were not included.

† Key study

4.2.1.4 Acute toxicity: other routes

No other routes were tested.

4.2.2 Human information

Oral:

Cases of beta-cyfluthrin or cyfluthrin intoxication and signs of poisoning after oral ingestion are not known. Beta-cyfluthrin and cyfluthrin belong to the class of type II pyrethroid insecticides that are widely used, but there have been relatively few reports of systemic poisoning. These reports have, however, shown that pharmacotherapy is difficult and that the duration of poisoning can be unexpectedly long. Pyrethroids are ion channel toxins prolonging neuronal excitation, but are not directly cytotoxic. Two basic poisoning syndromes are seen. Type I pyrethroids produce reflex hyperexcitability and fine tremor. Type II pyrethroids produce salivation, hyperexcitability, choreoathetosis, and seizures. Both produce potent sympathetic activation. Systemic poisoning is difficult to control with anticonvulsants. Pentobarbitone, however, is surprisingly effective as therapy against systemic type II pyrethroid poisoning in rats, probably due to its dual action as a chloride channel agonist and a membrane stabilizer (study 43). Anyhow, it can be assumed that observations made after intoxication with other α-cyano-type II-pyrethroids are also applicable to beta-cyfluthrin. Patients with significant pyrethroid ingestion can present with severe symptoms and signs (Beasley and Wayne, National Poisons Centre, 2014; Table 23) which would constitute a medical emergency, and should be immediately referred to hospital for life support measures and ongoing monitoring.As for other α-cyano-pyrethroids, there is no specific effective antidote. Seizures can be resistant to benzodiazepines and other pharmacotherapy; thiopental may be used in a hospital setting (Giampreti A, Lampati L, Chidini G, et al. Recurrent tonic-clonic seizures and coma due to ingestion of type I pyrethroids in a 19-month old patient. Clin Toxicol 2013;51:497-500).

Table 23: Toxic effects of orally ingested pyrethroids

Mild pyrethroid toxicity	Moderate pyrethroid toxicity	Severe pyrethroid toxicity
Paresthaesia Nausea Headache Vomiting Dizziness Fatigue Anorexia	CNS depression Increased salivation Fasciculations Fever Diaphoresis Blurred vision	Seizures Coma Pulmonary oedema Respiratory failure

Exposure via inhalation:

For determination of the tolerability following exposure by the inhaled and topical routes of an insecticide spray aerosol with cyfluthrin, a human volunteer study was designed (study 44, see also Chapter 4.2.2). Initially it was intended to expose five healthy male volunteers to cyfluthrin twice – dependent on tolerability - for up to one hour. During the the first exposure session the used concentration should amount to ≤ 0.1 mg cyfluthrin/m^3 air and during the second session to 0.5-0.8 cyfluthrin/m^3 air. Furthermore, the exposure sessions should be 4h apart on the same day. However, the initial exposure concentration (≤ 0.1 mg cyfluthrin/m^3 air) was not tolerated and the higher exposure concentration was then cancelled. Laboratory analysis revealed that the initial actual concentration of the test substance had exceeded the defined concentration (ca. 0.2 mg cyfluthrin / m^3 air). The protocol was then amended to allow a further 5 subjects (no. 006-010), at a later date, to be exposed to a lower concentration of 0.075 mg cyfluthrin/m^3 air (corrected initial actual concentration: 0.1 mg cyfluthrin/m^3 air) for up to 1 h dependent upon tolerability. On this occasion, to alleviate anxiety, the subjects were exposed for 20 min to an atmosphere of placebo spray-can aerosol before exposure to the test substance. Adverse impact on human health was obtained by assessment of clinical pathology, ECG, urinanalysis, vital signs and irritation of mucous membranes. Whereas for the first exposure group (no. 001-005) preliminary pharmacokinetic data like drug concentrations in blood and plasma was obtained, data on drug concentrations of the second exposure group (no. 006-010) was limited to urine.
Only 2 of the 5 male volunteers in Group 1 tolerated the first exposure session for the defined period of 1 h. Adverse effects reported were: mild hyperaemia of the nasal mucosa, moderate nasal irritation (running nose), mild irritation of the throat, coughing, sneezing, and watering eyes.
No clinically significant or drug related abnormalities in vital signs, EKGs or clinical laboratory tests were observed after 1-h exposure to airborne cyfluthrin concentrations of up to 0.2 mg/m^3. The observed events were all expected side effects of the test substance with reference to preclinical studies and observations in agrochemical workers and reflected irritation of the mucous membranes of the nose, throat, upper respiratory tract and eyes in order of frequency. The adverse effects were all self-limiting and resolved within minutes after cessation of exposure. It can be concluded that the initial concentration of ≤ 0.1 mg cyfluthrin/m^3 air appeared to be in the range of an irritant threshold concentration for humans (see Chapter 4.2.1 Proposal for classification with STOT-SE 3).

Dermal:

Skin symptoms (paraesthesia) have been observed in people handling the active ingredient cyfluthrin or beta-cyfluthrin. Skin reactions such as pruritus, tautness and reddening of the facial skin, partial facial paraesthesia and signs of irritation in the oro-pharyngeal cavity or coughing, especially when concomitant with an elevated sensitivity, particularly to touch stimuli, may be signs of dermal contact with exposure via inhalation to cyfluthrin. These symptoms may appear immediately or shortly after contact with the substance. They may last up to 24 (rarely to 48) hours, and were often reported to be worsened by warmth (e.g. showering) (study 45).
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 skin irritation study in rabbits with beta-cyfluthrin (Study 42). There is no evidence for skin irritation as all mean scores for erythema, eschar formation as well as for oedema formation were 0. Therefore, and according to the "Guidance on the application of CLP criteria" (ECHA, 2012) no classification for skin irritation is needed.

Intravenous:

The American Journal of Emergency Medicine (Miller, 2014) reported that a 28-year-old man presented to the emergency department 20 minutes after injecting 20 mL of an insecticide containing 0.05 % beta-cyfluthrin. The cause for the injection remained unknown. The man showed sinus tachycardia as the only symptom and was treated with an intravenous fluid bolus of 2000 mL (ingredients unknown). After 3 hours he fully recovered.

Dermal / Inhalation:

The Occupational Health Branch (OHB) of the California Department of Health Services (CDHS) conducts surveillance of work-related pesticide illness with support from the National Institute for Occupational Safety and Health (NIOSH) and the U.S. Environmental Protection Agency (EPA). On May 12, 2005, CDHS received a report from the California Department of Pesticide Regulation (CDPR) of a suspected pesticide incident in Kern County involving 27 farmworkers (age range: 21-61 years; median: 32.5 years) and six emergency responders (age range: 28-51 years; median: 33.5 years). CDHS investigated this incident by conducting a site visit; reviewing medical and meteorological records; and interviewing affected workers, pesticide applicators, and the farmworker employer. Findings indicated that workers became ill from drift of a pyrethroid pesticide (cyfluthrin) that was being applied in a neighbouring field. Symptoms reported by the farmworkers were headache (96 %), nausea (89 %), eye irritation (70 %), muscle weakness (70 %), anxiety (67 %), and shortness of breath (64 %) (Study 46).

4.2.3 Summary and discussion of acute toxicity

The lowest LD_{50} values determined in acceptable studies with cyfluthrin were 14.3 mg/kg bw (Cremophor/water) in rats (Study 5) and 291 mg/kg bw (PEG 400) in mice (Study 14). The lowest LD_{50} values determined in acceptable studies with beta-cyfluthrin were 77 mg/kg bw (acetone/peanut oil, Study 22) in rats and 91 mg/kg bw (PEG 400) in mice (Study 25). The proposal for classification for acute oral toxicity is based on cyfluthrin (solvent: Cremophor/water; Study 5).

The LC_{50} values of cyfluthrin and beta-cyfluthrin were determined in rodents after exposure to dust. The lowest LC_{50} value for cyfluthrin determined in an acceptable inhalation study was 0.141 mg/L air (cyfluthrin in ethanol/PEG 400, 4h-exposure, head-nose only; study 33) and 0.047 mg/L air (cyfluthrin in ethanol/PEG 400, 5x6 h-exposure, nose only¸ study 32; supplemental study). Based on the worst-case LC_{50} value determined in an acceptable inhalation study (study 36), the LC_{50} 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 LC_{50} value after dust exposure was 0.532 mg/L air beta-cyfluthrin (4h-exposure, head-nose only) (study 36).

The dermal toxicity of cyfluthrin and beta-cyfluthrin is very low. The lowest dermal LD_{50} value in rats determined in an acceptable study with beta-cyfluthrin was used for classification decision (> 2000 mg/kg bw, solvent: PEG 400, study 42).

4.2.4 Comparison with criteria

The following table presents the critical results for acute toxicity used for classification and labelling and further lists the criteria required from CLP regulation.

Table 24: Results of acute toxicity studies in comparison with CLP criteria

Toxicological result	CLP criteria
Oral ATE, rat: 14.3 mg cyfluthrin/kg bw (Vehicle: Cremophor (water)	Cat. 2 (H300): 5 < ATE ≤ 50 mg/kg (oral)
Dermal ATE, rat: >2000 mg beta-cyfluthrin/kg bw (Vehicle: PEG 400)	Cat. 4 (H312): 1000 < ATE ≤ 2000 mg/kg (dermal)
Inhalation ATE, rat: 0.081 mg beta-cyfluthrin /L air (highest attainable conc. 0.097 mg/L, aerosol ethanol/PEG 400, as mist 4 h, head-nose only) Cyfluthrin inhalation ATE, mouse: 0.141 mg/L air (aerosol ethanol/PEG 400, 4 h, head-nose only)	Cat. 2 (H330): 0.05 < ATE ≤ 0.5 (dusts and mists)

4.2.5 Conclusions on classification and labelling

Based on the results listed above, the proposed classification and labelling for the rat oral ATE and inhalation ATE endpoint is

Acute Tox 2, H300 – Fatal if swallowed and

Acute Tox 2, H330 - Fatal if inhaled, respectively.

Cyfluthrin does not meet the criteria for dermal toxicity classification.

RAC evaluation of acute toxicity

Summary of the Dossier Submitter's proposal

Acute oral toxicity

The DS summarised data from 20 acute oral toxicity studies with cyfluthrin and six with beta-cyfluthrin. The acute oral toxicity of cyfluthrin depends on the vehicle, with Cremophor/water leading to the lowest LD_{50} values, down to 14.3 mg/kg bw for cyfluthrin (study 5). The lowest LD_{50} included in the CLH dossier for beta-cyfluthrin was 77 mg/kg bw from a study employing acetone/peanut oil as a vehicle (study 22), but the DS was not aware of any acute oral toxicity study with beta-cyfluthrin using Cremophor. The DS proposed classification as Acute Tox. 2 based on an LD_{50} of 14.3 mg/kg bw (study 5).

Acute dermal toxicity

Three acute dermal toxicity studies were available for cyfluthrin, all reporting LD_{50} values of >5000 mg/kg bw. However, these studies were considered supplementary by the DS

due to insufficient reporting. The DS proposed no classification for acute dermal toxicity based on a study with beta-cyfluthrin reporting an LD_{50} of >2000 mg/kg bw (study 42).

Acute inhalation toxicity

The DS summarised data from eight acute inhalation toxicity studies with cyfluthrin and two studies with beta-cyfluthrin. The DS proposed classification for cyfluthrin as Acute Tox. 2 based on an LC_{50} 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 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 LD_{50} 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.

Additional key elements

In their comment during public consultation, the manufacturer provided results from a non-guideline acute oral toxicity study in Wistar rats with beta-cyfluthrin using Cremophor as a vehicle (Anonymous, 1986) yielding an LD_{50} of 11 mg/kg bw. The study report was included the plant protection product (PPP) dossier of beta-cyfluthrin. Details of the study are presented in the table below.

Acute oral toxicity study (Anonymous , 1986)	
Method	**Observations**
Substance: beta-cyfluthrin technical, batch 16001/85 Vehicle: Cremophor EL/distilled water Species and sex: rat, male Kind of application: oral, fasted Doses: 10.0, 11.2, 12.5, 16.0 mg/kg bw Application volume: 10 mL/kg bw No. of animals per dose group: 5 Post-treatment observation period: 14 days	Mortality: 10.0 mg/kg bw: 1 out of 5 11.2 mg/kg bw: 1 out of 5 12.5 mg/kg bw: 4 out of 5 16.0 mg/kg bw: 5 out of 5 All animals at all doses showed clinical signs of toxicity LD_{50}: 11 mg/kg bw (10.7–12.6)

Assessment and comparison with the classification criteria

Acute oral toxicity

Out of the vehicles tested, aqueous Cremophor consistently yielded the lowest LD_{50} values for both cyfluthrin and beta-cyfluthrin. The rat LD_{50} values for cyfluthrin in Cremophor ranged between 14.3 and 20 mg/kg bw compared to ca. 160-250 mg/kg bw in acetone/oil. Other vehicles (including PEG 400) led to higher LD_{50} values.

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 LD_{50} in a relevant species should generally be used as a basis for classification. **RAC proposes to classify cyfluthrin for Acute Tox. 2; H300 with an ATE of 14 mg/kg bw** based on a rat acute toxicity study with cyfluthrin using aqueous Cremophor as a vehicle (study 5).

Acute dermal toxicity

Three acute dermal toxicity studies are available for cyfluthrin (studies 37, 38, 39; rat, vehicle Cremophor/water, PEG 400 or NaCl solution), all from the same author and all giving LD_{50} values of >5000 mg/kg bw. The available information on these studies is not very detailed.

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 LD_{50} values of >2000 mg/kg bw or >5000 mg/kg bw.

As all available dermal LD_{50} 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 LC_{50} in a standard acute study with cyfluthrin was 0.14 mg/L (study 33; mouse, head/nose only, vehicle ethanol/PEG 400; OECD TG 403, GLP). This LC_{50} value corresponds to Category 2 ($0.05 < ATE \leq 0.5$ mg/L). Thus, **RAC proposes to classify cyfluthrin as Acute Tox. 2; H330 with an ATE of 0.14 mg/L (dusts or mists).**

4.3 Specific target organ toxicity – single exposure (STOT SE)

4.3.1 Summary and discussion of Specific target organ toxicity – single exposure

4.3.2 Non-human information

Teratogenicity studies with exposure via inhalation in rats (study 77, 78) showed respiratory

disturbances and bradypnoea due to irritative aerosol concentrations of cyfluthrin.
In an inhalation study for embryotoxic effects with cyfluthrin (study 78), a physiological maternal compensation mechanism (hypothermia with respiratory alkalosis) followed by reflex bradypnoea due to sensory irritation (see section reproductive toxicity / teratogenicity) was observed. At doses of 11.9 and 12.8 mg cyfluthrin plus oxygen/m³ air clear signs of maternal toxicity occurred in the form of respiratory disturbances and hypoactivity in dams and a high-stepping gait and salivation at 11.9 mg/m³ air only. No gross pathological findings were recorded at necropsy of any dose group (including the satellite groups).
The animals of the lower dose groups exhibited a concentration-dependent hypothermia and bradypnoea (hypoventilation) after the 1st exposure at levels of 0.46 mg/m³ air and above. After the seventh exposure this hypothermia could still be determined in the high dose groups only, being less severe in the group with oxygen substitution. In the 2.55 mg/m³ air dose group concentrations were tolerated without an effect on body weight gain. No signs of toxicologically significant neurological or sensorimotor changes (reflex tests) were seen. Comparing the findings from the groups with and without oxygen substitution permits the conclusion that the increase in the partial pressure of oxygen in the inhalation chamber produced an attenuation of the maternal toxic effects. There were no significant differences in the plasma cyfluthrin levels in the groups with and without oxygen substitution.

4.3.3 Human information

For determination of the tolerability following exposure by the inhaled and topical routes of an insecticide spray aerosol with cyfluthrin, a human volunteer study was designed (Study 44). Initially it was intended to expose five healthy male volunteers to cyfluthrin twice – dependent on tolerability - for up to one hour. During the the first exposure session the used concentration should amount to ≤ 0.1 mg cyfluthrin/m^3 air and during the second session to 0.5-0.8 cyfluthrin/m^3 air. Furthermore, the exposure sessions should be 4h apart on the same day.
However, the initial exposure concentration (≤ 0.1 mg cyfluthrin / m^3 air) was not tolerated and the higher exposure concentration was then cancelled. Laboratory analysis revealed that the initial actual concentration of the test substance had exceeded the defined concentration (ca. 0.2 mg cyfluthrin / m^3 air). The protocol was then amended to allow a further 5 subjects (no. 006-010), at a later date, to be exposed to a lower concentration of 0.075 mg cyfluthrin / m3 air (corrected initial actual concentration: 0.1 mg cyfluthrin/m³ air) for up to 1 h dependent upon tolerability. On this occasion, to alleviate anxiety, the subjects were exposed to an atmosphere of placebo spray-can aerosol before the test substance. Adverse impact on human health was obtained by assessment of clinical pathology, ECG, urinanalysis, vital signs and irritation of mucous membranes. Whereas for the first exposure group (no. 001-005) preliminary pharmacokinetic data like drug concentrations in blood and plasma was obtained, data on drug concentrations of the second exposure group (no. 006-010) was limited to urine.

Only 2 of the 5 male volunteers in group 1 tolerated the first exposure session for the defined period of 1 h. Adverse effects reported were: mild hyperaemia of the nasal mucosa moderate nasal irritation (running nose), mild irritation of the throat, coughing, sneezing, and watering eyes.

Table 25: Group 1 – Adverse Effects

Volunteer No.	Initial expose con. (mg cyfluthrin / m3 air)	Time of exposure	Adverse effect	Severity	Reversibility
1	0.2	60 min	Hyperemia of nasal mucosa	Mild	yes

Volunteer No.	Initial expose con. (mg cyfluthrin / m3 air)	Time of exposure	Adverse effect	Severity	Reversibility
2	0.2	40 min	Hyperemia of nasal mucosa; Nose running clear mucous, Irritation of the throat	Mild/Moderate	yes
3	0.2	3 min	Coughing, Headache	Mild/Moderate	yes
4	0.2	60 min	Nose running, sneezing., eyes watering, intermittent coughing	Mild	yes
5	0.09	25 min	Nose streaming, nasal muscosa injected	Mild	yes

All 5 volunteers in group 2 tolerated a 20 min exposure to placebo spray-can aerosol to alleviate anxiety before the second exposure session and no adverse events were reported. All 5 volunteers tolerated the second exposure session for 1 h and 5 adverse events that were considered to be 'definitely' related to the test substance were reported. A single volunteer had objective evidence of mild hyperaemia of the nasal mucosa.

Table 26: Group 2 – Adverse Effects

Volunteer No.	Initial expose con. (mg cyfluthrin / m3 air)	Time of exposure	Adverse effect	Severity	Reversibility
6	0.1	60 min	Nasal irritation	Mild	yes
7	0.1	60 min	Nasal irritation	Mild	yes
8	0.1	60 min	No adverse effects noted	-	-
9	0.1	60 min	Nose running, irritation at back of throat	Mild	yes
10	0.1	60 min	Irritation at back of throat	Mild	yes

No clinically significant or drug related abnormalities in vital signs, EKGs or clinical laboratory tests were observed after 1-h exposure to airborne cyfluthrin concentrations of up to 0.2 mg/m³. The observed events were all expected side effects of the test substance with reference to preclinical studies and observations in agrochemical workers and reflected irritation of the mucous membranes of the nose, throat, upper respiratory tract and eyes in order of frequency. The adverse effects were all self-limiting and resolved within minutes after cessation of exposure. It can be concluded that the initial concentration of 0.1 mg cyfluthrin/m^3 air appeared to be in the range of an irritant threshold concentration for humans.

Based on the results obtained in this study, further information of people handling the active ingredient cyfluthrin (synthesis laboratory, manufacturing plant, formulation plant, toxicological laboratory) included signs of irritation in the oro-pharyngeal cavity and the eyes beside skin effects (Study 52-54).

Beside skin symptoms (paraesthesia), signs of irritation in the oro-pharyngeal cavity or coughing, were reported after inhalation exposure to cyfluthrin. These symptoms may appear immediately or shortly after contact with the substance, they may last up to 24 (rarely to 48) hours, and it was often reported to be worsened by warmth (e.g. showering). Likewise, symptoms reported from occupational

airborne exposures were skin irritation and/or “Cold Burn”, the paresthesias typical for skin contact to alpha-cyano pyrethroids, and airway irritation, in some cases provoking asthma-like reactions (no further details is reported) (Study 45).

4.3.4 Summary and discussion of Specific target organ toxicity – single exposure

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, 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.
The severity of the effects and the human health impact can indicate a borderline case for cyfluthrin classification criteria (e.g. even as STOT-SE, cat. 2). That is because the evidence in humans (asthma-like reactions, mild hyperaemia of the nasal mucosa, moderate nasal irritation, mild irritation of the throat, coughing, sneezing, and watering eyes) can also indicate a cytotoxic/inflammatory reaction.
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 (Guidance on the Application of the CLP criteria, p. 434). However, 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 (e.g. no appropriate histopathologic investigation of respiratory tract reported). Therefore, in order to make the user aware of the need for protection, the designation of Specific target organ toxicity-Single exposure, Cat. 3 May cause respiratory irritation (STOT SE; 3 H335) is proposed.

4.3.5 Comparison with criteria

Table 27: Categories for specific target organ toxicity-single exposure

Toxicological result	CLP criteria
Transient irritation of the mucous membranes (oro-pharyngeal cavity)	Transient target organ effects The category 3 only includes narcotic effects and respiratory tract irritation. These are target organ effects for which a substance does not meet the criteria to be classified in Categories 1 or 2. These are effects which adversely alter human function for a short duration after exposure and from which humans may recover in a reasonable period without leaving significant alteration of structure or function.

4.3.6 Conclusions on classification and labelling

Classification and labelling for respiratory irritation according to Regulation (EC) No 1272/2008 (GHS): STOT-SE 3, H335 (May cause respiratory irritation) based on data from cyfluthrin studies.

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 toxicity study 35 with beta-cyfluthrin reported hyperaemia of the visible nasal mucosa (as a clinical sign) from 11 mg/m^3 (LC_{50} ca. 90 mg/m^3; head/nose only, vehicle PEG/ethanol). However, no hyperaemia and no histopathological findings in the respiratory tract were observed at 24 mg/m^3 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/m^3. The findings included hyperaemia of nasal mucosa, running nose and coughing.

Human volunteer study, 1st 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/m^3 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, 2nd 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. Still, 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/m^3 (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/m^3 (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 = 14 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 = 0.14 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.

4.4 Irritation

4.4.1 Skin irritation

4.4.1.1 Non-human information

Cyfluthrin is not irritating to the skin. This result is supported by skin irritation studies with beta-cyfluthrin.

Table 28: Summary table of relevant skin irritation studies with cyfluthrin*

Parameter	Species	Vehicle	Result	Reference
skin irritation (GLP: no, unpublished)	Rabbit (Albino Japanese) 6 females	Undiluted (cyfluthrin lot no. Eg 3/81, purity: 95 %)	non-irritant[2,3]	Study 47
skin irritation (GLP: no, unpublished)	Rabbit (White New Zealand) 6 males	Unclear (cyfluthrin batch no. 16001/79, purity: 83.6 %)	non-irritant[2,3]	Study 48

* Not-acceptable studies were not included.
[2] The study is considered supplementary.
[3] These studies were not submitted by the applicant (but available to RMS e.g. from other procedures).

Table 29: Summary table of relevant skin irritation studies with beta-cyfluthrin*

Parameter	Species	Vehicle	Result	Reference
skin irritation (GLP: yes, OECD 404)	Rabbit (3 female albino Esd:NZW rabbits)	Water beta-cyfluthrin (batch no.: FFEBCTQ043, purity: 99.2 %)	non-irritant	Study 49 †

* Not-acceptable studies were not included.

†Key study

4.4.1.2 Human information

Skin symptoms (paraesthesia) have been observed in people handling the active ingredient cyfluthrin. Skin reactions such as pruritus, tautness and reddening of the facial skin, partial facial paraesthesia and signs of irritation in the oro-pharyngeal cavity or coughing, especially when concomitant with an elevated sensitivity, particularly to touch stimuli, may be signs of dermal contact with or inhalation exposure to cyfluthrin. These symptoms may appear immediately or shortly after contact with the substance, they may last up to 24 (rarely to 48) hours, and it was often reported to be worsened by warmth (e.g. showering). Likewise, symptoms reported from airborne exposures were skin irritation and/or "Cold Burn", the paresthesias typical for skin contact to alpha-cyno pyrethroids, and airway irritation, in some cases provoking asthma-like reactions. These too, are well known for pyrethroids (Study 45).
In order to make the user aware of the need for protection, the designation of STOT-SE 3 H335 'May cause respiratory irritation' according to Regulation (EC) No 1272/2008 is proposed (see Chapter 4.2.1).
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 skin irritation studies in rabbits (Study 47, 48, 49). There is no evidence for skin irritation as all mean scores for erythema, eschar formation as well as for oedema formation were 0. Therefore, and according to the "Guidance on the application of CLP criteria" (ECHA, 2012) no classification for skin irritation is needed.

4.4.1.3 Summary and discussion of skin irritation

Cyfluthrin is not irritating to the skin.

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 skin irritation study in rabbits (study 49). There is no evidence for skin irritation as all mean scores for erythema, eschar formation as well as for oedema formation were 0. Therefore, and according to the "Guidance on the Application of CLP criteria" (ECHA, 2012) no classification for skin irritation is needed.

4.4.1.4 Comparison with criteria

The following table presents the critical results for skin irritation used for classification and labelling and further list the criteria required from CLP regulation.

Table 30: Results of skin irritation tests in comparison with CLP criteria*

Toxicological result	CLP criteria
Mean erythema and oedema scores (24-72 h): 0.0 and 0.0, respectively (no animal ≥2.3). (Study 49)	Irritating to skin (Category 2, H315): at least in 2/3 tested animal a positive response of: Mean value of ≥2.3-≤4.0 for erythema/eschar or for oedema

* Only acceptable studies were used for classification.

4.4.1.5 Conclusions on classification and labelling

Based on the results above, no classification regarding skin irritation/corrosion is triggered.

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 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 based on the guideline study 49 with additional support of the non-guideline study 47.

4.4.2 Eye irritation

4.4.2.1 Non-human information

Table 31: Summary table of relevant eye irritation studies with cyfluthrin*

Parameter	Species	Vehicle	Result	Comment	Reference
eye irritation (GLP: no, unpublished)	Rabbit (Albino Japanese) 12 female	Undiluted (cyfluthrin lot no. Eg 3/81, purity 95 %)	irritant[1,2,3]	-cyfluthrin used in melted state -observation period only 3 days (TG 404, 1981) -only 100 µl instead of 500 µl tested (TG 404,	Study 47

				1981) -24 h instead of 4 h exposure (TG 404, 1981) -skin observed after 24 h and 72 h (not 48 h) (TG 404, 1981)	
eye irritation (GLP: no, unpublished)	Rabbit (White New Zealand) 3-5 males	Unclear (cyfluthrin batch no. 16001/79, purity: 83.6 %)	irritant[2,3, 4]	-24 h instead of 4 h exposure (TG 404, 1981) -material section refers to document which is not available -some details remain unclear (e.g. whether substance is moistened)	Study 48

[*] Not-acceptable studies were not included.
[1] From the data given it remains unclear whether from today's perspective the outcome would be positive, too.
[2] The study is considered supplementary.
[3] These studies were not submitted by the applicant (but available to RMS e.g. from other procedures).
[4] If gradings are comparable with today, the substance would be considered as not irritating to eyes (based on mean scores after 24, 48, 72 h).

Table 32: Summary table of relevant eye irritation studies with beta-cyfluthrin*

Parameter	Species	Vehicle	Result	Reference
eye irritation (GLP: yes, OECD 405)	Rabbit (3 male albino HC:NZW rabbits)	Unclear (beta-cyfluthrin batch no.: 16002/84, purity: 98.5 %)	non-irritant[1]	Study 50 †
eye irritation (GLP: yes, OECD 405)	Rabbit (3 female albino HsdIf:NZW rabbits)	Undiluted (beta-cyfluthrin batch no.: FFEBCTQ043, purity: 99.2 %)	non-irritant[1]	Study 51 †

* Not-acceptable studies were not included.
[1] Slight effect, does not fulfil the criteria for classification.
† Key study

Eye irritation studies with cyfluthrin (Table 31) showed a minimally irritating effect in Japanese rabbits (Study 47). It was assumed that the substance has some sensory irritant effect, because after treatment animals rubbed both eyes with both paws. Also technicians felt a sense of irritation after handling of the test substance. Observation and scoring for cornea, iris and conjunctivae were examined at 1, 3, 6, 24 hours and 2, 3, and 7 days after treatment. The treatment had no effect on the cornea. In the non-irrigation group, hyperemia of the iris was seen in two animals at 1 hour after the application. The effect disappeared after 6 hours post application. Redness, chemosis and secretion of the conjunctiva were seen regardless of non-irrigation or irrigation. Cyfluthrin was considered to be mildly irritating to the eye. Anyhow, a conclusion for classification cannot be drawn from this study as it remains unclear whether from today's perspective the outcome would be evaluated as positive (e.g. scoring not consistent with OECD TG and observation time < 21 days). Likewise, in study 48 redness of the conjunctivae was noted up to 72 hours post application, slight chemosis up to 24 hrs after application. The findings were all reversible. If gradings are comparable with today, the substance would be considered as not irritating to eyes (based on mean scores after 24, 48, and 72 h). Therefore, based on the severity and the reversibility of these findings classification is not warranted.

The following results were obtained with beta-cyfluthrin (study 50): Slightly irritating effects were noted after 1 h and 24 h to the conjunctivae (redness, swelling, tear flow). Considering the time points 24, 48 and 72 h, the mean values for corneal opacity and iritis were 0 and for all conjunctival parameters not above 1.3. All effects observed were reversible. Beta-cyfluthrin showed a slightly irritating effect on the eye but according to the EC criteria, beta-cyfluthrin is not to be classified as irritating to eyes.

Table 33: Test for irritant/corrosive impact of the test compound beta-cyfluthrin on the rabbit's eye (study 50)

Animal no.	grade after#																Mean value after			
	24h				48h				72h				7d				24h, 48h, 72h			
	CO	IR	CR	COE	CO	IR	CR	COE	CO	IR	CR	COE	CO	IR	CR	COE	CO	IR	CR	COE
J1	0	0	2	2	0	0	1	1	0	0	1	0	0	0	0	0	0	0	1.3	1
M27	0	0	2	1	0	0	1	1	0	0	1	0	0	0	0	0	0	0	1.3	0.7
M24	0	0	1	1	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0.7	0.3

CO = corneal opacity, IR = iritis, CR = conjunctival redness, COE = conjunctival oedema.

In addition, in the 2nd eye irritation study with beta-cyfluthrin (study 51) similar findings were noted: Three rabbits showed conjunctival erythema (Grade 1-2) and 2/3 animals chemosis (Grade 1) after

24 h post application. In one animal grade-1 conjunctival erythema persisted until 48 h post application. None of the animals showed signs of eye irritation at 72 h post application. Iris and cornea were not affected by treatment at any time point. Thus, beta-cyfluthrin is not irritating to eyes.

Table 34: Test for irritant/corrosive impact of the test compound beta-cyfluthrin on the rabbit's eye (study 51)

Animal no.	grade after#												Reversibility (days)				Mean value after			
	24h				48h				72h								24h, 48h, 72h			
	CO	IR	CR	CC	CO	IR	CR	CC	CO	IR	CR	CC	CO	IR	CR	CC	CO	IR	CR	CC
1	0	0	2	1	0	0	1	0	0	0	0	0	n.a.	n.a	3	2	0	0	1	0.3
2	0	0	1	0	0	0	0	0	0	0	0	0	n.a	n.a	2	1*	0	0	0.3	0
3	0	0	2	1	0	0	0	0	0	0	0	0	n.a	n.a	2	2	0	0	0.7	0.3

CO = corneal opacity, IR = iritis, CR = conjunctival redness, CC = chemosis conjunctivae, n.a: not applicable
* = in respect of the result 1 h post application.

4.4.2.2 Human information

Skin and eye symptoms have been observed in workers in connection with the handling of cyfluthrin (Study 52, 53, 55, 56).The observations relate to people who have handled the active substance (synthesis laboratory, manufacturing plant, formulation plant, toxicological laboratory). Symptoms included skin reactions such as pruritus, tautness and reddening of the facial skin, partial facial paraesthesia, signs of irritation in the oro-pharyngeal cavity and the eyes. After onset of the irritation signs, an elevated sensitivity, particularly to touch stimuli, was observed. The effects were reversible within a few hours.

No health problems or changes in well-being were mentioned in connection with handling of cyfluthrin when the work rules were observed. Conclusions were drawn that by precautionary measures such as the wearing of protective clothing and avoidance of direct and indirect contamination of the relevant skin areas and the eyes, effects of cyfluthrin can be prevented.

Extensive training, more sophisticated plant technology and stricter protective measures are needed when handling the active ingredient cyfluthrin as a dust formulation. Even slight contact of dust with the skin or mucosa of the eye, initially unnoticed, results in an unpleasant irritation and burning sensation at the site of contact within a few hours (first signs generally occur after showering) (study 54).

In a human volunteer study, inhalation exposure to different concentrations of cyfluthrin resulted in irritation of the eyes, and beside other adverse effects (irritation of the mucous membranes of the nose, upper respiratory tract, and throat) (study 44) (see also Chapter 4.3.1 Proposal for classification with STOT-SE 3).

The Occupational Health Branch (OHB) of the California Department of Health Services (CDHS) conducts surveillance of work-related pesticide illness with support from the National Institute for Occupational Safety and Health (NIOSH) and the U.S. Environmental Protection Agency (EPA). In 2005, CDHS received a report from the California Department of Pesticide Regulation (CDPR) of a suspected pesticide incident in Kern County involving 27 farmworkers (age range: 21-61 years; median: 32.5 years) and six emergency responders (age range: 28-51 years; median: 33.5 years). After spraying of a cyfluthrin containing pesticide the following symptoms were reported by the exposed farmworkers: headache (96 %), nausea (89 %), eye irritation (70 %), muscle weakness (70 %),

anxiety (67 %), and shortness of breath (64 %). Illness symptoms were not reported by the applicators, who were wearing appropriate protective equipment (study 46). See also chapter 4.1.2 Human information – Dermal / Inhalation.

During the production period since 2005 two accidents with beta-cyfluthrin occurred in workers, both being irritation of face and eyes, respectively, which both resolved very quickly. This effect is well known for pyrethroids. No further consultations of the Medical Department due to handling or contact with beta-cyfluthrin were required (study 45).

4.4.2.3 Summary and discussion of eye irritation

Eye irritation studies in rabbits revealed slight or no eye irritating effects and do not trigger a proposal for classification. Human data showed some slight, reversible eye symptoms on different occasions, mainly in connection with the handling of cyfluthrin and beta-cyfluthrin. No former proposal on classification for eye irritation was made.

4.4.2.4 Comparison with criteria

The following table compares the critical results for eye irritation used for classification and labelling and further list the criteria given in the CLP regulation.

Table 35: Results of eye irritation studies in comparison with CLP criteria*

Toxicological result	CLP criteria
Mean score (24-72 h): corneal opacity: 0.0 (no animal ≥1) iris leson: 0.0 (no animal ≥1) conjuntival redness: not above 1.3 (no animal ≥2) oedema of the conjunctivae (chemosis): not above 1 (no animal ≥2) (study 50) Mean score (24-72 h): corneal opacity: 0.0 (no animal ≥1) iris leson: 0.0 (no animal ≥1) conjuntival redness: not above 1.0 (no animal ≥2) oedema of the conjunctivae (chemosis): not above 0.3 (no animal ≥2) (study 51)	Irritating to eyes (Category 2, H319): at least in 2/3 tested animal a positive response of: corneal opacity: ≥1 and/or iritis: ≥1 and/or conjunctival redness: ≥2 and/or conjunctival oedema (chemosis): ≥2 Calculated as the mean scores following grading at 24, 48 and 72 hours after installation of the test material, and which fully reverses within an observation period of 21 days.

* Only acceptable studies were used for classification.

4.4.2.5 Conclusions on classification and labelling

Based on the results above, no classification regarding eye irritation/corrosion is triggered.

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 based on the guideline-compliant *in vivo* studies with beta-cyfluthrin (study 50 and 51).

4.4.3 Respiratory tract irritation

On the basis of the findings mentioned above, it is proposed to also classify beta-cyfluthrin for respiratory irritating properties (see Chapter 4.3: Specific target organ toxicity – single exposure (STOT-SE)).

4.5 Corrosivity

Cyfluthrin does not meet the criteria for skin/eye irritation/corrosion. Thus, no classification is triggered.

4.5.1 Conclusions on classification and labelling

Based on the results of the studies on acute dermal toxicity, skin and eye irritation studies, no classification regarding skin/eye corrosion is triggered.

4.6 Sensitisation

4.6.1 Skin sensitisation

4.6.1.1 Non-human information

Table 36: Summary table of relevant skin sensitisation studies with cyfluthrin*

Parameter	Species	Vehicle	Result	Comment	Reference
Skin sensitization (GLP: yes, Magnussen Kligman Test)	Guinea pig (Hsd/Win:DH) 50 male	PEG 400 (cyfluthrin batch no. 380368010, purity 96.2 %) -Intraderm. ind.: 5 % -Topical Ind.: 50 % -Challenge: 50 % and 25 %	no sensitizer[1]	-unclear why dose-range-finding study was not extended to higher concentrations (TG 406 1992)	Study 57 †

* Not-acceptable studies were not included.
†Key study

Table 37: Summary table of relevant skin sensitisation studies with beta-cyfluthrin*

Parameter	Species	Vehicle	Result	Reference
Skin sensitization (Buehler Patch Test) (GLP: yes, OECD 406)	Guinea pig (Crl:HA) (10 females)	cremophor/saline beta-cyfluthrin (batch no.: FFEBCTQ043, purity: 99.2)	no sensitizer[1]	Study 58

* Not-acceptable studies were not included.
[1] The study is considered supplementary.

No evidence of a skin-sensitizing potential was found in a Magnussen Kligman Test in guinea pigs with cyfluthrin (Study 57) and a Buehler Patch Test with beta-cyfluthrin (Study 58). The Buehler Patch Test with beta-cyfluthrin was considered supplemental based on the following deviations of OECD-Guideline no. 406 (adopted in July 17, 1992):

1. Dose-range-finding studies were performed in order to find the dose for sensitization induction and challenge. OECD-Guideline no. 406 requires the highest dose to cause mild irritation for the induction exposure. For challenge exposure the highest non-irritating dose should be applied. A test item concentration of 66.6 % was chosen for the induction and challenge procedure even though no skin reaction was observed in the whole pilot study. This concentration did not show a mild irritation (for induction) and it is unclear whether this concentration matches the highest non-irritating dose (for challenge).Therefore, it remains questionable why the dose-range-finding study was not extended to higher concentrations above 66.6 % to investigate possible skin irritating effects at higher concentrations.
2. Although the test for skin sensitisation was conducted with a concentration of 66.6 %, both analyses for stability and homogeneity were performed with 0, 1 and 40 % but not with 66.6 %

of the test item. Neither a rationale for this study deviation nor the method of these analyses was given.

3. Occlusive conditions were neither claimed nor documented for the main study.
4. This Buehler Patch Test was conducted with three applications only. Nine applications are considered valid for the evaluation of skin sensitization (EFSA Handbook for the experts' meetings, Section 2: Mammalian toxicology, 2010).

4.6.1.2 Human information

No information on skin sensitisation in humans is available.

4.6.1.3 Summary and discussion of skin sensitisation

Results of the GPMT (study 57) (5 % of animals with erythema at >1 % intradermal induction dose) and the absence of skin effects in the Buehler test (Study 58) do not show evidence of a skin-sensitizing potential.

4.6.1.4 Comparison with criteria

Table 38: Results of skin sensitisation tests in comparison with CLP criteria

Toxicological result	CLP criteria
Intradermal induction 5 % Cyfluthrin (in PEG 400) Topical induction: 50 % Cyfluthrin (in PEG 400) Challenge: 25 % and 50 % Cyfluthrin (in PEG 400) No skin reaction at 48 h after challenge; 1/20 animals showed skin reddening at 72 h after challenge (Study 57)	Category 1B (H317): ≥ 30 % to <60 % responding at > 0.1 % to ≤ 1 % intradermal induction dose or ≥30 % responding at >1 % intradermal induction dose
There were no skin effects in the animal of the test item group and the control group during the three induction treatments. The challenge with the 66.6 % test item paste did not lead to skin effects in the animals of the test item group and in the control group. The study was considered supplemental (Study 58).	Category 1B (H317): ≥ 15 % to < 60 % responding at > 0.2 % to ≤ 20 % topical induction dose or ≥ 15 % responding at > 20 % topical induction dose

4.6.1.5 Conclusions on classification and labelling

Cyfluthrin does not meet the criteria for skin sensitization. Thus, no classification is triggered.

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

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

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 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 based on a negative GPMT with cyfluthrin (study 57) and a negative Buehler test with beta-cyfluthrin (study 58).

4.6.2 Respiratory sensitisation

No data available.

4.7 Repeated dose toxicity

4.7.1 Non-human information

4.7.1.1 Repeated dose toxicity: oral

Table 39: Summary table of relevant repeated dose oral toxicity studies with cyfluthrin*

Study	Dose levels	Test substance	NO(A)EL [mg/kg bw/d]	Targets / Main effects	Reference
90-day oral (feeding) toxicity in rats (GLP: no, Partly OECD 408)	0-100-300-1000 ppm (corr. to 6.21-18.98-60.90 mg/kg bw/d males, 7.29-21.22-68.47 mg/kg bw/d females) Sprague-Dawley rats (28 males and 28 females/group)	Cyfluthrin, batch no.: 816170019, purity: 95 % no vehicle (covered in basal diet)	100 ppm (6.21 mg/kg bw/d)	≥300ppm: Gait abnormalities, salivation, slight axonal degeneration of sciatic nerve (reversible)	Study 59 †
12-month, feeding, Beagle dog (GLP: yes, OECD 452)	0-1.36-2.43-10.64-15.47 mg/kg bw/d in males 0-1.46-3.61-10.74-17.99 mg/kg bw/d in females (corr. to 0-50-100-360-640/500 ppm) Beagle dogs (4 males and 4 females/group)	Cyfluthrin, batch no.: 4030059/BF9340-71, purity: 94.8-95.1 % no vehicle (covered in basal diet)	2.43 / 3.61 mg/kg bw/d (100 ppm)	640/500 ppm: Premature sacrifice for welfare reasons ≥360 ppm: reduced bw, neurological disorders (gait abnormalities)	Study 60 †

* Not-acceptable studies were not included.

†Key study

Table 40: Summary table of relevant repeated dose oral toxicity studies with beta-cyfluthrin

Study	Dose levels	Test substance	NO(A)EL [mg/kg bw/d]	Targets / Main effects	Reference
28-day, gavage; Wistar rat (4-week recovery) (GLP: yes, OECD 407)	0-0.25-1-4-16 mg/kg bw/d (5 males and 5 females/group)	Beta-cyfluthrin batch no.: 16002/84, purity: 98.5 % Vehicle: Cremophor/water	1	≥4 mg/kg bw/d: Mortality, clinical signs, reduced bw development, increased liver weight	Study 61 †
90-day, feeding; Wistar rat (GLP: yes, OECD 408)	Males: 2.3, 9.5, 38.9/37* mg/kg bw/d Females: 2.5, 10.9, 42.4/43* mg/kg bw/d * Recovery (correspond to: 0, 30, 125 and 500 ppm) (15 males and 15 females/group)	Beta-cyfluthrin batch no.: 16001/85, purity: 99.7 % no vehicle (covered in basal diet)	9.5/10.9 (125 ppm)	≥500ppm: Mortality, clinical signs, reduced bw and water intake, skin lesions, reduced red blood cell parameters, increased calcium levels in urine	Study 62 †
90-day, feeding; beagle dog (GLP: yes, OECD 409)	0-0.4-2.4-14 mg/kg bw/d (correspond to 0-10-60-360 ppm) Beagle dogs (4 males and 4 females/group)	Beta-cyfluthrin batch no.: 16001/85, purity: 99.7 % no vehicle (covered in basal diet)	2.4 22.1 mg/animal/d (60 ppm)	14 mg/kg bw/d: Motor disturbances (hind limb), vomiting, diarrhea, reduced bw	Study 63 †

† Key study

In short-term toxicity experiments in rats and dogs oral administration of cyfluthrin or beta-cyfluthrin led to similar adverse effects: increased mortality, general behavioural disturbances, motor disturbances, lower body weight development, choreoathetotic signs, vomiting and diarrhea. No relevant effects on haematological, clinico-chemical and urine analytical parameters were detected. With the exception of a 3-month oral study in rats in which a reversible slight axonal degeneration was reported in some rats dosed with 1000 ppm (60.9 mg/kg bw/d) (Study 59, see Table 43), gross or histopathological investigations did not afford any evidence of specific organ or tissue damage. This concerned also the tissues nerve, muscle, eye, which were investigated in detail in a 28-day study on rats with beta-cyfluthrin (Study 61).
A slight increase in liver weight, noticed in the 4-week rat study with beta-cyfluthrin (study 61) was not observed in a 13-week rat study at a higher dose of beta-cyfluthrin (study 62, see Table 42). Alterations (clinical signs, reduced body weight development, increased liver weight) during the course of 4-week test substance exposure were reversible in a recovery period without test substance intake.

The resulting NOAEL of 125 ppm in the 13-week study on rats with beta-cyfluthrin, corresponding to 9.5 mg/kg bw/d in male and 10.9 mg/kg bw/d in female rats was based on mortalities, clinical signs and a reduction of body weight gain at the next higher dose (500 ppm).

In a 90-day study on dogs with beta-cyfluthrin (study 63, see Table 44) the NOAEL of 60 ppm, equal to 2.4 mg/kg bw/d, was based on motor disturbances, vomiting, diarrhea in males and females and a reduced body weight gain in females at the next higher dose of 360 ppm. A 12-month feeding study in dogs with cyfluthrin (study 60, see Table 41) revealed slight to severe motor disturbances, vomiting, diarrhea and a reduction in body weight gain at ≥360 ppm (10.6-18 mg/kg bw/d). The study revealed a NOAEL of 100 ppm (2.4/3.6 mg/kg bw/d). This study supersedes the 12-month feeding study in dogs (study 64, see Table 45) which was considered not acceptable.

Table 41 Detailed findings in study 60

Detailed study findings							
Endpoint	**Sex**	**Concentration (ppm)**					**Comment**
		0	**50**	**100**	**360**	**500/640**	
No. animals/ group	Male/Female	4/4	4/4	4/4	4/4	4/4	
Mortalities	Male/Female	1/1	0/0	0/0	0/0	0/1	Control animals died from asymptomatic idiopathic epilepsy. High dose animal was sacrificed due to a compound-related neurologic condition.
Clinical signs							
Neurotoxicity signs (%)	Combined sexes	0	0	0	7 (87)	8 (100)	
Neuromuscular condition (%)	Combined sexes	1 (12)	0	0	0	2 (25)	
Body weight [g] at Day 371 (% control)	Male	13969 (100%)	13484 (97%)	13888 (99%)	14748 (106%)	11575 (83%)	No compound related effect on food consumption was observed. A non-statistically significant trend toward decreased body weight was noted in the high dose group.
	Female	13588[D] (100%)	10412 (77%)	11385 (84%)	10721 (79%)	10382 (76%)	
Ovary abs. wt (g) (% control)	Female	1.940 (100%)	0.889* (46%)	1.217* (63%)	1.034* (53%)	0.789* (41%)	In the absence of statistically significant changes in relative ovary weight and the lack of corresponding histopathological changes, changes in ovary weight are considered unlikely to be treatment-related
Ovary rel. wt (%) ± SD (% control)	Female	0.014 ± 0.001 (100%)	0.009 ± 0.002 (64%)	0.011 ± 0.003 (79%)	0.010 ± 0.005 (71%)	0.008 ± 0.002 (57%)	
Gross Pathology/ Histopathology	Male/Female	-	-	-	-	-	No substance-related gross pathology or histopathology findings were observed.

* = $p \leq 0.05$; D= Premature death of small female from the control group has biased the mean upward in this group; abs. wt = absolute weight; rel. wt = relative weight

Table 42 Detailed findings in study 62

Endpoint	Sex	Concentration [ppm]			
		0	30	125	500
No. animals/group (No. animals/ 4-week recovery group)	Male/Female	15/15 (15/15)	15/15	15/15	15/15 (15/15)
Mortality (recovery group)	Male/Female	0/0 (0/0)	2/1	0/1	1/0 (1/0)
Clinical signs					
Necrosis in head/neck region (maximum incidence)	Male/Female	0/0	0/0	0/0	4/4 (week 2-11)
Uncoordinated gait (maximum incidence)	Male/Female	0/0	0/0	0/0	14/14 (week 1-5)
Poor general condition (maximum incidence)	Male/Female	0/0	0/0	0/0	14/14 (week 1-5)
Haematology					
Erythrocytes (tera/L) after 4 weeks treatment	Male/Female	6.81/7.14	6.89/6.92	7.11/6.94	6.74/6.68**
Erythrocytes (tera/L) after 13 weeks treatment	Male/Female	8.26/7.80	7.99/7.82	8.14/7.81	7.84*/7.48
Haemoglobin (g/L) after 4 weeks treatment	Male/Female	144/146	147/142*	146/140**	133**/138**
Haemoglobin (g/L) after 13 weeks treatment	Male/Female	155/142	149/142	152/148	148/141
Haematocrit (L/L) after 4 weeks treatment	Male/Female	0.453/0.446	0.467/0.439	0.467/0.431**	0.423**/0.427**
Haematocrit (L/L) after 13 weeks treatment	Male/Female	0.472/0.449	0.461/0.435	0.462/0.444	0.456/0.431
Body weight [g] after 13 weeks	Male	324 -	328 (101)	317 (98)	292** (90)

Endpoint	Sex	Concentration [ppm]			
		0	30	125	500
treatment main group (% control)	Female	184 - 	180 (98) 	185 (101) 	172 (93)
Body weight [g] after 13 weeks treatment (% control) (after 4 weeks recovery) recovery group	Male	306 - 331 -	- 	- 	283** (92) 311 (94)
	Female	178 - 193 -	- 	- 	174 (98) 185* (96)
Liver weight [mg] after 13 weeks treatment	Male, abs. (rel.)	12406 (3774)	11949 (3554*)	11997 (3686)	11299* (3738)
	Male, abs. (rel.) [% control]	100 (100)	96 (94)	97 (98)	91 (99)
	Female, abs. (rel.)	6519 (3441)	6516 (3535)	6570 (3465)	6562 (3708**)
	Female, abs. (rel.) [% control]	100 (100)	100 (103)	101 (101)	101 (108)
Pathology/ Histopathology	Male/Female	-	-	-	-

*=p<0.05; **=p<0.01
abs = absolute weight
rel = liver weight relative to 100 g terminal body weight

Table 43 Detailed findings in study 59

Endpoint	Sex	Concentration (ppm)			
		0	100	300	1000
animals/group (No. animals/ 4-week recovery group)	Male/Female	20/20 (8/8)	20/20 (8/8)	20/20 (8/8)	20/20 (8/8)
Mortality (recovery group)	Male/Female	0/0 (0/0)	0/0 (0/0)	1/0 (0/0)	0/0 (0/0)
Clinical signs observed during 13 week treatment					
Straddle gait	Male	0/20	0/20	0/20	16/20
	Female	0/20	0/20	0/20	15/20
Salivation	Male	0/20	0/20	0/20	5/20
	Female	0/20	0/20	0/20	5/20
Body weight [g] ± SD Main study group	Male after 13 weeks treatment	447 ± 32 (100)	442 ± 44 (99)	436 ± 38 (98)	394 ± 40** (88)

Endpoint	Sex	Concentration (ppm)			
		0	**100**	**300**	**1000**
(% of control) °	Female after 13 weeks treatment	251 ± 22 (100)	254 ± 21 (101)	247 ± 18 (98)	227 ± 24** (90.5)
Body weight [g] ± SD recovery group (% of control) °	Male after 13 weeks treatment	463 ± 43 (100)	450 ± 71 (97)	429 ± 32 (93)	396 ± 24** (86)
	Male after 4 weeks recovery	503 ± 50 (100)	490 ± 75 (97)	466 ± 35 (93)	435 ± 29** (86)
	Female after 13 weeks treatment	248 ± 18 (100)	247 ± 21 (100)	245 ± 15 (99)	230 ± 9* (93)
	Female after 4 weeks recovery	268 ± 23 (100)	251 ± 27 (94)	259 ± 17 (97)	252 ± 18 (94)
Organ weights		-	-	-	-
Pathology/ Histopathology Sciatic nerve, single fibre degeneration after 13 weeks treatment (after 4 weeks recovery)	Male	0	0	0	5 (1)
	Female	0	0	0	3 (0)

*=p<0.05; **=p<0.01
°= no statistical analysis performed

Table 44 Detailed findings in study 63

Endpoint	Sex	Concentration (ppm)			
		0	**10**	**60**	**360**
No. animals/group	Male/Female	4/4	4/4	4/4	4/4
Mortality	Male/Female	0/0	0/0	0/0	0/0
Clinical signs					
Motor disturbance (total occurrence)	Male/Female	0/0	0/0	0/0	3/1 (41x)
Vomiting (total occurrence)	Male/Female	1/0	0/0	0/1 (2x)	1/3 (9x)
Pasty faeces (total occurrence)	Male/Female	0/0	2/0 (2x)	2/0 (2x)	2/0 (5x)
Diarrhoea (total occurrence)	Male/Female	0/1 (2x)	2/0 (3x)	3/1 (5x)	2/3 (14x)
Body weight [kg] (% control)	Male	9.8 (100)	10.5 (107)	9.9 (101)	10.0 (102)
	Female	9.4	10.0	9.6	8.7

Endpoint	Sex	Concentration (ppm)			
		(100)	(106)	(102)	(93)
Body weight gain [kg] week 1-13 (% control)	Male	0.9 (100)	1.5 (167)	0.9 (100)	1.1 (122)
	Female	1.0 (100)	1.7 (170)	1.2 (120)	0.4 (40)
Liver weight [g]	Male, abs. (rel.)	368.8 (38.5)	368.0 (35.8)	371.8 (39.2)	374.8 (37.55)
	Female, abs. (rel.)	334.8 (36.05)	336.3 (33.8)	334.0 (35.55)	330.0 (38.3)
Liver weight [%]	Male, abs. (rel.)	100 (100)	100 (93)	101 (102)	102 (98)
	Female, abs. (rel.)	100 (100)	100 (94)	100 (99)	99 (106)
Gross Pathology/ Histopathology	Male/Female	-	-	-	-

Table 45 Detailed findings in study 64

Endpoint	Sex	Concentration (ppm)			
		0	**40**	**160**	**640**
No. animals/group	Male/Female	6/6	6/6	6/6	6/6
Mortality	Male/Female	0/0	0/0	0/0	0/0
Clinical signs					Slight disturbance of movement, especially in the hindlimbs observed in several animals. ↑ vomiting and ↑ diarrhoea
Body weight [kg] (% control)	Male	12.3 (100)	12.8 (104)	13.3 (108)	11.1 (90)
	Female	11.8 (100)	11.6 (98)	11.8 (100)	12.0 (102)
Body weight gain [kg] Week 1-52 (% control)	Male	3.7 (100)	4.2 (114)	4.8 (130)	2.6 (70)
	Female	3.4 (100)	3.4 (100)	3.6 (106)	3.8 (112)
Liver weight [g]	Male, abs. (rel.)	441.7 (36.42)	467.0 (37.25)	461.5 (35.47)	396.3 (36.55)
	Female, abs. (rel.)	421.2 (35.85)	380.7 (32.77)	435.0 (37.07)	431.5 (36.48)
Gross Pathology/ Histopathology	Male/Female	-	-	-	-

abs = absolute body weight
rel = liver weight relative to terminal body weight

4.7.1.2 Repeated dose toxicity: inhalation

Table 46: Summary table of relevant repeated dose inhalation toxicity studies with cyfluthrin

Study	Analyt. conc. [mg/m³ air]	Test substance	NO(A)EC [mg/m³ air]	Targets / Main effects	Reference

90-day, Wistar rat (GLP: no, OECD 413)	0-0-0.09-0.71-4.52 mg/m³ air Aerosol (10 males and 10 females/group)	Cyfluthrin batch no: 816170019, purity: 94.9 % Vehicle: polyethylene glycol E 400: ethanol (1 : 1)	0.09 (approx. 0.02 mg/kg bw/d)	≥0.71 mg/m³ air: Behavioural disturbances (agitation, (erected tail), reduction of bw	Study 65 †

†Key study

Table 47: Summary table of relevant repeated dose inhalation toxicity studies with beta-cyfluthrin

Study	Analyt. conc. [mg/m³ air]	Test substance	NO(A)EC [mg/m³ air]	Targets / Main effects	Reference
5 d, Wistar rat range finding (GLP: yes, OECD 403)	0*-0.25-3.8-28 Aerosol (10 males and 10 females)	Beta-cyfluthrin batch no: 16001/87, purity: 98 % Vehicle: ethanol/PEG 400 (1:1)	0.25	≥ 3.8 mg/m³ air : Clinical signs, transient reduction of bw, lung findings	Study 66 †
28-day, Wistar rat (GLP: yes, OECD 412)	0-0.2-2.7-23.5 Aerosol (10 males and 10 females/group)	Beta-cyfluthrin batch no: 16001/87, purity:97.9 %) Vehicle: ethanol/PEG 400 (1:1)	0.2 (0.07 mg/kg bw/d)	≥ 2.7 mg/m³ air : Clinical signs, reduction of bw	Study 67 †

* = air and vehicle control

†Key study

Behavioural disturbances and an effect on body weight gain were noted in inhalation studies with cyfluthrin and beta-cyfluthrin (see Table 46 and Table 47) on rats which failed to provide evidence of significant pathological lung changes but resulted in a slight, compensatory acidosis. In the 4-week study with beta-cyfluthrin (Study 67, see Table 49), no test substance related findings were apparent in the pathological and histopathological investigations. The slightly changed clinical parameters were interpreted as a result of compensatory reactions due to a slight respiratory acidosis. Additional lung function tests produced no evidence of pathophysiological lung changes. The NOAEC in this study was 0.2 mg beta-cyfluthrin/m³ air (corresponding to approx. 0.07 mg/kg bw/d), based on clinical signs and a reduced body weight gain at the next higher doses.

Table 48 Detailed findings in study 66

Detailed study findings					
Endpoint	Sex	Concentration (mg/m³ air)			
		0	0.25	3.8	28
No. animals/group	Male/Female	10/10	10/10	10/10	10/10
Mortalities	Male/Female	0/0	0/0	0/0	0/0
Clinical signs	Male/Female	0/0	0/0	10/10 piloerection,	10/10 reduced activity,

Detailed study findings					
Endpoint	**Sex**	**Concentration (mg/m³ air)**			
		0	**0.25**	**3.8**	**28**
				unpreened hair coat	piloerection, unpreened hair coat
Pathology/ Histopathology: Hepatoid foci (lung)	Male/Female	0/0	1/0	2/2	3/3*#
Body weight [g] after 4 day treatment (% control)	Male	203 (100)	205 (101)	196 (96)	190** (94)
	Female	190 (100)	187 (98)	185 (97)	178 (94)
Body weight [g] after 21 day treatment (% control)	Male	259 (100)	266 (103)	266 (103)	256 (99)
	Female	200 (100)	197 (99)	201 (101)	197 (99)

*=p<0.05; **=p<0.01
#: statistical analysis was performed over sum male/female

Table 49 Detailed findings in study 67

Detailed study findings						
Endpoint	**Sex**	**Concentration (mg/m³ air)**				**Comment**
		0 (vehicle)	**0.2**	**2.7**	**23.5**	
No. animals/group	Male/Female	10/10	10/10	10/10	10/10	
Mortality	Male/Female	0/0	0/0	0/0	0/0	
Clinical signs	Male/Female	0/0	0/0	0/0	10/10	signs included unkempt fur, piloerection, sometimes a slightly reduced motility but mainly an increased activity
Body and organ weights						
Liver, absolute (mg)	Male/Female	9059/ 7032	8189*/ 6743	8459/ 6506	7844**/ 6747	5885-10607/ 5038-8011#
Liver, relative (mg/100 g bw)	Male/Female	3848/ 3649	3601/ 3574	3833/ 3657	3658/ 3680	No histopathological correlates were observed.

#: 2-sigma ranges of historical control data (lower and upper area)
*=p<0.05; **=p<0.01

Table 50 Detailed findings in study 65

Detailed study findings						
Endpoint	**Sex**	**Concentration mg/m³ air**				**Comment**
		0	**0.09**	**0.71**	**4.52**	
No. animals/group	Male/Female	10/10	10/10	10/10	10/10	
Mortalities	Male/Female	0/0	0/0	0/0	0/0	
Clinical signs						
Non-specific disturbed behaviour	Male	0/10	0/10	0/10	10/10 (Day 13-88)	Agitation and erect tail observed at 4.52 mg/m³ air
	Female	0/10	0/10	10/10 (Day 42-86)	10/10 (Day 9-96)	
Body weight [g] after 12 week treatment	Male	277 (air) 276 (vehicle)	258*#	253**	236**	
	Female	193 (air) 185 (vehicle)	185	178**	182*	
Body weight [% air control] after 12 week treatment	Male	100	93	91	85	
	Female	96	96	92	94	
Histopathology	Male/female					No substance related findings in nerve tissues after histopathology.

*=p<0.05; **=p<0.01; #: statistical analysis compared to air control group data

4.7.1.3 Repeated dose toxicity: dermal

Table 51: Summary table of relevant repeated dose dermal toxicity studies with cyfluthrin*

Study	Dose levels	Test substance	NO(A)EL [mg/kg bw/d]	Targets / Main effects	Reference
3-week dermal toxicity in rabbits (GLP: no, similar to EPA no. 163, 1978)	0, 50, and 250 mg/kg bw/d (New Zealand White) (6 males and 6 females)	Cyfluthrin, batch no.: 16001/79, purity: 83.5 % Vehicle: polyethylene glycol 400	250	No effects at any dose level.	Study 68 †
22/23-day dermal toxicity in rats (GLP: yes, OECD 401)	0-100-340-1000 mg/kg bw/d (including recovery at 0 and 1000 mg/kg bw/d)	Cyfluthrin, batch no.: 2030025/BF9140-23,purity: 95.5-95.9 % No vehicle used (moistened pads)	Systemic: 340 Local: 100	Systemic effects at 1000 mg/kg bw/d: Dark red discharge from the nose in males (including recovery group), urine stains in	Study 69 †

Study	Dose levels	Test substance	NO(A)EL [mg/kg bw/d]	Targets / Main effects	Reference
3-week dermal toxicity in rabbits (GLP: no, similar to EPA no. 163, 1978)	0, 50, and 250 mg/kg bw/d (New Zealand White) (6 males and 6 females)	Cyfluthrin, batch no.: 16001/79, purity: 83.5 % Vehicle: polyethylene glycol 400	250	No effects at any dose level.	Study 68 †
				females, reduced food consumption Local effects (≥ 340 mg/kg bw/d): skin lesions	

* Not-acceptable studies were not included.

† Key study

Studies on dermal toxicity on rat and rabbit are available for cyfluthrin only (Table 51). In a 3-week study on rabbits no specific effects were observed (Study 68, see Table 53).

In a 22/23-day dermal toxicity study in rats (Study 69, see Table 52) systemic effects in the form of dark red discharge from the nose and urine staining in males and females, respectively, and a reduced food intake occurred at the highest dose of 1000 mg/kg bw/d. From 340 mg/kg bw/d onwards severe skin lesions were noted (ulceration, hyperkeratosis, acanthosis, inflammation, and dermal fibrosis). These changes persisted throughout the recovery period. The systemic NOAEL was established at 340 mg/kg bw/d, the local NOAEL at 100 mg/kg bw/d.

Table 52 Detailed findings in study 69

Detailed study findings						
Endpoint	Sex	Dose				Comment
		0	100	340	1000	
No. animals/group (recovery group)	Male/Female	8/8 (8/8)	8/8	8/8	8/8 (8/8)	
Mortalities	Male/Female	0/0	0/0	0/0	0/0	
Scabs [incidence] (%)	Male	0	0	0	5 (62)	6 (75) in recovery group
	Female	0	1 (12)	6 (75)	6 (75)	6 (75) in recovery group
Treated skin [incidence] (acanthosis, hyperkeratosis, inflammation, ulcer)	Male	-	1#	1	3	Severity: 1-3 (dose dependent)
	Female	-	-	1	7 (6 for ulcer)	Severity: ~3
Body weight [g] after 21 day treatment	Male	310	303.7	303.3	301.1	
	Female	238.6	236.3	232.3	228.3	
Body weight [g] after 14 day recovery	Male	304.7	ND	ND	296.1	
	Female	223.8	ND	ND	217.0	

Detailed study findings						
Endpoint	**Sex**	**Dose**				**Comment**
		0	**100**	**340**	**1000**	
Food consumption [g/day] after 7 (21) day treatment	Male	24.81 (22.38)	23.15 (21.16)	24.12 (20.99)	20.63* (20.88)	Food consumption comparable to control after 3 weeks and in recovery group at 4 and 5 weeks.
	Female	18.31 (21.3)	17.64 (20.49)	17.27 (21.53)	16.01* (21.26)	
Liver weight [mg], abs.	Male	9893 ± 1358	9544 ± 1010	10224 ± 1226	10727 ± 1874	
	Female	7363 ± 790	7315 ± 995	7240 ± 805	7493 ± 609	
Liver weight [mg], rel.	Male	3.756 ± 0.342	3.680 ± 0.331	3.939 ± 0.421	4.101 ± 0.497	
Liver weight [mg], rel.	Female	3.607 ± 0.206	3.608 ± 0.266	3.718 ± 0.288	3.761 ± 0.295	
Pathology, Histopathology						No test substance related findings. No findings in nervous system related tissues (brain, optic and sciatic nerve, spinal cord)

#: average severity of effects: 1 (minimal) to 5 (severe)
*=p<0.05; **=p<0.01
abs = absolute body weight
rel = liver weight relative to terminal body weight

Table 53 Detailed findings in study 68

Detailed study findings					
Endpoint	**Sex**	**Dose**			**Comment**
		0	**50**	**250**	
Mortalities/ Clinical signs	Male/Female	None	None	None	No substance-related skin findings were observed
Body weight [g] after 3 weeks treatment (% control)	Male, intact skin	2.71 (100)	2.63 (97)	2.77 (102)	No statistical analysis was performed. Groups were considered comparable.
	Female, intact skin	3.14 (100)	3.00 (96)	3.03 (96)	
	Male, abraded skin	2.92 (100)	2.66 (91)	2.86 (98)	
	Female, abraded skin	3.09 (100)	3.00 (97)	3.03 (98)	
Organ weights;	Male/Female	-	No findings	No findings	

Detailed study findings					
Endpoint	**Sex**	**Dose**			**Comment**
		0	**50**	**250**	
haematology, clinical chemistry, pathology/histopathology			observed, no deviations from control	observed, no deviations from control	
Liver weight [mg] (% control)	Male, intact skin	90535 (100)	88351 (98)	107259 (118)	
	Female, intact skin	79277 (100)	74849 (94)	86458 (109)	

4.7.1.4 Repeated dose toxicity: other routes

No other routes were tested.

4.7.1.5 Human information

No human information exists for repeat-dose exposure of cyfluthrin.

4.7.1.6 Summary and discussion of repeated dose toxicity

Oral:

In short-term toxicity experiments in rats and dogs oral administration of cyfluthrin or beta-cyfluthrin led to similar adverse effects: mortality, general behavioural disturbances, motor disturbances, lower body weight development, choreoathetotic signs, vomiting and diarrhea. No relevant effects on haematological, clinico-chemical and urine analytical parameters were detected.

The lowest NOAEL of 1 mg/kg bw/d was derived from a 4-week study with beta-cyfluthrin (study 61). At the next higher dose of 4 mg/kg bw/d mortality, clinical signs, reduced body weight development and an increased liver weight was noted.

In a 90-day oral study in rats with beta- cyfluthrin (study 62) mortality, clinical signs, reduced body weight and skin lesions was noted at approx. 37 mg/kg bw/d. The NOAEL was 9.5 mg/kg bw/d.

In a 90-day oral study in rats with cyfluthrin gait abnormalities, salivation and a reversible slight axonal degeneration was reported in some rats dosed with 300 and 1000 ppm (19 and 60.9 mg/kg bw/d) (study 59). The NOAEL was 6.2 mg/kg bw/d.

In a 90-day study on dogs with beta-cyfluthrin (study 63) the NOAEL of 60 ppm, equal to 2.4 mg/kg bw/d, was based on motor disturbances, vomiting, diarrhea and a reduced body weight gain in females at the next higher dose of 14 mg/kg bw/d.

A 12-month feeding study in dogs with cyfluthrin (study 60) revealed slight to severe motor disturbances, vomiting, diarrhea and a reduction in body weight gain at ≥360 ppm (10.6-18 mg/kg bw/d). The study revealed a NOAEL of 100 ppm (2.4/3.6 mg/kg bw/d). This study supersedes the 12-month feeding study in dogs (study 64) which was considered not acceptable.

Inhalation:

Behavioural disturbances and an effect on body weight gain were noted in 5-day and 28-day

inhalation studies on rats with beta-cyfluthrin which failed to afford evidence of significant pathological lung changes but resulted in a slight, compensatory acidosis. In the 28-day study (study 67), no test substance related findings were apparent in the pathological and histopathological investigations. The slightly changed clinical parameters were interpreted as a result of compensatory reactions due to a slight respiratory acidosis. Additional lung function tests produced no evidence of pathophysiological lung changes. The NOAEC in this study was 0.2 mg beta-cyfluthrin/m³ air (corresponding to approx. 0.07 mg/kg bw/d).

Dermal:

Studies on dermal toxicity on rat and rabbit are available for cyfluthrin only. In a 3-week study on rabbits with cyfluthrin no specific effects were observed (study 68).

In a 22/23-day dermal toxicity study in rats (study 69) systemic effects in the form of dark red discharge from the nose and urine staining in males and females, respectively, and a reduced food intake occurred at the highest dose of 1000 mg/kg bw/d. From 340 mg/kg bw/d onwards severe skin lesions were noted (ulceration, hyperkeratosis, acanthosis, inflammation, and dermal fibrosis). These changes persisted throughout the recovery period. The systemic NOAEL was established at 340 mg/kg bw/d, the local NOAEL at 100 mg/kg bw/d.

4.7.2 Comparison with criteria of repeated dose toxicity findings relevant for classification as STOT RE

Table 54: Results of repeat-dose toxicity studies in comparison with CLP criteria

Study type	STOT RE 1	STOT RE 2	Toxicological result (NOAEL/NOAEC and LOAEL/LOAEC)	Significant/severe effects at LOAEL
28-day oral rat	≤ 30mg/kg bw/d	≤ 300mg/kg bw/d	NOAEL: 1 mg/kg bw/d LOAEL: 4 mg/kg bw/d	Mortality, clinical signs, reduced body weight development, increased liver weight
90-day, oral, rat	≤ 10 mg/kg bw/d	≤ 100 mg/kg bw/d	NOAEL: 9.5 mg/kg bw/d LOAEL: 38.9 mg/kg bw/d (males); 42.4 mg/kg bw/d (females)	Mortality, clinical signs, reduced body weight and water intake, skin lesions, reduced red blood cell parameters, increased calcium levels in urine
			NOAEL: 6.2 mg/kg bw/d LOAEL: 18.98 mg/kg bw (males); 21.22 mg/kg bw (females)	Gait abnormalities, salivation, slight axonal degeneration of sciatic nerve (reversible)
90-day, oral, dog	-	-	NOAEL: 2.4 mg/kg bw/d LOAEL: 14 mg/kg bw/d	Motor disturbances (hind limb), vomiting, diarrhea, reduced body weight
12-month, oral, dog	-	-	NOAEL: 2.4 mg/kg bw/d (males); 3.6 mg/kg bw (females) LOAEL: 10.64 mg/kg bw (males); 10.74 mg/kg bw (females)	Reduced body weight, neurological disorders (gait abnormalities)
5-day, inhalation, rat	-	-	NOAEC: 0.25 mg/m³ air LOAEC: 3.8 mg/m³ air	Clinical signs, transient reduction of body weight, lung findings
28-day, inhalation, rat	≤ 0.6 mg/litre/6h/day	≤ 3 mg/litre/6h/day	NOAEC: 0.07 mg/kg bw/d LOAEC: 0.94 mg/kg bw/d	Clinical signs, reduction of body weight
90-day, inhalation, rat	≤ 0.2 mg/litre/6h/day	≤ 1 mg/litre/6h/day	NOAEC: 0.02 mg/kg bw/d LOAEC: 0.16 mg/kg bw/d	Behavioural disturbances (agitation, (erected tail), reduction of body weight
28-day, dermal, rabbit	≤ 60 mg/kg bw/d	≤ 600 mg/kg bw/d	21-day, dermal, rabbit: NOAEL: 250 mg/kg bw/d	No effects at any dose level
28-day, dermal, rat	≤ 60 mg/kg bw/d	≤ 600 mg/kg bw/d	22/23-day, dermal, rat: NOAEL: 340 mg/kg bw/d LOAEL: 1000 mg/kg bw/d	Dark red discharge from the nose in males (including recovery group), urine stains in females, reduced food consumption

4.7.3 Conclusions on classification and labelling of repeated dose toxicity findings relevant for classification as STOT RE

Even though some of the observed findings were severe (such as clinical signs, motor disturbances and/or gait abnormalities), they were considered to represent acute toxic/neurotoxic effects of cyfluthrin/beta-cyfluthrin. Due to intensive metabolism and rapid excretion of cyfluthrin/beta-cyfluthrin (see Chapter 4.1 ADME studies), daily administrations of cyfluthrin/beta-cyfluthrin are considered to represent a sequence of acute intoxications. A proposal for classification for acute effects is already made. Hence, it is proposed not to classify cyfluthrin/beta-cyfluthrin for STOT-RE/"Danger of serious damage to health by prolonged exposure".

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 LD_{50} 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**.

4.8 Germ cell mutagenicity (Mutagenicity)

Hazard class not assessed in this dossier.

4.9 Carcinogenicity

Hazard class not assessed in this dossier.

4.10 Toxicity for reproduction

4.10.1 Effects on fertility

4.10.1.1 Non-human information

Fertility studies were conducted with cyfluthrin only (Table 55).

Table 55: Summary table of relevant reproductive toxicity studies*

Study	Dose levels	Test substance	NO(A)EL	Targets / Main effects	Reference
2-gen. study OECD 416 Oral, diet, SD rat GLP: yes	0-50-125-400 ppm (3-7, 9-19, 29-59 mg/kg bw/day) Default calculation for males and females: 0-3.3-8.3-26.7 mg/kg bw/d (30 males and 30 females/group)	Cyfluthrin, batch no. 2030025, purity 94.6-96.2 %	NOAEL parental: 50 ppm (3.3 mg/kg bw/d) NOAEL offspring: 50 ppm (3.3 mg/kg bw/d) NOAEL reproductive: 400 ppm (26.7 mg/kg bw/d)	Parental: ≥125 ppm: Splaying of the hind limbs in females; ≥ 400ppm: decreased bw Offspring: ≥125 ppm: Coarse tremors, decreased bw	Study 70 †

Study	Dose levels	Test substance	NO(A)EL	Targets / Main effects	Reference
Supplemental 2-gen study OECD 416 Oral, diet; SD rat (supplemental) GLP: yes	0-25-50 ppm (1.9-4.1, 3.8-8.0 mg/kg bw/d) Default calculation for males and females: 0-1.7-3.3 mg/kg bw/d (30 males and 30 females/group)	Cyfluthrin, batch no. 2030025, purity 94.6-96.2 %	NOAEL reproductive, offspring, parental: 50 ppm (3.3 mg/kg bw/d)	No effects	Study 71

* Not-acceptable studies were not included; for further study details, please see also IUCLID ECHA DocIII cyfluthrin.

†Key study

In a 2-generation study in Sprague-Dawley rats (Study 70), the F_0 and F_1 adults received cyfluthrin in the diet throughout the entire study, beginning at seven weeks of age for the F_0 adults and at weaning for the F_1 adults. Prior to breeding, the animals received treated feed at least for a ten-week period. The following dose levels were administered female parental animals (for risk assessment purposes, a time-weighted conversion factor of 15 was used for calculation of the test substance intake based on the test substance feed concentration, as proposed by the WHO (2009): 50 ppm (default 3.3 mg/kg bw/d), 125 ppm (default 8.3 mg/kg bw/d), 400 ppm (default 26.7 mg/kg bw/d). During the study, adult animals were evaluated for the effect of the test compound on body weight, food consumption, clinical signs, oestrus cycling, mating, fertility, gestation length, and litter size. The offspring were evaluated for compound-related effects on sex ratio, pup viability, body weight gain, and clinical signs. Gross necropsy evaluations were performed on all adults and pups. Histopathologic evaluation of reproductive organs, the pituitary, and gross lesions was performed on all F_0 and F_1 adults. Additionally due to clinical signs of neurotoxicity, the brain, spinal cord, and one sciatic nerve were collected from all F1 adults and placed in buffered 10 percent formalin in the event that further microscopic examination was deemed necessary.

There were no compound-related clinical signs for adult males. In F_0 and F_1 females, a compound-related and statistically significant increased incidence of splayed hind limbs occurred at 400 ppm during the lactation phase (Table 56).

Table 56: Rat 2-gen. study: Incidence of splayed hind limbs in females during lactation (Study 70)

Generation	Incidence of splayed hind limbs in dose group females during lactation			
	0 ppm	50 ppm	125 ppm	400 ppm
F0 females	(0 / 30)	(0 / 27)	(0 / 26)	(15 / 29)**
F1 females	(0 / 25)	(0 / 27)	(0 / 27)	(9 / 25)**

Statistically significant (Fisher's Exact Test): * = $p \leq 0.05$; ** = $p \leq 0.01$

There were no compound-related mortalities in parental animals. Statistically significantly decreased terminal body weights were observed in F1 males at 125 ppm and 400 ppm and in F1 females at 400 ppm. There were no compound-related absolute or relative organ weight changes in the F_0 and F_1 adults. During the lactation period decreases in food consumption were observed at 400 ppm in both the F_0 and F_1 females (values ranged from 78 % - 85 % on the F_0 females and from 77 % - 88 % during days 0-21 post partum in the F_1 females compared to the control and lower dose groups). There were no effects on adult reproductive parameters (oestrus cycle staging; insemination length; mating, fertility and gestation indices; gestation length; number of implantation sites and birth index. No compound-related gross and histopathological lesions were observed.

Coarse tremors were observed in the F_1 and F_2 pups at and above 125 ppm (

Table 57). The tremors were observed as early as lactation day 5 and had ceased by lactation day 18. The increased incidence of coarse tremors and the decreased pup body weight in F_1 and F_2 pups at and above 125 ppm (19 and 59 mg/kg bw/d) occurred in the presence of maternal toxicity (splayed hind limbs, severity not indicated).

The excretion and concentration of cyfluthrin in rat milk has not been determined but it can be concluded that the presence of adverse effects in the offspring at 125 ppm 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.

Table 57: Rat 2-gen. study: Litter incidence of coarse tremors (Study 70)

Generation	Litter incidence of coarse tremors in pups observed during lactation			
	0 ppm	50 ppm	125 ppm	400 ppm
F1 pups	(0 / 30)	(0 / 27)	(4 / 25)	(15 / 28)*
F2 pups	(0 / 25)	(0 / 26)	(19 / 26)*	(9 / 25)*

Statistics: Chi-square test & Fisher's Exact test (Bonferroni adjustment of the p value)

In addition, at 400 ppm, clinical signs of neurotoxicity (splayed hind limbs) were observed in F0 and F1 females during lactation.

There was no substance-related effect on pup gender, litter size; live birth, viability and lactation indices, or gross lesions in the F_1 or F_2 pups. Cyfluthrin administration to F_0 and F_1 parents had no effect on birth weight of their offspring.

The parental and offspring NOAEL is 50 ppm, equivalent to 3.3 mg/kg bw/day (default calculation for males and females). Fertility parameters were not affected by cyfluthrin at doses up to and including 400 ppm (equivalent to 26.7 mg/kg bw/day).

The NOAEL of 50 ppm (3.3 mg/kg bw/d) was confirmed in a supplemental 2-generation study (Study 71) showing that transient reductions in pup weight noted in the previous study at 50 ppm were not test-substance related.

4.10.1.2 Human information

No data available.

4.10.2 Developmental toxicity

4.10.2.1 Non-human information

Teratogenicity studies with oral administration were conducted in rats and rabbits with cyfluthrin and beta-cyfluthrin.

Table 58: Summary table of relevant oral teratogenicity studies with cyfluthrin*

Study	Dose levels	Test substance	NO(A)E(C)L	Targets / Main effects	Reference
Teratogenicity; BAY:FB 30 rats Gavage 6th -15th day (GLP: no, OECD 414)	0-3-10-30 mg/kg bw/d (25 females/ group)	cyfluthrin (batch no: 16001/79, purity: approx. 85 %) vehicle: polyethylene glycol E 400	NOAEL maternal: 3 mg/kg bw/d NOAEL developmental: 30 mg/kg bw/d	Maternal: ≥10 mg/kg bw/d: High-stepping gait, ataxia, reduced motility Offspring: No effects	Study 72 †
Teratogenicity; Wistar rats Gavage 6th -15th day of gestation (GLP: yes, OECD 414)	0-1-3-10 mg/kg bw/d (25 females/ group)	cyfluthrin (batch no: 816170019, purity 93.4 %) vehicle: cremophor EL/distilled water (1 % v/v)	NOAEL maternal and developmental: ≥10 mg/kg bw/d	No effects	Study 73

Teratogenicity; Himalayan rabbits, gavage, 6th -18th day of gestation (GLP: no, OECD 414)	0-5-15-45 mg/kg bw/d (15 females/ group)	cyfluthrin (batch no. 816170019, purity: 95.0 %) vehicle: Cremophor EL/water (0.5 %)	Maternal: 15 mg/kg bw/d Developmental: 45 mg/kg bw/d	Maternal: ≥ 45 mg/kg bw/d: Abortion Offspring: No effects	Study 74 †
Teratogenicity; Chinchilla rabbits, gavage, 6th -18th day of gestation (GLP: yes, OECD 414)	0-20-60-180 mg/kg bw/d (16 females/ group)	cyfluthrin (batch no.: 2380051769, purity 96.0 %) formulated in corn oil	Maternal: 20 mg/kg bw/d Developmental: 20 mg/kg bw/d	Maternal: ≥60 mg/kg bw/d: decreased food consumption, bw loss Offspring: ≥60 mg/kg bw/d: Increased post-implantative resorptions	Study 75 †

* Not-acceptable studies were not included. For further study details, please see also IUCLID ECHA DocIIIA cyfluthrin

† Key study

Table 59: Summary table of relevant oral teratogenicity studies with beta-cyfluthrin*

Study	Dose levels	Test substance	NO(A)E(C)L	Targets / Main effects	Reference
Teratogenicity; Wistar rats Gavage 6th -15th day of gestation (GLP: yes, OECD 414)	0–3–10–40 mg/kg bw/d (20 females/group)	beta-cyfluthrin technical, batch-no.: 3030125, purity: 96.5-97.3 % vehicle: 1 % aqueous Cremophor	NOAEL maternal: 3 mg/kg bw/d NOAEL developmental: 10 mg/kg bw/d	Maternal: 40 mg/kg bw/d: Mortality, clinical findings (hypoactivity, locomotor incoordination, salivation); ≥10 mg/kg bw/d: decreased body weight gain and food consumption Offspring: 40 mg/kg bw/d: decreased weight; retarded ossification	Study 76 †

* Not-acceptable studies were not included. For further study details, please see also IUCLID ECHA Vol.3 beta-cyfluthrin.

† Key study

Teratogenicity studies with oral administration were conducted in rats and rabbits with cyfluthrin and beta-cyfluthrin. In rats, a maternal NOAEL of 3 mg/kg bw/d was derived in the teratogenicity study 72 with cyfluthrin (see Table 60). A high-stepping gait, occasionally ataxia and reduced motility were observed in a few dams after administration of the mid- and high-dose (10 and 30 mg/kg bw/d). Doses up to 30 mg/kg bw had no lethal effect and did not affect average weight gain. No general, embryotoxic and/or teratogenic effects were observed in the offspring, resulting in a developmental NOAEL of 30 mg/kg bw/d.

The maternal NOAEL of 3 mg/kg bw/d was confirmed in study 76 with beta-cyfluthrin. An increased incidence of mortality and clinical findings (hypoactivity, locomotor incoordination, salivation) were confined to the high-dose group (40 mg/kg bw/d). From 10 mg/kg bw/d onwards a reduction in body

weight gain was noted in the dams. A decrease in foetal weight gain and a retarded ossification was noted at 40 mg/kg bw/d and a developmental NOAEL of 10 mg/kg bw/d was derived.
Likewise, no effects were noted in the offspring of Himalayan rabbits up to oral doses of 45 mg cyfluthrin/kg bw/d. The maternal NOAEL was 15 mg/kg bw/d, based on abortion (study 74, see Table 62).
In Chinchilla rabbits (study 75, see Table 63, Table 64, Table 65, Table 66) the maternal and developmental NOAEL was 20 mg cyfluthrin /kg bw/d based on decreased food consumption and body weights loss in the dams and on an increased incidence of post-implantative resorptions in the offspring.

Table 60 Detailed findings in study 72

Detailed study findings in maternal rats						
Endpoint	**Sex**	**Dose mg/kg bw/day**				**Comment**
		0	**3**	**10**	**30**	
No. animals/group (inseminated rats)	Female	25	25	25	25	
Mortality	Female	0	0	0	0	
Clinical signs						Clinical signs were considered to be treatment-related
High stepping gait°	Female	0	0	6	6	Findings were observed occasionally from 2nd week of application
Ataxia°	Female	No	No	Yes #	Yes #	#: observed occasionally in individual animals (no numbers available)
Reduced motility°	Female	No	No	Yes #	Yes #	#: observed occasionally in individual animals (no numbers available)

°= no statistical analysis performed

Table 61 Detailed findings in study 73

Detailed study findings in maternal rats						
Endpoint	**Sex**	**Dose mg/kg bw/day**				**Comment**
		0	**1**	**3**	**10**	
No. animals/group (inseminated rats)	Female	25	25	25	25	

Detailed study findings in maternal rats						
Endpoint	**Sex**	**Dose mg/kg bw/day**				**Comment**
		0	**1**	**3**	**10**	
Mortality	Female	0	0	0	0	
Clinical signs (overall incidence)	Female	0	0	2	0	Clinical signs were considered to be not treatment-related, as they occurred in isolated animals and were not observed at the highest dose tested
Partial loss of hair (from day 8 after mating)°	Female	0	0	1	0	Female No. 62 was affected
Colporrhagia (on day 18 after mating)°	Female	0	0	1	0	Female No. 63 was affected

°= no statistical analysis performed

Table 62 Detailed findings in study 74

Detailed study findings: dams						
Endpoint	**Sex**	**Dose mg/kg bw/day**				**Comment**
		0	**5**	**15**	**45**	
No. animals mated/ group	♀	15	15	15	15	
No. animals fertilised / group	♀	15	15	13	14	
No. animals pregnant at termination/ group (%)	♀	15 (100)	15 (100)	13 (100)	11 (78.5)	At 45mg/kg bw/day two dams aborted on days 25 and 28 p.c. and one dam completely resorbed her implants.
Abortions [incidence]	♀	0	0	0	3	
Mortality [incidence]	♀	0	0	0	0	
Bodyweight gain (g) – dosing period [mean/ group]	♀	78.7	57.7	109.6	81.4	
Placenta weight (g) [mean/ group]	♀	4.27	4.26	4.20	4.60	
No. implantation sites	♀	7.3	6.3	8.5*	6.8	

Detailed study findings: dams						
Endpoint	**Sex**	**Dose mg/kg bw/day**				**Comment**
		0	**5**	**15**	**45**	
[mean/ group]						
No. pre-natal losses [mean/ group]	♀	0.6	0.7	1.4	1.8	
Detailed study findings: fetuses following caesarean section day 29 p.c.						
No. foetuses [total/group]	Both sexes	100	84	92	70	
No. foetuses [mean/ group]	Both sexes	6.7	5.6	7.1	5.0	
No. foetuses [mean/ sex/ group]	Male/female	3.3/3.4	2.7/2.9	3.8/3.3	2.8/2.2	
No. small foetuses/ group (<25g)	Both sexes	1	4	0	0	
Fetal weight (g) [mean/ group]	Both sexes	37.37	37.00	38.77	40.30	
Ossification changes [total foetuses/group] (%)	Both sexes	0 (0)	2 (2.4)	0 (0)	0 (0)	
Ossification changes [total litters/group] (%)	Both sexes	0 (0)	2 (13)	0 (0)	0 (0)	
Malformations						
Arthrogryposis [total foetuses/group] (%)	Both sexes	0 (0)	2 (2.4)	2 (2.2)	3 (4.3)	
Arthrogryposis [total litters/group] (%)	Both sexes	0 (0)	1 (7)	2 (15)	1 (9)	
Tail vertebrae located asymmetrically and adherent [total foetuses/group] (%)	Both sexes	0 (0)	0 (0)	4 (4.3)	0 (0)	
Tail vertebrae located asymmetrically and adherent	Both sexes	0 (0)	0 (0)	1 (7.7)	0 (0)	

Detailed study findings: dams						
Endpoint	**Sex**	**Dose mg/kg bw/day**				**Comment**
		0	**5**	**15**	**45**	
[total litters/group] (%)						

*=p<0.05; **=p<0.01

Table 63 Detailed findings in study 75, parental data

Dose: [mg/kg bw]	**0**	**20**	**60**	**180**
Group size (pregnant animals)	16	13	16	15
Food intake 6-11 p.c. (g/animal/day) [mean/ group]	146	124	107*	76**
Food intake 24-28 p.c. (g/animal/day) [mean/ group]	121	146	161**	178**
Body weight gain [g] (6-19 d) [mean/ group]	-40	-34	-189**	-233**
Body weight gain [g] (6-28 d) [mean/ group]	87	143	42	-6
Gravid uterus weight [g] [mean/ group]	508	450	455	464

*=p<0.05; **=p<0.01

Table 64 Detailed findings in study 75, reproduction data

Dose: [mg/kg bw]	**0**	**20**	**60**	**180**
Number of pregnant dams/ group	16	13	16	15
Implantation sites (% of corpora lutea) [mean/ group]	193 (96.0)	128 (90.8*)	183 (94.3)	186 (98.4)
Pre-implantation loss [No.] (% of corpora lutea) [mean/ group]	8 (4)	13 (9.2*)	11 (5.7)	3 (1.6)
Post-implantation loss [No.] (% of implantation sites) [mean/ group]	21 (10.9)	14 (10.9)	36 (19.7*)	53 (28.5**)
Post-implantation loss, dams affected [No.] (%) [per group]	11 (69)	7 (54)	13 (81)	12 (80)

Dose: [mg/kg bw]	0	20	60	180
Embryonic/fetal deaths, total (% of implantation sites) [mean/ group]	21 (10.9)	14 (10.9)	36 (19.7*)	47 (25.3**)
Embryonic resorptions, total (% of implantation sites) [mean/ group]	7 (3.6)	8 (6.3)	21 (11.5**)	28 (15.1**)
Embryonic resorptions, dams affected [No.] (%) [per group]	5 (31)	4 (31)	10 (63)	10 (67)
Fetal resorptions, total (% of implantation sites) [mean/ group]	14 (7.3)	6 (4.7)	15 (8.2)	19 (10.2)
Fetal resorptions, dams affected [No.] (%) [per group]	9 (56)	5 (38)	7 (44)	8 (53)
Total fetuses [No.] (% of implant. sites) [per group]	172 (89.1)	114 (89.1)	147 (80.3*)	133 (71.5**)
Total fetuses [No.] [mean/ dam]	10.8	8.8	9.2	8.9
Live fetuses [No.] [per group]	172	114	147	133
Abnormal foetuses [No.] (% of foetuses) [per group]	4 (2.3)	1 (0.9)	3 (2.0)	3 (2.3)
Abnormal foetuses, dams affected [No.] (%) [per group]	4 (25)	1 (8)	3 (19)	3 (20)
Sex of fetuses: male / female (% male) [mean/ group]	86/86 (50)	71/43 (62.3*)	80/67 (54.4)	72/61 (54.1)
Fetal weight (g): male / female, individual basis (male / female, litter basis) [mean/ group]	29/28 (30/29)	31/32** (31/33)	30/29 (31/30)	30/31* (31/32)

*=p<0.05; **=p<0.01

Table 65 Abnormal findings in study 75

Dose: [mg/kg bw]	0	20	60	180
Number of foetuses examined	172	114	147	133
Number of litters examined	16	13	16	15
Type of abnormal finding [No./ group] - External and visceral examination data				
Omphalocele	1	1	0	0

Dose: [mg/kg bw]	0	20	60	180
Arthrogryposis	1	0	0	0
Open eye	2	0	0	0
Runt	2	0	3	3
Cheilognathopalatotschisis	1	0	0	0
Cranioschisis	1	0	0	0
Hemidiaphragm	0	0	0	1
Head	0	0	0	0

Table 66 Skeletal examination data in study 75

Dose: [mg/kg bw]	0	20	60	180
Number of foetuses examined	172	114	147	133
Number of litters examined	16	13	16	15
Type of abnormal finding [No.] - Skeletal examination data				
Total No. of abnormal findings in fetuses (litters) / group	3 (3)	3 (3)	4 (2)	5 (4)
Abnormally Ossified and Fused Sternebrae, fetal data[No.] (%) [per group]	1 (0.6)	0 (0)	1 (0.7)	2 (1.5)
Abnormally Ossified and Fused Sternebrae, litter data [No.] (%) [per group]	1 (6.3)	0 (0)	1 (6.3)	2 (13.3)
Thoracic/Lumbar Vertebral Bodies/Arches Fused, Missing or Bipartite, fetal data [No.] (%) [per group]	1 (0.6)	2 (1.8)	0 (0)	2 (1.5)
Thoracic/Lumbar Vertebral Bodies/Arches Fused, Missing or Bipartite, litter data [No.] (%) [per group]	1 (6.3)	2 (15.4)	0 (0)	2 (13.3)
Ribs fused, bifurcated or missing, fetal data [No.] (%) [per group]	0 (0)	2 (1.8)	2 (1.4)	3 (2.3)
Ribs fused, bifurcated or missing, litter data [No.] (%) [per group]	0 (0)	2 (15.4)	2 (12.5)	2 (13.3)
Partial aplasia of the	1	0	0	0

Dose: [mg/kg bw]	0	20	60	180
cranium (Os nasale, frontale, parietale), fetal data [No.] (%) [per group]	(0.6)	(0)	(0)	(0)
Partial aplasia of the cranium (Os nasale, frontale, parietale), litter data [No.] (%) [per group]	1 (6.3)	0 (0)	0 (0)	0 (0)
Abnormal Structure of the Vertebral Column and Ribs; Scoliosis, Shortened Trunk, Fused, Bipartite or Missing Vertebral Bodies and Arches; Bifurcated or Missing Ribs, fetal data [No.] (%) [per group]	0 (0)	1 (0.9)	0 (0)	0 (0)
Abnormal Structure of the Vertebral Column and Ribs; Scoliosis, Shortened Trunk, Fused, Bipartite or Missing Vertebral Bodies and Arches; Bifurcated or Missing Ribs, litter data [No.] (%) [per group]	0 (0)	1 (7.7)	0 (0)	0 (0)
Os nasale distally incompletely ossified, fetal data [No.] (%) [per group]	0 (0)	0 (0)	1 (0.7)	0 (0)
Os nasale distally incompletely ossified, litter data [No.] (%) [per group]	0 (0)	0 (0)	1 (6.3)	0 (0)
Tip of the tail missing, fetal data [No.] (%) [per group]	0 (0)	0 (0)	0 (0)	1 (0.8)
Tip of the tail missing, litter data [No.] (%) [per group]	0 (0)	0 (0)	0 (0)	1 (6.7)

*=p<0.05; **=p<0.01

Table 67: Summary table of relevant inhalation teratogenicity studies with cyfluthrin*

Study	Dose levels	Test substance	NO(A)E(C)L	Targets / Main effects	Reference
Teratogenicity; Wistar rats, aerosol, head-nose exposure 6th -15th day of gestation, 6 h per day (GLP: yes, OECD 414)	1st exp.: 0-1.1-4.7-23.7 mg/m³ air 2nd exp.: 0-0.09-0.25-0.59-4.16 + O_2 mg/m³ air (30 females/group)	cyfluthrin (1st exp. batch no.: 233490583, purity: 92.9-93 %; 2nd exp. batch no.: 238005176, purity 96.2 %) formulated in ethanol/ polyethylene glycol E 400 as aerosol	Maternal and developmental: 0.59 mg/m³ air	≥1.1 mg/m³ air: reduced bw development, reduced fetal weight, retarded ossification In addition ≥ 4.16 mg/m³ air+O_2: Clinical signs of the dams In addition at 23.7 mg/m³ air: Increased incidence of resorptions increased frequency of microphthalmia	Study 77 †
Teratogenicity; Wistar rats, aerosol, head-nose exposure 6th -15th day of gestation, 6 h per day (GLP: yes, OECD 414)	0-0.46-2.55-11.9-12.8+O_2 mg/m³ air (25 females/group)	cyfluthrin (batch no.: 238005176 , purity 94.7-96.2 %) formulated in ethanol/ polyethylene glycol E 400	Maternal: <0.46 mg/m³ air Developmental: 0.46 mg/m³ air	≥0.46 mg/m³ air: Decreased food intake and bw development in dams, hypothermia and bradypnoea (hypoventilation) in dams In addition ≥2.55 mg/m³ air: Clinical signs in dams, retarded development of fetuses In addition ≥11.9 mg/m³ air: Respiratory disturbances and hypoactivity in dams, higher incidence of microphthalmia and anophthalmia	Study 78 †
Determination of the FCR 1272 concentration in the plasma of rats following inhalation exposure (GLP: no, guideline: not applicable)	0.5, 2.5, 12.5 and 12.5 + O_2 mg/m³ air (5 pregnant females/group)	Cyfluthrin (batch no.: 380267024, purity 92 %) first dissolved in 5 mL 1,4-dioxane, this solution made up to 50 mL with n-hexane	Not applicable	Very low plasma concentrations of cyfluthrin were found in the high-dose groups 12.5 mg/m³ air and 12.5 mg/m³ air (+39 % oxygen).	Study 79

* Not-acceptable studies were not included. For further study details, please see also IUCLID ECHA DocIIIA cyfluthrin.

†Key study

Inhalation exposure to cyfluthrin caused a physiological maternal compensation mechanism (hypothermia with respiratory alkalosis) followed by reflex bradypnoea after sensory irritation (

Table 67). In study 78, food intake of dams was decreased and body weight development was delayed at levels of 0.46 mg/m³ air and above (Table 68). Clinical signs (bloody snout, ruffled fur) were apparent in the dams at 2.55 mg/m³ air and above. Respiratory disturbances and hypoactivity were noted at 11.9 mg/m³ air and 12.8 mg/m³ air (plus oxygen), and a high-stepping gait at 11.9 mg/m³ air only. Placental weights were lower from 2.55 mg/m³ air onwards and fetuses showed signs of retarded development (reduction of fetal weight) (Table 68 and Table 69). No gross pathological findings were recorded at necropsy in any dose group (including the satellite groups). A NOAEL of <0.46 mg/m³ air resulted for maternal toxicity, based on decreased food intake and body weight development in dams at this dose.

Table 68: Selected symptoms and clinical observations in dams (study 78)

Dose [mg/m³ air]	0 a.	0 v.	0.46	2.55	11.9	O2+12.8
Number of dams per dose group	25	25	25	25	25	25
Ruffled fur	0	0	0	1 (4 %)	19 (76 %)	21 (84 %)
Retarded breathing	0	0	0	0	17 (68 %)	10 (40 %)
Laboured breathing	0	0	0	0	5 (20 %)	0
Hypoactivity	0	0	0	0	5 (20 %)	1 (4 %)
High stepping gait	0	0	0	0	5 (20 %)	0
Bloody snout	0	0	0	1 (4 %)	2 (8 %)	2 (8 %)

a = air control, v = vehicle control

Table 69: General examination and reproduction data (study 78)

Dose [mg/m³ air]	0 a.	0 v.	0.46	2.55	11.9	O2+12.8
Number of inseminated rats	25	25	25	25	25	25
Dams with viable fetuses	21	22	23	23	23	23
Number of implantations per dam	12.3	12.8	11.3	11.4	11.3	11.3
Food intake, pregnancy	19.9	20.0	19.1**	18.7**	17.7**	17.4**
Weight gain, pregnancy [g]	83.6	88.8	76.8	74.7**	58.7**	62.3**
Corrected weight gain [g]	20.0	23.0	19.8	19.3*	13.6**	12.5**
Corpora lutea per group	301	312	313	316	319	310
Preimplantation loss per group	42	31	53*	54*	59**	51*
Number of live fetuses per dam	11.6	12.0	10.7	10.9	10.4*	10.4*
Mean weight of fetuses [g]	3.41	3.50	3.48	3.13**	2.48**	2.83**
Mean placenta weight [g]	0.61	0.60	0.62	0.56*	0.46**	0.51**

a = air control, v = vehicle control; * = p <0.05, ** = p <0.01 in relation to air and vehicle control.

At 2.55 mg/m³ air and above, fetuses exhibited signs of retarded ossification of the phalanges, metacarpals and metatarsals, sternebrae, vertebrae, pelvis or the skull. With oxygen supplement the embryotoxic findings in the high dose group were less pronounced.

Table 70: Summary of selected skeletal findings of fetuses (study 78)

Dose [mg/m³ air]	0 a.	0 v.	0.46	2.55	11.9	O2+12.8
Number of fetuses examined	126	138	128	133	124	126
Distal Phalanx – unossified (1st right %)	4.8	3.6	1.6	7.5	45.2***	10.3
Metacarpals – incompl. ossified (2nd right %)	0.8	0.0	0.8	3.0	41.1***	15.1***
Sternum – unossified (2nd segment %)	0.0	0.0	0.0	0.8	19.4***	7.9***

a = air control, v = vehicle control; *** = p <0.001

An increased incidence of malformations was also observed at levels of 2.55 mg/m³ air and above (Table 71). With the exception of the occurrence of microphthalmia and anophthalmia in the high dose groups, the nature of malformations were comparable to those in the controls of this or previous studies and did not indicate a specific teratogenic potential of cyfluthrin after inhalation exposure (hydrocephalus internus: 1/0/0/0/0/0; skeletal dysplasia of legs: 0/1/1/4/1/3; filiform tail: 0/0/0/1/0/0; spinal malformation: 0/0/0/0/2/0; rib malformation: 0/0/0/0/1/0; malformation of exoccipital bone and cervical vertebral arches: 1/0/0/0/3/0; dysplasia of exoccipital bone: 0/0/0/0/1/0; umbilical hernia: 0/0/0/0/1/0). The incidence of microphthalmia was outside the historical control values (1983-1992) (no. of foetuses per year: 2/6/3/2/5/6/3/1/1/2).

Table 71: Summary of malformations in fetuses (study 78)

Dose [mg/m³ air]	0 a.	0 v.	0.46	2.55	11.9	O_2+12.8
Microphthalmia (Fetuses / Litters affected)	1/1	2/2	1/1	3/2	13/8**	7/5
Anophthalmia (Fetuses / Litters affected)	-	-		-	1/1	1/1
Fetuses per group (n)	243	263	245	251	239	240
Total malformed fetuses (n)	3	3	2	8	21***	10
Litters with malformations (n)	2	3	2	4	10*	7

a = air control, v = vehicle control; * = p <0.05, ** = p <0.01, *** = p <0.001

In another teratogenicity study (with two separate experiments) with inhalation exposure of cyfluthrin (study 77), a maternal and developmental NOAEL of 0.59 mg cyfluthrin /m³ air was based on reduced body weight development in the dams, reduced foetal weight (Table 72) and retarded ossification at the next higher dose of ≥1.1 mg/m³ air.

In addition, at ≥ 4.16 mg/m³ air (+O_2) clinical signs occurred in the dams and an increased incidence of microphthalmia at 23.7 mg cyfluthrin /m³ air was noted in the offspring.

In the dams no deaths occurred as a result of the treatment. At 4.16 mg/m³ air (+O_2) (experiment 2) and from 4.7 mg/m³ air (experiment 1) onwards clinical signs in the form of reduced motility, piloerection, ruffled/unkempt fur, irritation of the visible eye mucous membranes and labored breathing were observed (incidences in 48 % of the animals at 4.16 mg/m³ air, 87 % of the animals at 4.7 mg/m³ air, and 100 % of the animals at 23.7 mg/m³ air). The rats with oxygen substitution tolerated the exposure better (lower intensity of clinical signs) than the corresponding rats without the oxygen exposure.

Body weight development of dams was reduced from the dose of 1.1 mg/m³ air both during the

administration and the remaining gestation period. At 4.16 mg/m³ air with oxygen substitution the body weight development was retarded only during the administration period. Both, clinical signs and the decreased body weight gain were interpreted as an indication of maternal toxicity.

At 1.1 mg/m³ air onwards mean foetus and placenta weights were lower, the number of runts higher.

Table 72: General examinations (parental data, experiment 1) (study 77)

Dose [mg/m³ air]	**0**	**1.1**	**4.7**	**23.7**
Number of inseminated rats	30	30	30	30
No. of animals with clinical signs	0	0	26	30
Number of pregnant rats	25	29	27	29
Number of implantations	11.5	12.2	11.7	11.6
Weight gain during pregnancy [g]	75.5	66.6*	57.1**	45.6**
Number of losses of fetuses (per dam)	0.7	0.9	1.6	2.3*
Number of live fetuses	10.8	11.3	10.1	9.3
Mean weight of fetuses [g]	3.4	3.16*	2.89**	2.43**
Mean weight of placenta [g]	0.57	0.52*	0.48**	0.40**

* = p <0.05, ** = p <0.01.

Table 73: General examinations (parental data, experiment 2) (study 77)

Dose [mg/m³ air]	**0**	**0.09**	**0.25**	**0.59**	**O_2+4.16**
Number of inseminated rats	30	30	30	30	30
No. of animals with clinical signs	0	0	0	0	16
Number of pregnant rats	23	29	25	29	22
Number of implantations	10.7	11.4	11.2	11.0	11.2
Weight gain during pregnancy [g]	58.4	63.0	60.2	85.9	56.4
Number of losses of fetuses (per dam)	1.7	1.8	2.4	1.8	1.7
Number of live fetuses	9.0	9.6	8.8	9.2	9.5
Mean weight of fetuses [g]	3.48	3.51	3.53	3.47	3.29*
Mean weight of placenta [g]	0.61	0.61	0.62	0.58	0.56*

* = p <0.05, ** = p <0.01.

The slightly increased frequency of microphthalmia (unilateral) at 23.7 mg/m³ air was outside the historical control values (6 incidences in 8 studies in 1984, 2 incidences in 15 studies in 1985) for this finding. These effects were interpreted as signs of a non-specific retardation of embryonic development and are attributed to a maternal hypoxia induced by the treatment rather to an embryotoxic potential of cyfluthrin. Accordingly, the effects were considerably less pronounced at 4.16 mg/m³ air with oxygen substitution than at 4.7 mg/m³ air without oxygen substitution.
No further evidence of a teratogenic potential was found at doses up to and including the highest, clearly maternal-toxic dose.

Table 74: Anomalies (mean values / standard deviation, experiment 1) (study 77)

Dose [mg/m³air]	0	1.1	4.7	23.7
Skeletal variations	1.80 / 171	2.62 / 1.59	3.89* / 2.47	5.32** / 2.65
Runts	0.20 / 0.50	2.00* / 3.13	4.89** / 4.64	7.57** / 4.15
Malformations (all)	0.04 / 0.20	0.07 / 0.26	0.15 / 0.46	0.29 / 0.71
Microphthalmia: absolute number of pups	1/271	2/319	2/292	8/261

* = p <0.05, ** = p <0.01.

Table 75: Anomalies (mean values / standard deviation, experiment 2) (study 77)

Dose [mg/m³ air]	0	0.09	0.25	0.59	O_2+4.16
Skeletal variations	2.52 / 2.19	2.45 / 1.92	1.64 / 1.41	1.86 / 1.77	2.82 / 1.30
Runts	0.35 / 0.78	0.38 / 0.73	0.32 / 0.69	0.21 / 0.49	1.14* / 1.58
Malformations (all)	0.04 / 0.21	0.10 / 0.31	0.20 / 0.65	0.03 / 1.19	0.05 / 0.21
Microphthalmia: absolute number of pups	1/206	1/278	2/221	1/268	1/209

* = p <0.05, ** = p <0.01.

The data of an addendum provide explanations for the reproductive effects observed. Accordingly, the reflex bradypnoea of the dams which is compensated by hypothermia and a reduction in metabolic activity seems responsible for the impairment of intra-uterine processes.

Conclusions of the Pesticides Peer Review:

The increased frequency of microphthalmia and the proposed mode of action (secondary effect due to hypoxic conditions) were discussed during the Pesticides Peer Review Meeting 172. The existence of the proposed mode of action could not be confirmed in open literature. It was noted that with additional oxygen exposure in the high dose group, the incidence of microphthalmia was lower than without oxygen supplementation, but remained higher than control values (study 78, for data refer to table 54). Therefore, the mode of action proposed by DS was not supported by the meeting and the finding of microphthalmia in inhalation developmental toxicity studies was regarded potentially relevant to humans. A proposal for classification as developmental toxicant category 2 (H361d "Suspected of damaging the unborn child") was agreed by majority of experts at this meeting.

Effects via lactation:

After Annex I inclusion according to Directive 91/414/EC (concerning the placing of plant protection products on the market) a developmental neurotoxicity screening study with beta-cyfluthrin in rats has been conducted. The study was submitted for renewal procedure for beta-cyfluthrin under Regulation (EC) No 1107/2009 and was previously not evaluated on EU level (study 80, see Table 81).

Table 76: Summary of developmental neurotoxicity study

Table Study	Dose levels	Test substance	NO(A)EL	Targets / Main effects	Reference
Developmental Neurotoxicity Screening Study in Rats; diet (GLP: yes,OECD TG 426)	0-30-125-200 ppm (equal to 0-2.4-11.0-17.8 mg/kg bw/d during gestation and 0-5.9-25.4-40.9 mg/kg bw/d during lactation) (Wistar rats) (30 females/group)	beta-cyfluthrin batch-No. 8030130/380566042, purity: 95.1-97.6 %; vehicle: none (covered in diet)	125 ppm (equivalent to 11 mg/kg bw/d during gestation)	Maternal: 200 ppm: Lower bw development during gestation and lactation Offspring: 200 ppm: Reduced pup weight gain, FOB: minimal resistance during handling, reduced startle response	study 80 †

* FOB: Functional observation battery

†Key study

Technical grade beta-cyfluthrin was administered via the diet from gestation day (GD) 0 through lactation day (LD) 21 to mated female Wistar rats at nominal concentrations of 0, 30, 125 and 200 ppm (equal to 0, 2.4, 11.0 and 17.8 mg/kg/day, respectively during gestation and 0, 5.9, 25.4 and 40.9 mg/kg/day, respectively during lactation). The adult males served only as "breeders" and were not exposed to the test substance or included in any tests.

On postnatal day (PND) 4, litters with a minimum of eight pups, including at least three per sex, were culled to yield, as closely as possible, four males and four females. Subsets of surviving offspring, representing at least 20 litters per level, were subjected to evaluation using the following observations and measurements - detailed clinical observations (an abbreviated functional observational battery), preputial separation or vaginal patency, body weight, food consumption, body temperature, automated measures of activity (figure-eight maze), acoustic startle habituation, learning and memory (passive avoidance after weaning and a water maze task on PND 60) and an ophthalmic examination. Neural tissues were collected from 10/sex/dietary level (representing approximately 20 litters) on PND 21 (brain only) and at study termination (approximately 75 days of age) for microscopic examination and morphometry. The concentration of beta-cyfluthrin in the whole-brain from the dams (LD 21) and offspring (PND 4 and PND 21) was also measured to verify exposure.

In the maternal animals there were no deaths prior to terminal sacrifice. Lower body weight development during gestation day 6 was noted in high dose dams (200 ppm). During lactation (days 0-21) body weight development and food consumption was reduced in dams of the 200 ppm group.
During lactation hair loss was noted in few dams of groups 3 and 4 (125 and 200 ppm).
The FOB was unaffected in dams during gestation and lactation until PND 21.
Pup weight gain was reduced from days 11 to day 21 in pups of the 200 ppm group. Further litter data were not affected by the treatment.

Table 77: Body weight development of pups during lactation [g ± SE]

PND	Dietary level [ppm]							
	0		30		125		200	
	Males	Females	Males	Females	Males	Females	Males	Females
0	5.8±0.08	5.5±0.09	5.7±0.09	5.4±0.08	5.8±0.08	5.5±0.07	5.7±0.09	5.4±0.10
4	9.7±0.22	9.3±0.24	9.2±0.19	8.9±0.17	9.6±0.17	9.2±0.18	9.0±0.21	8.6±0.21
11	24.7±0.48	23.5±0.48	23.3±0.57	23.0±0.55	23.9±0.36	23.3±0.36	22.2±0.21**	21.4±0.54*
17	39.0±0.64	36.9±0.64	37.0±0.67	36.2±0.65	37.3±0.52	36.3±0.52	35.2±0.72**	34.0±0.75**
21	49.6±0.85	46.7±0.87	46.5±0.79*	45.3±0.75	47.1±0.65	45.6±0.65	44.3±0.83**	42.9±0.86**

Dunnett's test*p≤0.05, **p≤0.01

In the FOB for pups on PND 4, minimal resistance during handling was noted for pups of the high dose group (200 ppm). No further changes were noted in animals up to PND 60.
Automated measures for motor and locomotor activity were not affected by treatment at any dietary level. There were no compound-related ophthalmic findings.
Reduced response amplitude following acoustic startle habituation was observed in male high-dose pups at PND 22. This finding was associated with reduced body weight. It was not observed at later time points, in females or other dose groups.

There were no effects of treatment on developmental landmarks (balano-preputial separation or vaginal patency).

Table 78: Developmental landmarks

	Dietary level [ppm]			
	0	30	125	200
Preputial separation				
Age at landmark [days ± SE]	43.6±0.34	43.9±0.29	43.8±0.32	44.2±0.35
BW at landmark [g ± SE]	185±2.0	178±1.7*	178±1.7*	171±1.8**
Vaginal opening				
Age at landmark [days ± SE]	34.0±0.27	35.0±0.25*	34.4±0.23	34.6±0.24
BW at landmark [g ± SE]	106±1.7	107±1.3	105±1.4	101±1.1*
Pupil constriction				
Pups reaching criteria [%]	100	100	100	100

Dunnett's test, Fisher's exact test *p≤0.05, **p≤0.01

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 (

Table 79). These findings provide clear evidence of exposure during lactation.

Table 79: Concentration of beta-cyfluthrin in whole-brain tissue

Dietary level [ppm]	Tissue level of beta-cyfluthrin [ppm]		
	Pups (PND 4)[1]	Pups (PND 21)	Dams (LD 21)
0	0.000	0.002	0.000
30	0.004	0.006	0.006
125	0.016	0.024	0.026
200	0.026	0.034	0.046

Based on 16-22 pups (representing a minimum 16 litters) and 18-22 dams per group.
[1] Samples were pooled to provide adequate amounts for analysis.

Compound-related gross lesions were not evident in males or females at terminal sacrifice. There were no effects on brain weight, brain morphometry or histology of brain, neural tissues or skeletal muscle at study termination.
Treatment did not affect reproduction parameters, including the fertility index (Table 80).

Table 80: Reproductive parameters

	Dietary level [ppm]			
	0	30	125	200
No. of animals cohoused	30	30	30	30
No. of animals mated	30	30	30	30
Mating index	100.0	100.0	100.0	100.0
Fertility index	86.7	96.7	96.7	86.7

The overall NOAEL was 125 ppm (equivalent to 11.0 mg/kg bw/day during gestation) based on effects on body weight and food consumption in high-dose dams and effects on body weight and startle response in high-dose pups at 17.8 mg/kg bw/day.

Table 81 Detailed findings in study 80

Detailed study findings:						
Endpoint	Generation	Dietary Level (ppm)				Comment
		0	30	125	200	
Clinical observations during gestation						
No. animals/group	F0	30	30	30	30	Compound-related clinical signs were not evident at any dietary level. No mortality occurred.
No remarkable clinical observations		30	30	29	27	
Lacrimal stain, red		0	0	0	1	
Hair loss		0	0	1	2	
Clinical observations during lactation						
No. animals/group	F0	26	29	29	26	Compound-related clinical signs were not evident at any dietary
No remarkable		26	29	28	24	

Detailed study findings:						
Endpoint	**Generation**	**Dietary Level (ppm)**				**Comment**
		0	30	125	200	
clinical observations						level. No mortality occurred.
Hair loss		0	0	1	2	
Clinical observation during PND 0-21						
No. litters examined	F1	26	29	29	26	No compound-related signs were observed during lactation in males or females at any dietary level. Incidental findings that were evident on occasion in individuals from various dose groups, including controls, included bruising, raised area on the dorsal neck (one high-dose pup), wounds/bite marks or cuts, a missing hindfoot (one control) and a swollen forelimb (one high-dose pup).
Bruise on face/back/body		5/2/1	7/3/0	5/1/2	5/6/0	
Clinical observations post weaning	F1					Compound-related clinical signs were not evident at any dietary level.
Alopecia (back)	Male/ female	-/1	-	-	1/2	
Lesion, sore	Male/ female	-	1/-	2/-	4/-	
Lesion, scab	Male/ female	4/0	2/0	2/1	4/5	
Dehydrated, bod	Male/ female	-	-	3/-	2/-	
Dead	Male/ female	-	-	1/-	2/-	
Nasal stain	Male/ female	-	-/1	-	-	
Urine/perianal stain	Male/ female	-/3	-/1	-	-	
Exophthalmos	Male/ female	-	-/1	-	-	
Eye, small, left	Male/ female	-	-	1/-	-	

Detailed study findings:						
Endpoint	**Generation**	**Dietary Level (ppm)**				**Comment**
		0	30	125	200	
Functional Observational Battery	F0					Compound-related functional observations were not evident at any dietary level.
Rearing Mean ± S.D.	Females	3.1±1.9	2.7±1.7	3.7±1.8	2.4±1.7	
Defecation Number of Boluses Mean ± S.D.		0.7±1.3	0.3±0.7	0.6±1.0	0.6±1.0	
Urination Number of Pools Mean ± S.D.		1.2±1.2	1.3±1.6	1.1±1.3	0.8±0.9	

4.10.2.2 Human information

Toxicity via lactation:

Human data are available for monitoring of pesticide residues in breast milk. Measurements in humans show that pesticide residues, including cyfluthrin, were detected in breast milk samples (Anupama et al., 2014; Bouwman and Kylin, 2009; Bouwman et al., 2006; Feo et al., 2012; Sereda et al., 2009). Anupama et al. (2014) reported that cyfluthrin was the leading pesticide detected in breast milk contributing 31.28 % to the total residue load. Infants under malaria control conditions in South Africa are exposed to combinations of chemicals, i.e. cyfluthrin, alpha-cypermethrin, DDT, deltamethrin, that would have deleterious effects if the intakes were high enough. Levels of up to 459 µg /L whole milk were recorded for cyfluthrin, of up to 28 µg /L whole milk for alpha-cypermethrin, of up to 725 µg /L whole milk for DDT and of up to 83 µg /L whole milk for deltamethrin (Bouwman and Kylin, 2009).

Organochlorine (i.e. DDT and its metabolites, fipronil, endosulfan), organophosphate (i.e dimethoate, carbaryl, chlorpyrifos) and synthetic pyrethroids (i.e. cyfluthrin, alpha-cyhalothrin and deltamethrin) pesticides are widely used for the purpose of enhancing food production and improving health by destroying insects and pests of food crops and vectors of human and animal diseases like malaria, dengue, encephalitis, filariasis etc. However, accumulation of these pesticides in the food chain results in accumulation in human (and animal) body. Residues of these pesticides get accumulated in the lipid-rich tissue in the body and are finally excreted in the mother's breast milk. The results of Anupama et al. (2014), Bouwman and Kylin (2009), Bouwman et al. (2006) indicated that the infant daily intake of these pesticides from some of the breast-milk samples exceeded health-based acceptable levels, like the respective ADI value. Thus, a risk of infants to these pesticides cannot be excluded. Adverse health effects of breast-milk fed infants are not reported in these publications.

Likewise, in the Renewal Assessment Report (RAR, 2015) of beta-cyfluthrin as an active substance in plant protection products, and in the Summary Report of cyfluthrin for use in veterinary medicines (2002) certain investigations have shown that residues after oral administration of cyfluthrin and beta-

cyfluthrin were found in lactating cows and goats, respectively (Study 81, 82).
See also Chapter 4.10.4 Summary and discussion of reproductive toxicity.

4.10.3 Other relevant information

No data available.

4.10.4 Summary and discussion of reproductive toxicity

There are no appropriate epidemiological studies available on developmental effects in humans. Hence, classification with Category 1A according CLP regulation is not possible.

Fertility:

Under the conditions of the two-generation reproductive toxicity study, cyfluthrin had no effect on fertility when administered via the diet to rats up to 400 ppm, the highest dose tested.

Development:

The prenatal developmental toxicity of cyfluthrin and beta-cyfluthrin was investigated in rats and rabbits and the studies were considered acceptable.

In the inhalational teratogenicity studies in rats with cyfluthrin (study 77, 78), the increased frequency of malformations (microphthalmia, anophthalmia, bone malformations) observed in the offspring at 11.9, 12.8 (with oxygen supplement), and 23.7 mg cyfluthrin /m³ air was considered a secondary effect following hypoxic conditions in the dams. Due to the irritating properties of the test substance at these dose levels a reflex bradypnoea occurred in the dams which was compensated by hypothermia and a reduction in metabolic activity. In addition, an increased incidence of resorptions occurred at a dose level of 23.7 mg/m^3 (study 77). It can be assumed that the occurrence of the mentioned malformations, especially microphthalmia, in the offspring does not represent a direct toxic effect of the test substance. This assumption is supported by reproductive toxicity studies with orally administered cyfluthrin/beta-cyfluthrin, which are systemically available by oral absorption (60 % (beta-cyfluthrin) and 90 % (cyfluthrin). After oral administration no treatment-related malformations were observed.

Even though some of the observed findings in the dams were severe findings (such as clinical signs, motor disturbances and/or gait abnormalities), they were considered to represent acute toxic/neurotoxic effects of cyfluthrin/beta-cyfluthrin. Due to intensive metabolism and rapid excretion of cyfluthrin/beta-cyfluthrin (see Chapter 4.1 ADME), daily administrations of cyfluthrin/beta-cyfluthrin are considered to represent a sequence of acute intoxications.

Due to signs of respiratory irritation observed in humans and in appropriate animal teratogenicity studies after cyfluthrin exposure via inhalation it is proposed to classify and label cyfluthrin/beta-cyfluthrin according to the respiratory irritating effects (STOT SE 3; H335 May cause respiratory irritation).

Manifestations of developmental toxicity seen in rats and rabbits were accompanied by maternal toxicity. Abortion was observed in two (top dose) rabbits, and one dam resorbed its implants completely (study 74). From 60 mg/kg bw/d an increase in the number of post-implantative resorptions was the only observed change in rabbits interpretable as a sign of reproduction toxicity (study 75). Taken together, based on the small number of animals affected, these findings are

considered not severe enough to justify a classification in Category 2 (H361d).

In a developmental neurotoxicity screening study with beta-cyfluthrin in rats (study 80), no effect on developmental landmarks (balano-preputial separation or vaginal patency) and on reproduction parameters, including the fertility index in the offspring were noted.

Lactation:

The NOAEL for parental toxicity was established at 50 ppm, based on reduced body weights of F_1 males at and above 125 ppm. At 400 ppm, clinical signs of neurotoxicity (splayed hind limbs) were observed in F_0 and F_1 females during lactation and body weights and food consumption were reduced in both sexes. The NOAEL for offspring toxicity was established at 50 ppm, based on increased incidences of coarse tremors and decreased pup body weights at and above 125 ppm during the lactation period.

Cyfluthrin has lipophilic properties and dependent on the extent of exposure, the substance get accumulated in the lipid-rich tissue of the breast and transfer of this substance into human or animal breast milk will occur.

No measurements of cyfluthrin concentration in the rat milk after exposure have been provided and according to our literature research, no such information does exist.

Measurements of beta-cyfluthrin concentration in whole-brain tissue were performed in the developmental neurotoxicity study in rats (study 80). 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.

Additionally, residues of cyfluthrin were detected in human breast milk samples (see Chapter 4.10.2.2). It can be concluded that the presence of adverse effects in the offspring in the 2-generation toxicity study in rats during lactation was due to transfer of cyfluthrin and/or its metabolite(s) in the milk, which will result in a proposal for classification and labelling (see chapter 4.10.6)

4.10.5 Comparison with criteria

Toxicological result	Hazard category for lactation effects
Residues cyfluthrin were detected in human breast milk samples and beta-cyfluthrin has lipophilic properties; Increased incidences of coarse tremors and decreased pup body weights at and above 125 ppm cyfluthrin during the lactation period was observed in the rat 2-generation toxicity study.	EFFECTS ON OR VIA LACTATION Effects on or via lactation are allocated to a separate single category. It is recognised that for many substances there is no information on the potential to cause adverse effects on the offspring via lactation. However, substances which are absorbed by women and have been shown to interfere with lactation, or which may be present (including metabolites) in breast milk in amounts sufficient to cause concern for the health of a breastfed child, shall be classified and labelled to indicate this property hazardous to breastfed babies. This classification can be assigned on the: (a) human evidence indicating a hazard to babies during the lactation period; and/or (b) 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; and/or (c) absorption, metabolism, distribution and excretion studies that indicate the likelihood that the substance is present in potentially toxic levels in breast milk.

4.10.6 Conclusions on classification and labelling

Cyfluthrin exposure through the milk is considered to be the main determinant of offspring neurotoxicity in the 2-generation toxicity study in rats and it is proposed to classify cyfluthrin as a reproductive toxicant in category for effects on or via lactation.
Classification and labelling for reproductive toxicity according to Regulation (EC) No 1272/2008 (GHS): Lact H362: May cause harm to breast-fed children.

4.10.6.1 Neurotoxicity

Hazard class not assessed in this dossier

4.10.6.2 Immunotoxicity

Hazard class not assessed in this dossier

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 receive 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 LD_{50} values differed 7-fold between weanlings and adults but the brain concentrations at the LD_{50} 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).

<u>Two-generation study in rats with cyfluthrin (study 70)</u>

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 PNDT studies via gavage, rabbit PNDT studies via gavage, rat PNDT 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 PNDT studies (increased post-implantation loss in study 75) and in the rat PNDT studies via inhalation (increased incidence of microphthalmia in studies 77 and 78).

Rat PNDT 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 PNDT studies via gavage.

Rabbit PNDT 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 the 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] (%; ±SD)	10 (±11)	14 (±21)	19 (±15)	31/26[b] (±29/23)
Embryonic resorptions[a] (%; ±SD)	4 (±7)	10 (±21)	12 (±15)	22/17[b] (±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. Statistical evaluation: post-implantation loss 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≤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/m^3. Clinical signs (dyspnea, reduced motility, piloerection, ruffled/unkempt fur, irritation of the visible eye mucous membranes) were observed from 4.7 mg/m^3. 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/m^3)	**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 foetuses 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 foetuses	271	329	292	261
Foetal weight (g)	3.40	3.16*	2.89**	2.43**
No. of foetuses 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/m^3. The test atmosphere at the top concentration of 4.16 mg/m^3 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/m^3 in the first experiment could be related to foetal hypoxia. The clinical signs at 4.16 mg/m^3 + O_2 were less pronounced than those at 4.7 mg/m^3 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/m^3 in either experiment.

Rat inhalation PNDT study 77, 2nd experiment					
Concentration (mg/m^3)	**0 (vehicle)**	**0.09**	**0.25**	**0.59**	**4.16+O_2**
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 ± 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 ± 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 ± 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/mg^3 and 12.8 mg/m^3 + O_2 (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/m^3). 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/m^3. 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/m^3)	**0 (a.)**	**0 (v.)**	**0.46**	**2.55**	**11.9**	**12.8+O_2**
Dams with implantations	21	22	24	24	23	23
Dams with viable foetuses	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 foetuses 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, 1st right (%)	4.8	3.6	1.6	7.5	45.2**	10.3
Metacarpal incompletely ossified, 2nd right (%)	0.8	0.0	0.8	3.0	41.1**	15.1**
Sternum unossified, 2nd segment (%)	0.0	0.0	0.0	0.8	19.4**	7.9**
Microphthalmia; foetuses (litters)	1 (1)	2 (2)	1 (1)	3 (2)	13 (8)	7 (5)
Anophthalmia; foetuses (litters)	0	0	0	0	1 (1)	1 (1)
Eye malformations; foetuses (litters)	1 (1)	2 (2)	1 (1)	3 (2)	14 (9)	7 (5)
Foetuses 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 foetuses, 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, which indicates a relatively high background incidence, 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 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 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.

<u>Two-generation study in rats with cyfluthrin (study 70)</u>

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 2-generation study (study 70) attributable to transfer of the test substance via milk and occurring in the absence of maternal toxicity.

Supplemental information – In depth analyses by RAC

Comparison of plasma levels after oral and inhalation exposure

The available information on plasma levels of cyfluthrin or beta-cyfluthrin (parent substance) in rats after oral and inhalation exposure is summarised in the following table.

Plasma concentration of cyfluthrin or beta-cyfluthrin (parent substance) after oral and inhalation exposure

Type of study	Method	Concentration in plasma	Reference
Oral absorption after single administration	Rat, Wistar (BOR:WISW), males	Cremophor EL/water: T_{max} 1 h C_{max} 0.30 µg/mL (blood)	Study 88

	Single dose of 10 mg/kg bw, gavage, cyfluthrin (non-radiolabelled) Vehicle Cremophor EL/water or PEG 400 Sacrifice at 0.5, 1, 2, 4, 6, 16, 24 h after administration 2 animals per vehicle and time point of sacrifice Cyfluthrin determined in the blood and in stomach extracts	PEG 400: T_{max} 6 h C_{max} 0.075 µg/mL (blood) Note: plasma levels assumed to be approx. 2-fold higher than blood levels (based on the results of studies 85 and 87)	
Toxicokinetics after single oral and intravenous administration	Rat, Wistar, males Oral part: Single dose of 20 mg/kg bw, gavage, cyfluthrin (non-radiolabelled) Vehicle corn oil Sacrifice at 0.16, 0.33, 0.5, 1, 2, 4, 6, 8, 12 and 24 h after administration 8 animals per time point of sacrifice Cyfluthrin determined in the plasma and in the brain by LC-MS	Corn oil: T_{max} 3.4 h C_{max} 0.39 µg/mL	Rodríguez *et al.* (2018)
ADME, single oral administration	Rat, Wistar, males Single dose of 10 mg/kg bw, gavage, beta-cyfluthrin (radiolabelled on the fluorophenyl) Vehicle PEG 400 4 animals per group	PEG 400, sampling time 6 h: Beta-cyfluthrin 0.15 µg eq./g The remaining extractable fractions 9.61 µg eq./g, non-extractable 0.89 µg eq./g	Study 87
PNDT study, inhalation	Rat, Wistar (BOR:WISW), pregnant females Toxicokinetic part: Exposure GD 6-13, 6 h/d Concentrations 0 (air), 0 (vehicle), 0.46, 2.55, 11.9, 12.8+O_2 mg/m^3, cyfluthrin Vehicle ethanol/PEG 400 5 animals per concentration Cyfluthrin determined in the plasma immediately post-exposure (GD 13)	At 11.9 mg/m^3: mean 19.0 pmol/mL = 8.3 ng/mL range (8.5–38.5) pmol/mL = (3.7–17) ng/mL At 12.8 mg/m^3+O_2: mean 14.7 pmol/mL = 6.1 ng/mL range (9.2–18.3) pmol/mL = (4.0–7.9) ng/mL Recovery rate from plasma ca. 30–60%, no correction for recovery made	Study 78/79

There are two key oral PNDT studies in the rat (studies 72 and 76), both negative. The top doses in these PNDT studies were 30 or 40 mg/kg bw/d, Cremophor or PEG 400 were employed as vehicles. The C_{max} (plasma) values for the parent substance in oral toxicokinetic studies ranged from 0.15 µg/mL (PEG 400) to ca. 0.6 µg/mL (Cremophor); these plasma levels relate to an administered dose of 10 mg/kg bw, which is 3 to 4 times lower than the top doses in the PNDT studies. In comparison, plasma levels of the parent substance at a concentration causing microphthalmia in the inhalation PNDT study 78 ranged from ca. 0.008 to 0.04 µg/mL (after correction for incomplete recovery). Based on this information, systemic exposure to the parent substance was markedly (at least 10-fold) higher in the negative oral PNDT studies than in the positive inhalation PNDT studies.

RAC notes that the oral toxicokinetic studies were conducted in males while developmental toxicity relates to a female situation. The higher sensitivity of males compared to females in some acute toxicity studies suggests some toxicokinetic or toxicodynamic difference. Nevertheless, the sex difference in C_{max} is expected to be rather small given that a ca. 50-fold difference in LD_{50} between studies with Cremophor vs. PEG 400 corresponds to a ca. four-fold difference in C_{max} (study 88), and the difference between female and male LD_{50} values was two-fold or less.

Cyfluthrin and beta-cyfluthrin are extensively metabolised upon oral exposure. According to study 87, only about 1.5% of the radiolabel in the plasma is the parent substance, the rest are metabolites. The metabolism after inhalation exposure is not expected to be significantly higher than after oral exposure. Consequently, the difference between plasma levels after oral vs. inhalation exposure found for the parent substance is considered to apply also to the parent substance plus metabolites.

Rabbit PNDT study 75: relationship between maternal food consumption and post-implantation loss

The table below shows that there was no strong correlation between post-implantation loss and maternal food consumption during the treatment period at the top dose of 180 mg/kg bw/d.

Post-implantation loss and food consumption at 180 mg/kg bw/d in study 75

Dam no.	Food consumption GD 6-19 (g/animal/d)	Post-implantation loss (%; absolute numbers)	Embryonic resorptions (%; absolute numbers)
49	34	0 (0/15)	0 (0/15)
50	25	53 (9/17)	29 (5/17)
51	93	13 (1/8)	13 (1/8)
52	50	37 (7/19)	32 (6/19)
53	63	0 (0/12)	0 (0/12)
54	71	100 (9/9)	100 (9/9)
55	77	18 (2/11)	0 (0/11)
56	38	75 (9/12)	75 (9/12)
57	87	60 (6/10)	50 (5/10)
58	123	0 (0/9)	0 (0/9)

59	146	31 (5/16)	7 (1/16)
60	114	38 (6/16)	7 (1/16)
61	97	14 (1/7)	0 (0/7)
62	52	20 (2/10)	10 (1/10)
63	98	27 (4/15)	27 (4/15)
64	45	11 (1/9)	11 (1/9)
Mean	76	31	22
Control mean	131	11	4

Human relevance of tremors in rat sucklings

Neonatal rats are more sensitive than adults to cyfluthrin-induced neurotoxicity, presumably due to lower metabolic capacity (US EPA, 2010; Anand *et al.*, 2006). Industry proposed that this age dependence of metabolic capacity towards pyrethroids does not exist in humans.

The major contributors to pyrethroid metabolism in humans are P450 enzymes CYP2C8, CYP2C19 and CYP3A4 together with carboxylesterhydrolases CES1 and CES2 (Song *et al.*, 2017). In general, for many drug metabolising enzymes a substantial increase in expression is observed within the first one or two years after birth. This seems to be the case for CYP3A4 while the increase for CYP2C19 is rather moderate (Hines, 2008). A steep increase of CYP2C8 content in human microsomes was found to occur around postnatal day 35 (Song *et al.*, 2017). Hines *et al.* (2016) reported an increase in human microsomal and cytosolic CES 1 and CES 2 around three weeks of age. Overall, these data indicate that human infants younger than three weeks would exhibit significantly lower pyrethroid clearance compared with adults.

5 ENVIRONMENTAL HAZARD ASSESSMENT

5.1 Degradation

Table 82: Summary of relevant information on degradation

Method	Test substance	Results	Remarks	Reference
comparable to OECD Guideline No. 111	Cyfluthrin Beta-Cyfluthrin	Half-lives at 12 °C: pH 4 and 5 = stable pH 7 = 212 - 512 d pH 9 = 2.0 – 3.3 d	Hydrolysis was studied on mixtures of four diastereomers of cyfluthrin 2 degradation products have been identified: 4-fluoro-3-phenoxy benzaldehyde (FPB-ald, FCR 1260) permethric acid (DCVA)	Sandie, F.E. (1983) **A7.1.1.1.1/02**
OECD No. 111	Cyfluthrin Beta-Cyfluthrin			Krohn, J. (1997a) **A7.1.1.1.1/01**
OECD Guideline No. 111	Permethric acid (DCVA)	stable	Hydrolysis on metabolite permethric acid (DCVA)	Krohn, J. (1997b) **A7.1.1.1.1/03**
No guideline study, laboratory own method	Cyfluthrin	< 1 day	Study with natural sunlight Formation of degradation products: 4-fluoro-3-phenoxybenzaldehyd (FPB-ald) and 4-fluoro-3-phenoxybenzoic acid (FPB-acid)	Gronberg, R.R. (1987) **A7.1.1.1.2-01**
No guideline study, laboratory own method	Cyfluthrin	12.2 days	Study with mercury lamp Formation of degradation products: 4-fluoro-3-phenoxybenzaldehyd (FPB-ald) and 4-fluoro-3-phenoxybenzoic acid (FPB-acid)	Puhl, et al. (1983) **A7.1.1.1.2-02**
UBA, Berlin, FRG (1990).	Cyfluthrin	Using GC-Solar: 2.8 d (summer 30-50° latitude) 58 d (winter 60° latitude) Using calculation model according to Frank & Kloeppfer: 3 to 5 days	Using different calculation models GC Solar and Frank & Kloeppfer	Hellpointer, E. (1991) **A7.1.1.1.2-04**
Photodegradation in soil; no guideline study, laboratory own method	Cyfluthrin	Half-life at 12 °C: 12.3 d biphasic degradation pattern	Photodegradation in 1 soil (sandy loam) by natural sunlight	H.M. Chopade (1986) **A7.2.2.4-03**

Method	Test substance	Results	Remarks	Reference
Aerobic aquatic degradation no guideline study, laboratory own method	[fluoro-benzene-UL-^{14}C] Cyfluthrin	DT_{50} 9.4 days (20 °C), no mineralization, metabolites: FPB-acid, 4'OH-FPB-acid, COOH-cyfluthrin	Laboratory study/ No guideline	Anderson, C. (1986) **III-A7.1.2.2.1**
Degradation in water-sediment	[Fluoro-benzene-UL-^{14}C]Cyfluthrin [cyclo-propane-1-^{14}C] Cyfluthrin	DT_{50} 1.95 – 4.9 days (20 °C), 14.2 % – 67 % CO_2, metabolites: FPB-acid, FPB-ald, DCVA, COOH-cyfluthrin, $CONH_2$-cyfluthrin, 4'OH-FPB-acid	Four systems tested (orchard drainage ditch, fish pond, small closed gravel-pit, catchment basin)	Anderson, C. (1987) Hammel, K. (2007) **III-A7.1.2.2.2/01&02,** Sneikus, J. (2000) Hammel, K. (2007) **III-A7.1.2.2.2/03&04**
Aerobic soil degradation	[fluoro-benzene-UL-^{14}C] Cyfluthrin [phenyl-UL-^{14}C] Cyfluthrin [cyclo-propane-1-^{14}C]Cyfluthrin	DT_{50} 11.4 – 67.9 (20 °C), 32.0 % – 48.5 %, metabolites: FBP-acid, DCVA	Three laboratory studies with three German soils as well as two American soils	Wagner et al. (1983a); **IIIA7.2.1/ 01-04,** Riegner (1997), Jersch-Schmitz (1997), **IIIA7.2.2.1/01&02** Hiler (2013) **IIIA7.2.1/09**

5.1.1 Stability

Hydrolysis:

Table 83: Hydrolytic degradation – a.s.

Method /Guideline	**pH**	**Temperature [°C]**	**Initial TS concentration, C_0 [mg L^{-1}]**	**Reaction rate constant, K_h [$days^{-1}$]**	**Half-life, DT_{50} [days]**	**Coefficient of correlation, r_2**	**Reference**
comparable to OECD Guideline No. 111	5	25	0.02, 1 % aceto-nitrile	stable	stable	n. a.	Sandie, F.E. (1983) A7.1.1.1.1 /02
	7			3.6 x 10^{-3}	193	0.97	
	9			3.7 x 10^{-1}	1.9	0.99	
OECD No. 111	4	50	4.0 x 10^{-3}	5.0 x 10^{-3} - 1.0 x 10^{-2}	137 - 67	0.168 - 0.518	Krohn, J. (1997a) A7.1.1.1.1 /01
	7	50, 60, 70		0.2 - 3.7	3.5 - 0.19	0.935 - 0.979	
	9	40, 50		4.9 - 19.4	0.14 - 0.035	0.871 - 0.989	

The hydrolysis of Cyfluthrin and beta-Cyfluthrin was studied as function of both pH-value and temperature as well as in consideration of conversion processes of the different diastereomers I to IV. Due to the latter process, Cyfluthrin and beta-Cyfluthrin form in water mixtures of diastereomers with identical composition. The values for DT_{50} for 20 and 25 °C (calculated by extrapolation) are

indicated in the following table for diastereomer compositions I+II and III+IV. The hydrolysis half-lives were recalculated to reflect an average EU outdoor temperature of 12 °C for fresh water. Conversion of above mentioned values for DT_{50} to a pseudo first-order rate constant is stated.

Cyfluthrin is stable in pH 4 and 5, as well as relatively stable at pH 7. The hydrolysis rates increase at pH 9, mean half-life of around 2.6 days was calculated. Significant hydrolysis products were 4-fluoro-3-phenoxy benzaldehyde (FPB-ald, FCR 1260) up to 89 % and 11 % at pH 9 and 7, respectively and permethric acid (DCVA).

Table 84: Overview of DT_{50} and hydrolysis rate constants for Cyfluthrin diastereomers

pH		**DT_{50}**			**k_{water} [$days^{-1}$]**
		20 °C	**25 °C**	**12 °C**	**12 °C**
4	Diastereomers I + II	> 1 year	> 1 year	> 2 years	n.a.
	Diastereomers III + IV	> 1 year	> 1 year	> 2 years	n.a.
7	Diastereomers I + II	270 d	120 d	339 - 512 d	2.0 - 1.3 x 10^{-3}
	Diastereomers III + IV	160 d	75 d	212 - 303 d	3.3 - 2.3 x 10^{-3}
9	Diastereomers I + II	42 h	21 h	2.5 - 3.3 d	0.28 - 0.21
	Diastereomers III + IV	33 h	17 h	2.0 - 2.6 d	0.35 - 0.27

Cyfluthrin is stable in pH 4 and 5, as well as relatively stable at pH 7. The hydrolysis rates increase at pH 9, mean half-life of around 2.6 days was calculated. Significant hydrolysis products were 4-fluoro-3-phenoxy benzaldehyde (FPB-ald, FCR 1260) up to 89 % and 11 % at pH 9 and 7, respectively and permethric acid (DCVA).

Hydrolysis - Metabolites:

While FPB-ald was found stable to hydrolysis, chemical degradation due to hydrolysis of permethric acid (DCVA) was studied according to OECD test guideline No. 111.

Table 85: Hydrolysis - Permethric acid (DCVA)

Method /Guideline	**pH**	**Tempe-rature [°C]**	**Initial TS con-centration, C_0 [mg L^{-1}]**	**Reaction rate constant, k_h [$days^{-1}$]**	**Half-life, DT_{50} [days]**	**Coefficient of corre-lation, r^2**	**Reference**
OECD Guideline No. 111, preliminary test	4, 7, 9	50	100	no reaction constant can be determined	Stable over one week	n. a.	Krohn (1997b) A7.1.1.1.1/03

Permethric acid was found to be stable during the preliminary test at 50 °C at pH 4, 7 and 9. Thus, the corresponding half-life at 25 °C (and 12 °C certainly) is greater than 1 year.

Photolysis in water:

Table 86: Photolysis in water

Method /Guideline	Initial molar TS concentration	Total recovery of test substance [% of appl. a.s.]	Photolysis rate constant (k^c_p)	Direct photolysis sunlight rate constant (k_{pE})	Reaction quantum yield (Φ^c_E)	Half-life ($t_{1/2E}$)	Reference
No guideline study, laboratory own method	5 µg/L, 1 % acetonitrile	76 - 92	>0.693 day^{-1}	No actino-meter study	Not deter-mined	< 1 day	Gronberg, R.R. (1987) A7.1.1.1.2-01
No guideline study, laboratory own method	5 µg/l, 1 % acetonitrile	81 - 99	0.00236 h^{-1}	Not deter-mined	Not deter-mined	12.2 days	Puhl, et al. (1983) A7.1.1.1.2-02
UBA, Berlin, FRG (1990).	5.10 or 5.14 mg/L, acetonitrile (1:1)	--	0.00333 - 0.00695 h^{-1} (calculation model Frank and Klöpffer)		0.0052	3 to 60 days	Hellpointer, E. (1991) A7.1.1.1.2-04

During the study by Gronberg cyfluthrin samples were irradiated outdoors with natural sunlight (Kansas, USA 38°N) in August 1984 over a maximum period of 14 days. The tubes were tilted, so that the sun's rays would be perpendicular to the samples. Light intensity range was measured between 1150 and 4950 µW/cm². Analysis of parent as well as metabolites was carried out by thin-layer-chromatography. In the study by Puhl et al. the irradiation of sterile aqueous solutions of cyfluthrin was performed for 144 hours in a merry-go-around reactor using a medium pressure mercury vapour lamp. The intensity of the light source during the aqueous study was about 6700 µW/cm^2 at the sample surface. Transformation products were analysed by TLC as for parent compound. Even if the measured photolysis rate constant from the Gronberg study was not traceable, the photolysis rate constant measured during sunlight study at 38° latitude (Gronberg) exceeds more than 12 times the rate constant measured during mercury light exposure (Puhl et al.) leading to the difference in half-lives. The studies by Gronberg and Puhl et al. miss GLP standards and reference to approved test guidelines. Hence, only partly the identification of major photoproducts including percent of parent compound are an accepted study result.

The photodegradation study by Hellpointer allowed calculation of environmental half-lives based on reaction quantum yield of 0.0052. Using GC-solar half-lives between 2.8 days (summer 30-50° latitude) and 58 days (winter 60° latitude) are estimated in dependence on degree of latitude and seasonal conditions. Applying the model of "Frank & Klöpffer" environmental half-life yields to about 3 to 5 days. These arithmetic models take only direct photodegradation mechanisms into consideration. However, indirect photodegradation should also contribute to degradation processes in the environment.

Photolysis of Cyfluthrin results in rapid cleavage of the ester bond and formation of 4-fluoro-3-phenoxybenzaldehyd (FPB-ald) and 4-fluoro-3-phenoxybenzoic acid (FPB-acid), which are formed sequentially. During the sunlight study (Gronberg) the amounts of photodegradation products are

maximum 18 % and 37 % for FPB-ald and FPB-acid, respectively. The major metabolites detected during mercury light exposure (Puhl et al.) were FPB-ald (max. 3 %) and FPB-acid (max. 8.5 %).

In conclusion, solar radiation will contribute to the degradation of the test substance in aquatic systems.

Phototransformation in air:

Table 87: Phototransformation in air

Guideline / Test method	Time-dependent OH radical concentration [OH radicals cm^{-3}]	Overall reaction rate constant k [cm^3 $molecule^{-1} \times s^{-1}$]	Half-life [h]	Chemical lifetime [h]	Reference
Theoretical estimation according to Atkinson, using US EPA AOPWIN, version 1.4	Global 24-hours-mean concentration of 5×10^5	21.67 x 10^{-12}	17.8	25.8	Hellpointer, (1992) A7.3.1
No Guideline available, Estimation method by AOPWIN, version 1.91	Global 24-hours-mean concentration of 5×10^5	12.5 x 10^{-12}	30.8	44.4	C.A. (2006)

Based on half-life as well as chemical lifetime of Cyfluthrin, accumulation in the air is not to be expected.

Phototransformation in soil:

Table 88: Phototransformation in soil

Guideline/ Test method	Initial molar TS concentration	Photolysis rate constant (kcp)	Direct photolysis sunlight rate constant (kpE)	Half-life (t1/2E)	Reference
No guideline study, laboratory own method	1.075 mg of Cyfluthrin in 2.5 ml of acetonitrile	Phase I : 0.338 day^{-1} Phase II : 0.104 day^{-1}	No data.	Phase I : 2.1 days Phase II : 6.6 days	H.M. Chopade (1986) A7.2.2.4-03

The photo-decomposition of Cyfluthrin on soil (sandy loam) by natural sunlight was studied by Chopade (1986) at a concentration of 37 mg a.i./kg soil for up to 6 days. The photo decomposition of Cyfluthrin on sandy loam followed a biphasic degradation pattern. CA recalculated the DT50-value (4.4 days at mean T = 25 °C) by application of a Hockey-Stick-Model. This corresponds to DT50 = 12.3 days at an average EU outdoor temperature of 12 °C.

5.1.2 Biodegradation

5.1.3 Biodegradation estimation

No estimation of biodegradation was conducted.

5.1.4 Screening tests

No screening tests were performed.

5.1.4.1 Simulation tests

5.1.2.3.1 Surface water

Table 89: Aerobic aquatic degradation

Method	Test system	Test substance conc.	DT_{50}[1]	Mine-rali-sation	Degradation products	Reference
Laboratory study/ **No guideline**	Filtered Rhine water, in dark, 25±2 °C, pH 7.7-9.3	20 µg/L [fluoro-benzene-UL-^{14}C] Cyfluthrin	6.3 days (25 °C) 9.4 days (20 °C)	None	**FPB-acid** ($C_{13}H_9FO_3$, (4-fluoro-3-(4-hydroxyphenoxy)-benzoic acid) max 70 % **4'OH-FPB-acid** ($C_{13}H_9FO_4$, 4-fluoro-3-(4-hydroxyphenoxy)-benzoic acid) max 1.7 % **COOH-Cyfluthrin** ($C_{22}H_{19}Cl_2FNO_5$, α-[[[3-(2,2-dichloroethenyl)-2,2-dimethylcyclopropyl] carbonyl]oxy]-4-fluoro-3-phenoxy-benzeneacetic acid) max 2.3 %	Anderson, C. (1986) III-A7.1.2.2.1

[1] Recalculation by eCA according to FOCUS degradation kinetics report (2006) using ModelMaker 4.0

Dissipation of [fluorobenzene-UL-^{14}C] cyfluthrin was investigated in a study comparable to the relevant OECD guideline 309 (non-sterile, non-light exposed test system) under aerobic aquatic conditions with a non-adapted inoculum. Cyfluthrin dissipated rapidly in surface water during the first days of incubation under the given test conditions with a DT_{50} (25 °C) of 6.3 days. After day 7, dissipation clearly decelerated. Since turbidity and the microbial count increased considerably with incubation time, it was assumed that dissipation of cyfluthrin decelerated because of sorption to colloids. No mineralization to $^{14}CO_2$ was observed and dissipation of cyfluthrin seemed to be predominantly caused by abiotic chemical processes involving ester cleavage. Three metabolites were identified during incubation: FPB-acid, 4'OH-FPB-acid, and COOH-cyfluthrin. The content of metabolite FPB-acid increased continuously up to 70 % of applied radioactivity at day 21, whereas 4'OH-FPB-acid and COOH-cyfluthrin were found at only small amounts (up to 2.5 % of applied radioactivity). No information is available, weather the identified degradation products pose a hazard to the aquatic environment.

5.1.2.3.2 Water-Sediment

Table 90: Water-sediment degradation studies

Method	Test system	Test subst. conc.	DT_{50}[1]	Mine-rali-sation	Degradation products	Reference
US EPA § 162-4 (aerobic at 22 ± 2 °C in the dark, 70 days)	IJzendoorn system (IJS): orchard drainage ditch (NL), loamy sand: Corg 0.51 %, water: pH 6.8 Lienden system (LiS): fish pond (NL), loamy sand: Corg 1.05 %, water: pH 7.8	12 µg/L [Fluoro-benzene-UL-^{14}C]Cyflu-thrin	IJS (total system): 3.3 days (22 ± 2 °C) LiS (total system): 1.95 days (22 ± 2 °C)	IJS: 61.3 % (70 d) LiS: 67 % (70 d)	IJS: FPB-acid: max 44.5 % (11 d, total system) FPB-ald: max 15.7 % (1 d, total system) 3 further metabolites <10 % LiS: FPB-acid: max 35.7 % (1 d, total system) FPB-ald: max 9.5 % (1 d, total system) 2 further metabolites <10 %	Anderson, C. (1987) Hammel, K. (2007) III-A7.1.2.2.2/01 &02
SETAC (1995) & German BBA Part IV, 5-1 (aerobic at 20 ± 1 °C in the dark, 100 days)	Barmener See system (BSS): small closed gravel-pit (DE), sand: TOC 0.48 %, water: pH 8.2 Genkel system (GS): catchment basin Genkel creek (DE) silt loam: TOC 4.9 %, water: pH 7.6	8.1 µg/L [cyclo-propane-1-^{14}C] Cyflu-thrin	BSS (total system): 2.5 days (20 ± 1 °C) GS: (total system): 4.9 days (20 ± 1 °C)	BSS: 36.7 % (100 d) GS: 14.2 % (100 d)	BSS: DCVA: maximum 40.4 % (2 d, total system) 3 further metabolites <10 % GS: DCVA: maximum 47.6 % (28 d, total system) 3 further metabolites <10 %	Sneikus, J. (2000) Hammel, K. (2007) III-A7.1.2.2.2/03 &04

[1] Recalculation by eCA according to FOCUS degradation kinetics report (2006) using ModelMaker 4.0

The dissipation of [fluorobenzene-UL-^{14}C]cyfluthrin was studied in two Dutch water-sediment systems (a) IJzendoorn system, (b) Lienden system) under aerobic conditions in the dark at 22 ± 2 °C over a period of 70 days by Anderson (1987). Two water-sediment systems originating from Germany (c) Barmener See system, (d) Genkel system) were investigated by Sneikus (2000) under aerobic conditions in the dark at 20 ± 1 °C over a period of 100 days using [cyclopropane-1-^{14}C]cyfluthrin. In all systems, cyfluthrin was translocated very rapidly from the aqueous phase into the sediment and showed fast dissipation. Already after 30 minutes, 45 % and 65 % of applied radioactivity was found in the sediment in system (c) and (d), respectively. For system (a) and (b) in the study of Anderson (1987), DT_{50} values (22 °C) of cyfluthrin of 1.95 and 3.3 days, respectively, were determined for the entire system. In the study of Sneikus (2000), DT_{50} values (20 °C) of 2.5 and 4.9 days for system (c) and (d), respectively, were observed for the entire system.

System (a) IJzendoorn and (b) Lienden (loamy sand sediments) were characterised by a high degree of mineralization. After 70 days, more than 60 % of the applied radioactivity was found as $^{14}CO_2$. In

the systems (c) Barmener See (sand sediment) and (d) Genkel (silt loam sediment), the extent of ultimate degradation were less with 37 % and 14 % of applied radioactivity measured as $^{14}CO_2$ after 100 days.

The main metabolites observed in the water-sediment systems were FPB-acid (4-fluoro-3-phenoxybenzoic acid), FPB-ald (4-fluoro-3-phenoxybenzaldehyde, CAS-no.: 68359-57-9), and permethric acid (3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylic acid (DCVA), CAS-no.: 55701-05-8). In the total systems, FPB-acid reached a maximum of 44.5 % of applied radioactivity. For FPB-ald, the maximum was 15.7 %, for DCVA 47.6 %. Additionally, COOH-cyfluthrin, $CONH_2$-cyfluthrin (cyclopropanecarboxylic acid, 3-(2,2-dichloroethenyl)-2,2-dimethyl-, 2-amino-1-(4-fluoro-3-phenoxyphenyl)-2-oxoethyl ester), and 4'OH-FPB-acid were identified (<10 %) in the study of Anderson (1987). Small amounts of several unknown metabolites, never reaching 10 % of applied radioactivity, were observed in all water-sediment systems. The metabolites indicated an ester cleavage of cyfluthrin and subsequent oxidation.

The metabolite FPB-ald is classified to be toxic to aquatic life with long-lasting effects (H 411) according to (EG) No. 1272/2008. Environmental hazards have not been reported for permethric acid.

5.1.2.3.3 Soil

Table 91: Soil degradation studies

Method	Test system	Test subst. conc.	DT_{50}[1]	Mine-rali-sation	Degradation products	Reference
Accor-ding to existing German guide-lines in 1983 (aerobic at 20 ± 2 °C in the dark, 190 days)	<u>Laacherhof B:</u> Germany, loam: Corg 0.95 %, water: pH 6.2 moisture: 17 % <u>Laacherhof C:</u> Germany, sandy loam Corg 0.95 %, water: pH 5.9 moisture: 13 %	1 mg [fluoro-benzene-UL-^{14}C] cyflu-thrin/kg soil	58.9 days (20 ± 2 °C) 67.9 days (20 ± 2 °C)	32.0 % (190 d) **36.0 % (190 d)**	FPB-acid max 7 % (day 1) FPB-acid max 10 % (day 1)	Wagner et al. (1983a); IIIA7.2.1/ 01-04
SETAC Europe Proce-dures (1995) (aerobic at 9.4 in the dark, 121 days)	<u>Laacherhof A II:</u> Germany, silt loam Corg 0.9 %, water: pH 7.3 moisture: 40 % MHWC	0.089 mg [phenyl-UL-^{14}C] cyflu-thrin/kg soil	23.0 days (20 ± 2 °C)	39.8 % (121 d)	FPB-acid max 4.9 % (day 14)	Riegner (1997), Jersch-Schmitz (1997), IIIA7.2.2.1/01 &02
Accor-ding to OECD 307, US EPA OPPTS 835.4100, Canadian guidance PMRA DACO 8.2.3.4.2 (aerobic at 20 ± 2 °C in the dark, 122 days)	<u>Fresno:</u> California, sandy loam Corg 1.0 %, water: pH 7.6 moisture: pF 2 – 2.5 <u>Grand Forks County:</u> North Dakota, clay loam Corg 5.5 %, water: pH 5.7 moisture: pF 2 – 2.5	0.12 mg [cyclo-propane-1-^{14}C]cyflu-thrin/kg soil	<u>Fresno:</u> 11.4 days (20 ± 2 °C) <u>Grand Forks County:</u> 18.4 days (20 ± 2 °C)	<u>Fresno:</u> 48.5 % (122 d) <u>Grand Forks County:</u> 39.9 % (122d)	<u>Fresno:</u> DCVA max. 25.2 % day 7 <u>Grand Forks County:</u> DCVA max. 16.6 % day 7	Hiler (2013) IIIA7.2.1/09

[1] **Recalculation by eCA according to FOCUS degradation kinetics report (2006) using ModelMaker 4.0**

Degradation of ^{14}C-labeled cyfluthrin in soil was investigated in three aerobic laboratory studies with three German soils at 20 °C, 22 °C and 9.4 °C as well as two American soils at 20 °C. Half-lifes (20 °C) between 11.4 and 67.9 days were calculated. Mineralisation was low, ranging between 32.0 %

and 48.5 % at the end of incubation. Two metabolites, FBP-acid and permethric acid (DCVA) have been detected.

5.1.5 Summary and discussion of degradation

Studies on ready (OECD 301 A-F) and inherent biodegradability (OECD 302 B-C) of cyfluthrin were not performed. From this reason, the degradability of the substance was assessed by considering the results of higher tier biodegradation studies in water, water-sediment, and soil systems as well as abiotic degradation studies (hydrolysis). The substance was ultimately degraded to a maximum of 67.7 % within 70 days in a water-sediment system, whereas no mineralization was observed in a surface water simulation test. Mineralization was also low in soil, reaching a maximum of 48.5 % after 122 days of incubation in a laboratory experiment conducted under aerobic conditions. In the latter study, cyfluthrin was primarily degraded with a half-life of 11.4 days (20 °C). However, no information is available, whether the identified three degradation products (FPB-acid, 4'OH-FPB-acid, and COOH-cyfluthrin) pose a hazard to the aquatic environment.

Finally, the longest hydrolysis half-life (pH 4-9) for the cyfluthrin-diastereomers I-IV was 270 days at a temperature of 20 °C, corresponding to 512 d at 12 °C. Two degradation products 4-fluoro-3-phenoxybenzaldehyd (FPB-ald) and permethric acid (DCVA) were quantitatively identified during hydrolysis. Cyfluthrin is photolytically degraded with half-lives up to 58 days in dependence on degree of latitude and seasonal conditions. Photolysis of Cyfluthrin results in rapid cleavage of the ester bond and formation of 4-fluoro-3-phenoxybenzaldehyd (FPB-ald) and 4-fluoro-3-phenoxybenzoic acid (FPB-acid), which are formed sequentially. Of the resulting metabolites, FPB-ald is classified to be toxic to aquatic life with long-lasting effects (H 411).

Based on the available information, cyfluthrin does not fulfil the criteria to be considered as rapidly degradable.

5.2 Environmental distribution

5.2.1 Adsorption/Desorption

Table 92: Adsorption/desorption – Cyfluthrin

Method /Guideline	Tested Soils	Adsor-bed a.s.	K_a[1]	K_{aOC}[2]	K_d[3]	K_{dOC}[4]	K_a / K_d[5]	Degradation products		Reference
								Name	[%] of a.s.	
		[%]	[L.kg^{-1}]	[L.kg^{-1}]	[L.kg^{-1}]	[L.kg^{-1}]				
OECD 106 and US EPA 163-1										Burhenne, J. (1996) A7.1.3.-01
Soil 1	Laacher Hof	85.6	1116	124000	1448	160889	0.77			
Soil 2	Borstel	84.2	1244	180290	974	141159	1.28			
Soil 3	Howe	88.1	1321	117946	1307	116696	1.01			
Soil 4	Sable91	88.4	1793	73484	1705	69877	1.05			

[1] K_a = Adsorption coefficient
[2] K_{aOC} = Adsorption coefficient based on organic carbon content
[3] K_d = Desorption coefficient
[4] K_{dOC} = Desorption coefficient based on organic carbon content
[5] K_a / K_d = Adsorption / Desorption distribution coefficient

Based on the adsorption/desorption study, Cyfluthrin could be classified as being immobile in soil. The substance is strongly adsorbed to the soil (arithmetic mean K_{oc} of 4 soils: 123930 L.kg^{-1}). Cyfluthrin as well as the distribution of isomers of Cyfluthrin (diastereoisomers I-IV) remained unchanged in soil.

Table 93: Adsorption/desorption – metabolite DCVA

Method /Guideline	Tested Soils	pH H_2O	Ad-sorbed a.s.	K_a[1]	K_{aOC}[2]	K_d[3]	K_{dOC}[4]	K_a / K_d[5]	Degradation products		Reference
									Name	[%] of a.s.	
			[%]	[L.kg^{-1}]	[L.kg^{-1}]	[L.kg^{-1}]	[L.kg^{-1}]				
OECD 106 and US EPA 163-1											Slangen, P.M. (1999) A7.1.3. -02
Soil 1	Speyer 2.1	6.9	19	0.184	31.0	0.676	114.2	0.27			
Soil 2	Cranfield 115	8.1	17	0.224	13.9	0.498	31.1	0.45			
Soil 3	Cranfield 230	5.1	77	2.893	356.2	5.678	699.2	0.51			

[1] K_a = Adsorption coefficient
[2] K_{aOC} = Adsorption coefficient based on organic carbon content
[3] K_d = Desorption coefficient
[4] K_{dOC} = Desorption coefficient based on organic carbon content
[5] K_a / K_d = Adsorption / Desorption distribution coefficient

Adsorption of DCVA depends on pH of the soils: leading to higher K_{oc} in acid soils. The metabolite DCVA (permethric acid) was classified as being mobile in soils Speyer 2.1 and Cranfield 115 and

moderately mobile in soil Cranfield 230. The arithmetic mean K_{oc} of 3 soils is 133.7 L.kg^{-1} leading to a classification for DCVA to be mobile in soil. DCVA was stable during the adsorption/desorption study.

Table 94: Adsorption/desorption – metabolite FPB-acid

Method /Guideline	Tested Soils	pH H_2O	Adsor-bed a.s.	K_a[1]	K_{aOC}[2]	K_d[3]	K_{dOC}[4]	K_a / K_d[5]	Degradation products		Reference
									Name	[%] of a.s.	
			[%]	[L.kg^{-1}]	[L.kg^{-1}]	[L.kg^{-1}]	[L.kg^{-1}]				
OECD 106 and US EPA 163-1											Oddy, A. and Brett, R. (2005) A7.1.3. -03
Soil 1	Pikeville	6.1	23-54	1.23	123	2.32	232	0.53			
Soil 2	Stanley	6.4	23-72	1.80	86	2.13	101	0.85			
Soil 3	Hofchen	7.2	27-78	1.03	50	1.22	59	0.84			
Soil 4	Laacher Hof	6.8	22-54	0.65	39	0.89	54	0.73			
Soil 5	Wurm-wiese	6.4	31-82	1.39	67	1.76	85	0.79			

[1] K_a = Adsorption coefficient
[2] K_{aOC} = Adsorption coefficient based on organic carbon content
[3] K_d = Desorption coefficient
[4] K_{dOC} = Desorption coefficient based on organic carbon content
[5] K_a / K_d = Adsorption / Desorption distribution coefficient

FPB-acid was found to be mobile (arithmetic mean K_{oc} of 5 soils: 73 L.kg^{-1} ; with marginal indication of pH-dependence). Due to limited duration of the adsorption period, the determined K_{OC} are shifted to lower values. The compound was stable during the adsorption/desorption study in the limit of 5 hours investigation duration.

5.2.2 Volatilisation

The vapour pressure of the diastereomers I-IV of Cyfluthrin ranges from 1.4 x 10^{-8} to 9.6 x 10^{-7} Pa at 20 °C, direct evaporation is not expected, consequently. The Henry's Constants between 3.2 x 10^{-3} and 1.9 x 10^{-1} Pa × m^3 mol^{-1} at 20 °C point to potential of volatility from water. On the other hand, the strong tendency to soil partition minimizes atmospheric entry.

The chemical lifetime of Cyfluthrin in the troposphere was estimated to be 25.8 hours and 44.4 hours (calculated by RMS) considering a global 24-hours mean OH-radical concentration. Gathering from these results, accumulation of Cyfluthrin in the air is not to be expected.

Methods for determination of effects of chemicals on species arising from atmospheric contamination have not yet been fully developed. Furthermore, accumulation of a.s. Cyfluthrin in air is not to be expected and therefore no estimation of ecotoxicological effects on animal species for the air compartment is required.

5.2.3 Distribution modelling

Table 95: Leaching study – Cyfluthrin

Guide-line / test method	Exposure duration, design	Soil			Residue in leachates [%]				Reference
		Type	org. C %	pH	total	a. s.	Meta-bolites	others	
German BBA Guideline IV.4-2 formerly Bulletin (Merkblatt) No. 37	0 days	BBA Speyer standard soil 2.1	0.69	7.0	5.5	1	3.5	< 1	Scholz, K. Umgelder, U. (1985) A7.2.3.2
	90 days				3	< 1	< 2	1	

Aging study of Cyfluthrin in soil type 2.1 refers to rapid formation of CO_2 amounting between 25 and 40 % of the applied Cyfluthrin.

During both the leaching and aged-leaching tests Cyfluthrin was determined at values below 1 % in the leachate. Identified metabolites in the water phase are FPB-acid (maximum value 3.5 %), CONH2-Cyfluthrin and FPB-ald (values below 1 %).

Cyfluthrin was found only in the upper layer of the soil columns leading to the conclusion, that Cyfluthrin can be considered as immobile in soil.

5.3 Aquatic Bioaccumulation

Table 96: Summary of relevant information on aquatic bioaccumulation – Cyfluthrin

Method	Results	Remarks	Reference
Log K_{OW} values	Isomer I = 6.00 Isomer II = 5.94 Isomer III = 6.04 Isomer IV = 5.91	-	III A 7.4.2
Calculated Kinetics BCF [$L/kg_{wet\ fish}$]	1822	Due to a malfunction of the flow system no steady state-based BCF values were used, but only a kinetic BCFk was derived.	Anonymous. (2014), Study No. D78913 (2014) IIIA7.4.3.3.1/02

5.3.1 Aquatic bioaccumulation

5.3.1.1 Bioaccumulation estimation

Table 97: Estimation of aquatic bioaccumulation – Cyfluthrin

Basis for estimation	Diastereoisomer No.	log K_{OW} (measured)	Estimated BCF for fish (freshwater) [$L/kg_{wet\ fish}$]	Estimated BCF for fish eating bird/predator	Reference
Standard equation (74), TGD on Risk Assessment (2003), Part II, chapter 3.8.3.2	1	6.00	25119	-	-
	2	5.94	22336	-	
	3	6.04	27164	-	
	4	5.91	21062	-	

According to CLP a log $K_{OW} \geq 4$ is used to indicate a potential for bioaccumulation. Cyfluthrin consists of four diastereoisomers I-IV with log K_{OW} values ranging from 5.91 for diastereoisomer IV to 6.04 for diastereoisomer III. Since the log K_{OW} values of all diastereoisomers lie above the level of concern, the intrinsic potential for bioaccumulation in aquatic organisms has to be considered as being high for all diastereoisomers.

On the basis of these log K_{OW} values an approximate estimation of the bioconcentration factor BCF_{fish} was performed for the four diastereoisomers of Cyfluthrin using the standard equation (74) given in the EU Technical Guidance Document (TGD) on Risk Assessment (2003), Part II, 3.8.3.2. The calculated BCF is ranging between 27164 $L/kg_{wet\ fish}$ for diastereoisomer 3 with a log K_{OW} of 6.04 and 21062 $L/kg_{\ wet\ fish}$ for diastereoisomer 4 with a log K_{OW} of 5.91.

Both the log K_{OW} values and the calculation of the BCF_{fish} indicate a bioaccumulation potential for all four diastereoisomers of Cyfluthrin.

5.3.1.2 Measured bioaccumulation data

Table 98: Bioaccumulation studies

Guideline /Test method	**Expo-sure [d]**	**Initial concentr. (nominal) [ng/L]**	**Measured BCF (max.) [$L/kg_{wet\ fish}$]**	**Calculated Kinetics BCF [$L/kg_{wet\ fish}$]**	**Depuration time (DT_{50}) [d]**	**Identified Metabolites**	**Reference**
No guideline specified, laboratory's internal test method similar to OECD 305	28	140 (measured) Cyfluthrin (96 % purity)	854	-	9.0	no	Anonymous (1984) Report 455 III A7.4.3.3.1/01
OECD 305	28	120 (nom) beta-cyfluthrin (>98 % purity)	n.d.	1822	8.66	no	Anonymous (2014) Report D78913 III A7.4.3.3.1/02

A study with Bluegill sunfish (*Lepomis macrochirus*) from 1984 is available, which was conducted similar to OECD 305. Fish were exposed to a nominal concentration of 130 ng/L 14C-phenyl labelled Cyfluthrin for 28 days. Measured exposure concentrations varied from 64 ng/L to 206 ng/L. Total 14C residue BCF values for whole fish increased to a maximum of 854 $L/kg_{wet\ fish}$ on day 14 and then fluctuated down to 684 $L/kg_{wet\ fish}$ on day 21 and up to 791 $L/kg_{wet\ fish}$ on day 28. A stable steady state concentration was not reached, as only the two last mean concentrations of Cyfluthrin in fish tissue at day 28 and day 21 were within ± 20 % of each other. Metabolites were not found. BCF values for edible and nonedible portions as well as uptake and depuration rate constants were not determined. During the following depuration period of 28 days mean 14C residues in whole fish declined fairly rapidly in the depuration phase from 63 ng/g on day 0 to 23 ng/g (day 1) down to 4 ng/g (day 28) with a half-life of approximately 9 days. At the end of the depuration time, 96 % of the maximum tissue concentration was eliminated. A BCF of 854 $L/kg_{wet\ fish}$ was derived from the study which represents the highest value from the study, despite no stable steady state plateau was reached within the uptake period of 28 days.

According to the revised OECD 305 guideline a normalization to a standard lipid content of 5 % is foreseen. However, in this study from 1984 neither the lipid content of whole fish was determined nor sufficient data for an approximation was provided. Considering this, together with high variability

in fish weight, high variations between nominal and measured concentration of test substance in water in the uptake phase, high variability in cyfluthrin concentrations in fish between sampling dates and that the OECD guideline was significantly updated in the meantime, only a reduced reliability can be assigned to this study.

Another study on bioaccumulation was conducted with radio-labelled β-cyfluthrin, following a flow-through test design according to OECD 305 (2012) with *Lepomis macrochirus*. During the accumulation period, total radioactivity levels remained sufficiently constant to show equilibrium. However, due to a malfunction in the flow system on day 22, resulting in a level of 0.18 µg/L instead of 0.12 µg/L β-cyfluthrin. As this deviation significantly interferes with the approach of the steady-state, no steady state-based BCF values were used, but only a kinetic BCF_k was derived. Although provided in the original study report, the $BCF_{steady\text{-}state}$ cannot be considered as reliable. Mainly the parent substance accumulates in fish, contributing 95 % of total radioactive residue in fish, whereas only around 60 % of the radioactivity in the water phase could be assigned to the parent.

β-Cyfluthrin consists of 30 – 40 % of Diastereomer II (1R,3R, αS + 1S,3S, αR = 1:1; cis) and 57 – 67 % Diastereomer IV (1R,3S, αS + 1S,3R αR =1:1; trans). Cyfluthrin contains 17 – 21 % of Diastereomer II and 21 – 25 % of Diastereomer IV. Isomers II and IV are known to exhibit higher biological activity than I and III. Based on the significant amounts of Isomers II and IV in cyfluthrin and their known biological activity, it can be concluded that the assessment of β-cyfluthrin has high relevance for the evaluation of cyfluthrin. In the case of bioaccumulation it is appropriate to conclude that data for β-cyfluthrin are relevant for cyfluthrin, especially because the study available for cyfluthrin exhibits significant shortcomings. It should therefore be concluded that also for cyfluthrin there exists a potential for bioaccumulation.

5.3.2 Summary and discussion of aquatic bioaccumulation

With log K_{OW} values ranging from 5.91 for isomer IV to 6.04 for isomer III all existing isomers of Cyfluthrin are above the trigger value of 4. Hence, according to CLP criteria Cyfluthrin has to be considered as potentially bioaccumulative.

This is also confirmed by a calculated kinetic BCF_k = 1822 [$L/kg_{wet\ fish}$] for beta-Cyfluthrin. Although Cyfluthrin contains less of the isomers II and IV (17 – 21 % of Diastereomer II and 21 – 25 % of Diastereomer IV), the nevertheless significant amount of 38 – 46 %, in combination with the high biological activity of these two isomers, leads to the conclusion that this data is also relevant for cyfluthrin. Hence, the available BCF_k for beta-Cyfluthrin supports the potential for bioaccumulation identified in the screening step. As the BCF in fish significantly exceeds the trigger (≥ 500 L/kg), Cyfluthrin is considered as having a high potential for bioaccumulation.

5.4 Aquatic toxicity

Table 99: Summary of relevant information on aquatic toxicity

Method	Results	Remarks	Reference
Fish			
US EPA FIFRA G. 72-1 equivalent to OECD 203 *Oncorhynchus mykiss* flow-through, 96 h	LC_{50} = 302 ng/l	results based on mean measured concentrations test substance: cyfluthrin (purity 97.6 %)	Anonymous (1994) Report 106652 A 7.4.1.1/01
FIFRA G. 72-1 equivalent to OECD 203 *L. macrochirus* flow-through, 96 h	LC_{50} = 998 ng/l	results based on mean measured concentrations test substance: cyfluthrin (purity 97.6 %)	Anonymous (1994) Report 106774 A 7.4.1.1/02
OECD 203 *C. carpio* flow-through, 96 h	LC_{50} = 5570 ng/l	results based on mean measured concentrations test substance: cyfluthrin (purity 96.6 %)	Anonymous (2004) Report EBBDU004 A 7.4.1.1/03
Test laboratory's internal method, equivalent to EPA - FIFRA § 72-4 and OECD 210 *Oncorhynchus mykiss* flow-through, 58 d	NOEC = 10 ng/l	results based on mean measured concentrations test substance: cyfluthrin (purity 96 %)	Anonymous (1985) Report 683 A 7.4.3.2/01
US-EPA FIFRA § 72-4 guideline, 40 CFR, Section 158.145 *Pimephales promelas* flow-through, 307 d	NOEC = 140 ng/L	results are based on mean measured concentrations test substance: 14C-cyfluthrin (purity 99 %)	Anonymous (1990) Report 100097
Invertebrates			
EPA G. 72-2 (1982) equivalent to OECD 202 *Daphnia magna* flow-through, 48 h	LC_{50} = 160 ng/l	results are based on mean measured concentrations test substance: cyfluthrin (purity 98.6 %)	Burgess, D. (1990) A 7.4.1.2/01
ASTM, 1980 *Procambarus clarkii* flow-through, 96 h	LC_{50} = 62 ng/l	results are based on mean measured concentrations test substance: cyfluthrin (purity 97 %)	Suprenant, D.C. (1990) A 7.4.1.2/02
OCSPP draft 850.1020 *Hyalella azteca* flow-through, 96 h	LC_{50} = 0.55 ng/l	results are based on mean measured concentrations	Bradley, M.J. (2013) A7.4.1.2/05

		test substance: cyfluthrin (purity 95,8 %)	
ASTM Draft No. 3 (1981) equivalent to OECD 211 *Daphnia magna* flow-through, 21 d	NOEC = 20 ng/l	results are based on mean measured concentrations test substance: cyfluthrin (purity 94.7 %)	Forbis, A. D. (1984) A 7.4.3.4
OCSPP draft 850.1350 *Americamysis bahia* flow-through, 28 d	NOEC = 0.41 ng/l	results are based on mean measured concentrations test substance: beta-cyfluthrin (purity 99.2 %)	Schwader, A.L. (2013) A7.4.3.4/02
Algae			
Draft Proposal for Updating OECD Guideline 201 (2004), JMAFF guideline (2000) *Pseudokirchneriella subcapitata* static, 72 h	NOE_rC = 4.45 mg/l E_rC50 > 8.05 mg/l	results are based on initial mean measured concentrations test substance: cyfluthrin (purity 96.6 %)	Dorgerloh, M. (2004) A 7.4.1.3
Other aquatic organisms (including sediment)			
EPA - Springborn Smithers Protocoll No.: 051704 *Chironomus tentans* spiked sediment with renewal of overlying water per day, 10 d	LC_{50} = 280 µg /kg dw	results are based on mean measured sediment concentrations test substance: cyfluthrin (purity 99 %)	Putt, A (2005) A7.4.3.5.1/01
EPA 100.5, 850.SUP and SS-1069 *Chironomus dilutus* spiked sediment with renewal of overlying water, 63 d	Emergence: 6.2 µg/kg dw	results are based on mean measured sediment concentrations test substance: cyfluthrin (purity 95.8 %)	Picard, C.R. (2013a) A 7.4.3.5.1/02
EPA 100.5, 850.SUP and SS-1069 *Hyalella azteca* spiked sediment with renewal of overlying water, 42 d	NOEC = 20 µg/kg dw	results are based on mean measured sediment concentrations test substance: cyfluthrin (purity 95.8 %)	Picard C.R. (2013b), A 7.4.3.5.1/03
EPA Guideline series 850 *Leptocheirus plumulosus* spiked sediment with renewal of overlying water, 28 d	NOEC = 13 µg/kg dw	results are based on mean measured sediment concentrations test substance: cyfluthrin (purity 93.3 %)	Putt, A.E. (2005a) A 7.4.3.5.1/04

5.4.1 Fish

5.4.1.1 Short-term toxicity to fish

Table 100: Short-term toxicity data

Guideline /Test method	Species	Endpoint / Type of test	Exposure		Results [ng/L]			Remarks	Reference
			design	duration	LC_0	LC_{50}	LC_{100}		
US EPA FIFRA G. 72-1 equivalent to OECD 203	*O. mykiss* (rainbow trout)	mortality	flow-through	96 h	NOEC 104.5	302	-	results based on mean measured concentrations test substance: cyfluthrin	Anonymous (1994) Report 106652 A 7.4.1.1/01
FIFRA G. 72-1 equivalent to OECD 203	*L. macrochirus* (bluegill sunfish)	mortality	flow-through	96 h	509	998	1567	results based on mean measured concentrations test substance: cyfluthrin	Anonymous (1994) Report 106774 A 7.4.1.1/02
OECD 203; JMAFF 12 Nohsan No. 8147; EPA-FIFRA G. 72-1	*C. carpio* (common carp)	mortality	flow-through	96 h	2560	5570	20800	results based on mean measured concentrations test substance: cyfluthrin (96.6 % purity)	Anonymous (2004) Report EBBDU004 A 7.4.1.1/03

Acute toxicity of Cyfluthrin to fish was investigated in studies which can be considered equivalent to OECD Guideline 203. Three different fish species were exposed under flow-through conditions for 96 h. The first study (Report 106652) was performed with rainbow trout (*Oncorhynchus mykiss*). A total of twenty fish per test concentration (instead of 10) and a solvent control and dilution water control were used. The nominal concentrations were 130, 216, 360, 600 and 1000 ng cyfluthrin/L corresponding to a mean measured concentrations of 104.5, 145.8, 240.1, 432.3, 642.1 ng/l, respectively. Mean measured ^{14}C-cyfluthrin concentrations were less than 70 % of nominal in two concentrations, however the variability of the measured concentrations within each test level over the test period did not deviate significantly (factor of <1.2 in each concentration). The temperature range was 11.8 – 12.5 °C and the pH range 6.4 – 7.4. All validity criteria were fulfilled and the study is scored with a reliability of 1.

There were no mortalities or adverse effects observed with the control or solvent control fish. The 96 h LC_{50} was 302 ng/L (95 % confidence limits 240 to 432 ng/l). The no observed effect level was 104.5 ng/l. The results are based on mean measured concentrations.

In the second study (Report 106774) twenty bluegill sunfish (*Lepomis macrochirus*) were exposed to ^{14}C Cyfluthrin at each of the following nominal test concentrations 194, 324, 540, 900, 1500 and 2500 ng/l. A dilution water control and solvent control were also included. The mean measured concentrations for the exposure period ranged from 56 to 64 % of nominal. However, all other validity criteria were fulfilled and the results are therefore based on mean measured concentrations. The

temperature range was 21.7 – 22.2 °C and the pH range 7.2 – 7.6. The reliability of the study was considered to be 1.

Mortality of bluegill exposed for 96 hours to ^{14}C-cyfluthrin was 0 % in the mean measured concentrations of 111, 187, 348, and 509 ng/l. At 845 ng/L there was 25 % mortality and 100 % mortality at 1567 ng/l. Furthermore behavioural and sublethal effects were observed at these concentrations, included erratic behaviour and loss of equilibrium. There were no mortalities or adverse effects observed with the control or solvent control fish. Based on the mortality data the 96 hour LC_{50} was 998 ng/L with 95 percent confidence limits of 845 to 1567 ng/l.

In the third study (Report EBBDU004) ten species of *Cyprinus carpio* were exposed at each of the following nominal test concentrations 0.625, 1.25, 2.5, 5.0 and 10 µg/l. A dilution water control and solvent control were also included in the study. The mean measured concentrations for the exposure period ranged from 30 % to 215 % of nominal as a dosing above the water solubility of the test compound was required to fulfil requirements from MAFF. The results are therefore based on mean measured concentrations. The temperature range was 22.6 – 23.3 °C and the pH range 7.0 – 7.2. The test conditions met all the validity criteria and the reliability was considered to be 1.

There were behavioural observations on fish caused by the test item over the whole exposure period in all test levels > 2.56 µg a.s. /l. There were no mortalities or adverse effects observed with the control or solvent control fish. The 96 hour LC_{50} value for *Cyprinus carpio* was 5.57 µg/L (95 %-C.L.: 4.05 – 7.65 µg/l) based on mean measured concentrations).

The NOEC was considered to be 0.365 µg/l, the highest concentration with no sublethal effects. The maximum concentration causing no significant mortality, the no observed lethal effect concentration was 2.56 µg/l.

5.4.1.2 Long-term toxicity to fish

Table 70: Long-term toxicity data

Guideline /Test method	Species	Endpoint / Type of test	Exposure		Results [ng/L]		Remarks	Reference
			design	duration	NOEC	LOEC		
No guideline specified, test laboratory' s internal test method is equivalent to EPA - FIFRA § 72-4 and OECD 210	*O. mykiss* (rainbow trout)	- hatchability - growth rate - mortality in larvae and fish	flow-through	58 d	growth: 10	growth: 17.7	results based on mean measured concentrations test substance: cyfluthrin	Anonymous (1985) Report No. 683 A 7.4.3.2/01

US-EPA FIFRA § 72-4 guideline, 40 CFR, Section 158.145	*Pimephales promelas*		flow-through	307 d	140	290	results are based on mean measured concentrations test substance: ^{14}C-cyfluthrin (purity: 99.0 %)	Anonymous (1990) Report No. 100097

The long-term toxicity of Cyfluthrin to two fish species was investigated according to a test procedure, which can be considered equivalent to EPA-FIFRA G. 72-4 and OECD 210. In the first study (Report 683) the toxicity to early life stages of rainbow trout was tested under flow through conditions over a period of 58 days. No test guideline was stated within the study report, but the method described is equivalent to EPA-FIFRA and OECD guidelines. 100 trout eggs were exposed through larval stage using the test concentrations of 25, 50, 100, 200 and 400 ng/L (nominal) equivalent to 10.0, 17.7, 31.8, 84.8 and 160.0 ng Cyfluthrin/L (mean) in two replicates per concentration. The mean concentrations, as determined by chemical analysis, ranged from 32 to 48 % of the nominal concentrations. Hatching, mortality and growth of larvae and fishes were observed. The most sensitive parameter in this test was growth, measured as fish weight. The NOEC was determined to be 10 ng/L and the LOEC of this endpoint was 17.7 ng/L based on mean measured concentrations.

In the second study (Report 100097) newly fertilized eggs (<24 hours post-fertilization) were exposed for 301 days post-hatch. Mean measured exposure concentrations were 0.018, 0.033, 0.065, 0.14 and 0.29 µg/L ^{14}C-Cyfluthrin. These mean values ranged from 106 to 116 % of the nominal concentrations of 0.016, 0.031, 0.063, 0.13 and 0.25 µg/L. Of the 82 % average ^{14}C-activity recovered, 90 % was characterised as ^{14}C-Cyfluthrin. Hatching, mortality growth (standard length and wet weight), reproductive success were observed. The study is valid according to the current US EPA protocol OPPTS 850.1500 Fish life cycle toxicity. A mortality rate of 37.5 % in the control group 153 – 301 days post-hatch was determined. Hence, data about survival 153 – 310 d considered as not fully reliable. The no observed effect concentration (NOEC) was 0.14 µg/L based on mean measured concentration (corresponding to a nominal concentration of 0.13 µg/L).

5.4.2 Aquatic invertebrates

5.4.2.1 Short-term toxicity to aquatic invertebrates

Table 71: Aquatic invertebrates short-term toxicity data

Guideline /Test method	**Species**	**Endpoint / Type of test**	**Exposure**		**Results [ng/L]**			**Remarks**	**Reference**
			design	**duration**	**EC_0**	**EC_{50}**	**EC_{100}**		
EPA G. 72-2 (1982) equivalent to OECD 202	*Daphnia magna* (water flea)	mortality	flow-through	48 h	NOEC 28	LC_{50} 160	-	results are based on mean measured concentrations test substance: cyfluthrin	Burgess, D. (1990) A 7.4.1.2/01
"Standard Practice for Conducting Acute Toxicity Tests with Fishes, Macroinvertebrates, and Amphibians" (ASTM, 1980).	*Procambarus clarkii* (Crayfish)	mortality	flow-through	96 h	-	LC_{50} 62	-	results are based on mean measured concentrations test substance: cyfluthrin	Suprenant, D.C. (1990) A 7.4.1.2/02
OCSPP draft 850.1020	*Hyalella azteca*	mortality	flow-through	96 h	< 0.2	**LC_{50}** **0.55**	1.6	results are based on mean measured concentrations test substance: cyfluthrin	Bradley, M.J. (2013) A7.4.1.2/05

The acute toxicity of Cyfluthrin to invertebrates was investigated in flow-through tests with *D. magna, P.clarkii* and *H. azteca* according to ASTM and EPA methods, which can be considered as equivalent to the corresponding OECD Guidelines.

In the test with daphnids (Burgess 1990) 40 water fleas were exposed at each of the following nominal test concentrations 0.018, 0.036, 0.075, 0.15 and 0.30 µg/L, dilution water control and solvent control in four replicates per treatment. Measured test concentrations ranged from 67 – 89 % of nominal values, therefore the results based on mean measured concentrations.

The other acute test with invertebrates (Suprenant 1990) was conducted with 20 crayfishes, which were exposed in a flow-through test system in duplicate test chambers to the nominal test concentrations 18, 27, 42, 65 and 100 ng/L. A dilution water control and solvent control were also included in the study. Biological observations were made at 24, 48, 72 and 96 hours. Mean measured concentrations ranged from 58 – 79 % of nominal values, therefore the results are based on mean measured concentrations.

A further study (Bradley 2013), performed with the freshwater amphipod *Hyalella azteca*, has been evaluated and considered as relevant. The study followed an acute 96 h flow-through test design without sediment with nominal concentrations of 0.20, 0.40, 0.80, 1.6 and 3.2 ng/L Cyfluthrin (measured concentrations: 0.17, 0.32, 0.60, 1.2 and 2.6 ng/L). The study is considered as valid and reliable. Based on mortality and on mean measured concentrations, a LC_{50} = 0.55 ng/L (95 % confidence interval of 0.47 to 0.64 ng/L) was derived.

5.4.2.2 Long-term toxicity to aquatic invertebrates

Table 72: Aquatic invertebrates long-term toxicity data

Guideline /Test method	Species	Endpoint / Type of test	Exposure		Results [ng/L]		Remarks	Reference
			design	duration	NOEC	LOEC		
ASTM Draft No. 3 (1981) equivalent to OECD 211	*Daphnia magna* (water flea)	- mortality - adult length - young per adult per reproductive day	flow-through	21 d	reproduction and adult length: 20 adult survival: 41	reproduction: 41	results are based on mean measured concentrations test substance: cyfluthrin	Forbis, A. D. (1984) A 7.4.3.4
OCSPP draft 850.1350	*Mysidopsis bahia*	reproduction, length, body weight, mortality	flow-through	28 d	0.41	0.83	results are based on mean measured concentrations test substance: beta-cyfluthrin	Schwader, A.L. (2013) A7.4.3.4/02

Ten first instar daphnids per treatment in four replicates were exposed in a long-term reproduction test for 21 days under flow-through conditions to Cyfluthrin (Forbis 1984). The study was conducted in accordance with an ASTM method from 1981 and is in principle comparable to OECD 211. The nominal concentrations were 18, 29, 65, 120 and 240 ng/L, and the mean measured concentrations were 18, 20, 41, 80 and 220 ng/L Cyfluthrin, which represents 63 % to 100 % of nominal values. Control and solvent control were included. The 21 day NOEC value for reproduction and adult length was 20 ng/L based on mean measured concentrations of Cyfluthrin. The NOEC for adult survival was 41 ng/L, 100 % mortality occurred at the highest mean measured concentration of 220 ng/L. The validity criteria are fulfilled and the test is acceptable.

Considering the acute effect data for invertebrates, *Daphnia magna* has been shown to be two magnitudes less sensitive than the most sensitive species tested, *Hyalella azteca*. However, long-term data for Cyfluthrin is only available for *D. magna*, which would not cover the differences in species sensitivity observed in the acute dataset. However, for beta-Cyfluthrin a relevant additional study with the marine mysid *Americamysis bahia* is available and should be considered for hazard assessment: Cyfluthrin consists of approximately 40 % beta-Cyfluthrin, therefore representing a major constituent.

Cyfluthrin and beta-Cyfluthrin share the same chemical structure (c.f. section 4), 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, III and IV), beta-

cyfluthrin mainly consists of the two most active diastereomers II and IV (diastereomer II: 30.0 – 40.0 %, diastereomer IV: 57.0 – 67.0 % of the sum of the four diastereoisomers; see Table 11). Due to the common structure of the diastereomers it can be assumed that all diastereomers show a similar biological activity and share the same insecticidal mode of action. Therefore it was generally accepted for the biocidal (cyfluthrin) and plant protection evaluation (beta-cyfluthrin) that both substances share a similar ecotoxicological profile.

There are indications from scientific literature 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, Cyfluthrin would be approximately 2.4 times less toxic as beta-Cyfluthrin (Cyfluthrin consists of 40 % diastereomers II + IV). However it has to be 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 has to be assumed. Furthermore, it has been shown that isomer III can synergise the activity of isomer IV and as a consequence, 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).

Therefore equivalent effect levels for both substances can be concluded and effect studies with beta-Cyfluthrin can be considered for the hazard assessment of Cyfluthrin, at least in case of additional species tested.

The chronic study with *Americamysis bahia* covers 28 days under flow-through conditions and was 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. The test substance showed less acute toxicity than observed in the acute study with *H. azteca* (LC_{50} > 1.5 ng/L). Based on female body length and reproduction (mean number of offspring), a NOEC of 0.41 ng/L beta-Cyfluthrin (mean measured) was derived after 28 days.

5.4.3 Algae and aquatic plants

Table 73: Algae and aquatic plant data

Guideline / Test method	**Species**	**Endpoint / Type of test**	**Exposure**		**Results [mg/L]**			**Remarks**	**Reference**
			design	**duration**	**NOE_rC**	**E_bC_{50} [1]**	**E_rC_{50} [2]**		
Draft Proposal for Updating OECD Guideline 201 (2004), JMAFF guideline (2000)	*Pseudokirchneriella subcapitata* (freshwater microalgae)	growth inhibition	static	72 h	4.45		> 8.05	results are based on initial mean measured concentrations test substance: cyfluthrin	Dorgerloh, M. (2004) A 7.4.1.3

Pseudokirchneriella subcapitata was exposed for three days under static exposure conditions to the nominal concentrations of 1.0, 3.1, 10, 31 and 100 mg/L plus control and solvent control. The study (Dorgerloh 2004) was performed in accordance with draft proposal for updating OECD guideline 201. The measured concentrations on day 0 were 0.325, 0.977, 3.61, 4.45 and 8.05 mg/L, which

represents 8 to 37 % of nominal concentrations (average 24.8 %). The measured concentrations on day 3 were 0.539, 1.32, 9.08, 2.60 and 35.3 mg/L, representing 8 to 91 % of nominal concentrations (average 46.4 %). The discrepancy between the nominal and the measured concentrations of Cyfluthrin in the test medium may be caused by its limited solubility under test conditions and its tendency to adsorb easily to glass surfaces. The concentrations determined at day 3 were generally higher than those determined at day 0, therefore all effect results based on initial measured test concentrations reflects as such worst case exposure concentrations. The algae growth in the control and solvent control cultures did not follow a monotone exponential growth, which is a prerequisite for growth rate evaluation. In addition, it has to be considered that the effect value exceeds the water solubility of Cyfluthrin by orders of magnitude. This may be due to the use of DMF as solvent. However, as algae are not the critical species for the aquatic hazard assessment, the test is acceptable and used for the assessment.

5.4.4 Other aquatic organisms (including sediment)

Table 74: Further data for aquatic organisms

Guideline / Test method	Species	Endpoint / Type of test	Exposure		Results [µg/kg dw]			Remarks	Reference
			design	duration	NOEC	LOEC	LC_{50}/ EC_{50}		
EPA - Springborn Smithers Protocol ll No.: 051704	*Chironomus tentans* (midge)	survival growth	spiked sediment with renewal of overlying water per day	10 d	survival: 63 growth: 240	survival: 120 growth: 460	survival: 280 growth: 740	results are based on mean measured sediment concentrations test substance: cyfluthrin	Putt, A (2005b) A7.4.3.5.1/01
EPA 100.5, 850.SUP and SS-1069	*Chironomus dilutus*	survival growth emergence reproduction	Spiked sediment with renewal of overlying water	63 d	Survival: 13 Growth: 13 **Emergence: 6.2**	Survival: 40 Growth: > 13 Emergence: 13	Survival: 17 Growth: > 13 Emergence: 16	results are based on mean measured sediment concentrations test substance: cyfluthrin	Picard, C.R. (2013a) A 7.4.3.5.1/02
EPA 100.5, 850.SUP and SS-1069	*Hyalella azteca*	Survival Growth reproduction	Spiked sediment with renewal of overlying water	42 d	Survival: 20 Growth: 20 Reproduction:20	Survival: > 20 Growth: > 20 Reproduction: > 20	Survival: 75 Growth: > 130 Reproduction: 32	results are based on mean measured sediment concentrations test substance: cyfluthrin	Picard C.R. (2013b), A 7.4.3.5.1/03
EPA Guideline series 850	*Leptocheirus plumulosus*	Survival growth	Spiked sediment with renewal of overlying water	28 d	Survival: 13 Growth: 13	Survival: 35 Growth: 35	Survival: 35 Growth: 36l	results are based on mean measured sediment concentrations test substance: cyfluthrin	Putt, A.E. (2005a) A 7.4.3.5.1/04

The short-term toxicity of Cyfluthrin to *Chironomus tentans* in a water-sediment system was determined according an EPA test method for ten days (Putt 2005b). At start of test 300-mL glass test vessels were filled with 100 mL sediment (equivalent to 151 g wet weight per vessel) and 175 mL of overlying water. The sediment was spiked using a jar-rolling technique. The sediment was from natural source with 5.5 % organic carbon, 12 % silt, 5.5 % clay and a pH- value of 4.9. The renewal of overlying water was conducted by addition of two volumes of water per day with 50 mL per cycle and 14 cycles per day. Second to third instar larvae (10 days old) were exposed to 31, 63, 125, 250, 500 and 1000 µg/kg dw nominal concentrations of Cyfluthrin, these concentrations were chosen based on results of a preliminary testing. Analytical measurement was performed on day 0 and 10 in sediment, pore water and overlying water, the sediment mean measured concentrations are 29, 63, 120, 240, 460 and 870 µg/kg dw. During the exposure period, the test organisms were fed with fresh fish food in a rate of 1.5 mL fish food suspension (4 mg/L) once daily. Therefore, the exposure pathway of sediment ingestion is underestimated by this test. Survival of the midges was the most sensitive parameter resulting in an LC_{50} of 280 µg/kg dw.

Three tests are available that studied the long-term toxicity of cyfluthrin on benthic organisms. In a study according to EPA test method the effects of cyfluthrin applied to sediment on the life-cycle of the midge *Chironomus dilutus* (Picard 2013a) was determined. The study was performed for a period of 63 days with renewal of overlying water. Artificial sediment consisting of 6 % sphagnum peat, 20 % kaolin clay and 74 % fine sand with an organic carbon content of 2.3 % was used. Based on the results of preliminary testing, the nominal cyfluthrin treatment levels chosen for the definitive study were 1.6, 3.1, 6.7, 13 and 40 µg/kg nominal equivalenting to 1.6, 3.1, 6.2, 13 and 40 µg/kg mean measured, respectively. Exposure concentrations in sediment and pore water were measured on days 0 (test initiation), 20 and 63 (test termination). The midge larvae were fed a diet consisting of a finely ground flaked fish food suspension (4.0 mg/mL). During the exposure, the food was introduced at a rate of 1.5 mL of flaked fish food suspension per test vessel per day. Therefore, the exposure pathway via sediment ingestion was underestimated by this test. Studied endpoints were survival, growth, emergence, emergence rate, days to death and reproduction (e.g., egg masses per mated female, eggs per egg mass, number of eggs per mated female, egg hatchability and days to oviposition) of the midge. The most sensitive endpoint was emergence, resulting in a 63d-NOEC of 6.2 µg/kg dw. For the other endpoints a NOEC of 13 µg/kg dw was found.

In a further long-term study the effects of cyfluthrin applied to sediment on the freshwater amphipod, *Hyalella azteca* (Picard 2013b) was examined. The study was performed under static-renewal conditions for a period of 42 days with renewal of overlying water. Natural freshwater sediment consisting of 3 % clay, 8 % silt and 89 % sand with an organic carbon content of 3.1 % was used. Based on the results of preliminary testing, the nominal cyfluthrin treatment levels chosen for the definitive study were 3.3, 8.3, 21, 52 and 130 µg/kg nominal equivalent to 3.0, 8.0, 20, 54 and 130 µg/kg, mean measured. Exposure concentrations were measured on day 0 (test initiation), day 14 and day 28 (termination of sediment phase of the exposure) in the pore water and sediment. The amphipods were fed a diet consisting of yeast, cereals leaves and flaked fish food. During the exposure, the food was introduced at a rate of 1 mL per test vessel per day. Therefore, the exposure pathway via sediment ingestion was underestimated by this test. The primary endpoints used for determination of significant effects by statistical evaluation include the survival and growth (length) of adult amphipods at test day 28 and reproduction (based on cumulative young produced per female) on test days 28 through 42. In addition, test day 35 survival and reproduction, as well as test day 42 adult amphipod survival, growth (length) and male:female ratio were also evaluated as supplemental endpoints. For all studied endpoints the NOEC was 20 µg/kg dw.

A third study (Putt 2005a) examined the long-term toxicity of cyfluthrin applied to sediment on the marine amphipod *Leptocheirus plumulosus*. The study was performed under static-renewal conditions for a period of 28 days with renewal of overlying water. Natural marine sediment consisting of 13 % clay, 19 % silt and 68 % sand with an organic carbon content of 4.1 % was used. Based on the results of preliminary testing, the nominal cyfluthrin treatment levels chosen for the definitive study were 1.9, 5.6, 17, 50, 150 and 450 µg/kg nominal equivalent to 1.4, 3.8, 13, 35, 60 and 290 µg/kg, mean measured. Exposure concentrations were measured on day 0 and day 28 in the pore water and sediment. The amphipods were fed a diet consisting of finely ground flaked fish food. During the exposure, the food was introduced at a rate of 2-4 mL per test vessel per day. Therefore, the exposure pathway via sediment ingestion was underestimated by this test. Studied endpoints were survival and growth of the test organisms. For both endpoints a NOEC of 13 µg/kg dw was found.

5.5 Comparison with criteria for environmental hazards (sections 5.1 – 5.4)

Acute aquatic hazard

For Cyfluthrin acute studies are available for fish, crustaceae and algae. Crustaceae are the most sensitive trophic level and the most sensitive endpoint is a LC_{50} = 0.00000055 mg/L for *Hyalella azteca*.

The criterion for classification as H400 "Very toxic to aquatic life" is a $LC_{50} \leq 1$ mg/l. Hence, cyfluthrin fulfils this criterion and has to be classified as Aquatic Acute 1, H400 with an M factor = 1 000 000.

Long-term aquatic hazard

Cyfluthrin is considered as not rapidly degradable and the experimentally determined BCF exceeds the trigger value 500 indicating a high potential for bioaccumulation.

For Cyfluthrin adequate chronic toxicity data is available for all three trophic levels. Therefore according to EC No 286/2011 (2. ATP) the long-term aquatic classification has to be based on chronic aquatic toxicity data. The most sensitive trophic level are crustaceae with *Americamysis bahia* being the most sensitive organism with a 28d-NOEC = 0.00000041 mg/l.

For not rapidly degradable substances the criterion for classification as H410 "Very toxic to aquatic life with long lasting effects" is EC_{10}/NOEC $\leq$ 0.1 mg/l. Cyfluthrin fulfils this criterion and has to be classified as Aquatic Chronic 1, H410 with an M-factor = 100 000.

5.6 Conclusions on classification and labelling for environmental hazards (sections 5.1 – 5.4)

According to CLP Cyfluthrin has to be classified as:

Aquatic Acute 1; H400, M = 1 000 000

Aquatic Chronic 1; H410, M = 100 000

Labelling:

Signal word: Warning

Pictogram: GHS 09

Hazard statement: H410 Very toxic to aquatic life with long lasting effects

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), M = 1000 DS proposal: Aquatic Acute 1 (H400), M = 1000000, Aquatic Chronic 1 (H410), M = 100000

Degradation

Abiotic degradation

Hydrolysis of cyfluthrin has been 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) and later recalculated for 12°C for fresh water.

Cyfluthrin is found to be stable at pH 4 and 5 (> 2 years), as well as relatively stable at pH 7 (DT_{50} 193 - 270 days – the maximum value corresponding to 512 d at 12°C). The hydrolysis rates increase at pH 9 (DT_{50} < 2 days), mean half-life of around 2.6 days was calculated to 12°C.

Direct photodegradation half-lives were calculated based on a reaction quantum yield of 0.0052 and UV absorption data. Using GC-solar, half-lives between 2.8 days (summer 30-50° latitude) and 58 days (winter 60° latitude) were estimated, being dependent on degree of latitude and seasonal conditions; half-lives ranged from 2.8 to 32 days. Consequently, solar radiation is regarded to contribute to the degradation of cyfluthrin in aquatic systems.

The photodecomposition of cyfluthrin on sandy loam by natural sunlight at a concentration of 37 mg a.i./kg soil, for up to 6 days, followed a biphasic degradation pattern and showed ready degradation. A recalculated half-life value (4.4 days at mean 25 °C) corresponds to DT_{50} 12.3 days at 12 °C.

Photolysis of cyfluthrin in the natural sunlight results in DT_{50} <1 day and during mercury light exposure DT_{50} 12.2 days.

Biodegradation

No ready biodegradation screening test was available for cyfluthrin.

Cyfluthrin was shown to dissipate rapidly in surface water under aerobic aquatic conditions with a non-adapted inoculum during the first days of incubation with a DT_{50} (25°C) of 6.3 days, corresponding to DT_{50} 17.8 days at 12°C. Dissipation clearly decreased after day 7 due to sorption to colloids increased by turbidity and the microbial count with incubation time. No mineralisation was observed.

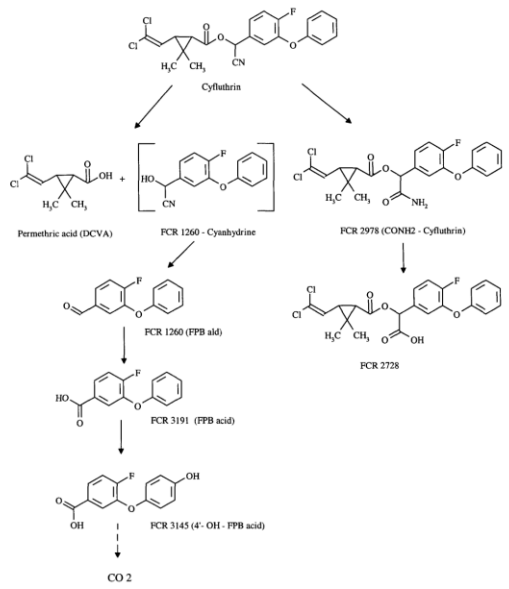
The dissipation of cyfluthrin was studied in four water-sediment systems where cyfluthrin was transferred rapidly from the water to the sediment and degraded in all systems. DT_{50} values < 10 days at 12°C were determined.

The metabolism/degradation pathway of cyfluthrin is mainly 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 CO_2 and bound residues. The DS gave no information on the hazards of the metabolites to the aquatic environment. However, the metabolite FPB-ald (4-fluoro-3-phenoxybenzaldehyde, FCR 1260, CAS-no.: 68359-57-9) appears to be classified as toxic to aquatic life with long-lasting effects (H411) according to Annex VI of the CLP Regulation.

Metabolites of cyfluthrin:

Environmental compartment	**Metabolites**
Abiotic degradation	

Hydrolysis	• FPB-ald (4-fluoro-3-phenoxybenzaldehyde, FCR 1260, CAS-no.: 68359-57-9) up to 89% of the radioactivity at pH 9 (day 21) up to 11% at pH 7 (day 35). *FPB-ald was stable to hydrolysis.* • Permethric acid ((DCVA) 3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylic acid, CAS-no.: 55701-05-8) *Also considered stable (DT_{50} < 1 years) during hydrolysis.*	
Photolysis	• FPB-ald Natural sunlight: max. 18% Mercury light: max. 3% • FPB-acid (4-fluoro-3-phenoxybenzoic acid, FCR 3191, CAS-no.: 77279-89-1) Natural sunlight: max. 37% Mercury light: max. 8.5%	
Biodegradation		
Aerobic aquatic degradation	• FPB-acid Content increased continuously up to 70% of applied radioactivity at day 21 • 4'OH-FPB-acid (4-fluoro-3-(4-hydroxyphenoxy)-benzoic acid, FCR 3145), • COOH-cyfluthrin (α-[[[3-(2,2-dichloroethenyl)-2,2-dimethylcyclopropyl]carbonyl]oxy]-4-fluoro-3-phenoxybenzeneacetic acid, FCR 2728). Up to 2.5% of applied radioactivity in total	

Water sediment 	• FPB-acid (4-fluoro-3-phenoxybenzoic acid, FCR 3191, CAS-no.: 77279-89-1) maximum of 44.5% of applied radioactivity • FPB-ald maximum of 15.7% of applied radioactivity • DCVA maximum of 47.6% of applied radioactivity • COOH-cyfluthrin • $CONH_2$-cyfluthrin (cyclopropanecarboxylic acid, 3-(2,2-dichloroethenyl)-2,2-dimethyl-, 2-amino-1-(4-fluoro-3-phenoxyphenyl)-2-oxoethyl ester, FCR 2947) • 4'OH-FPB-acid <10% of applied radioactivity in total

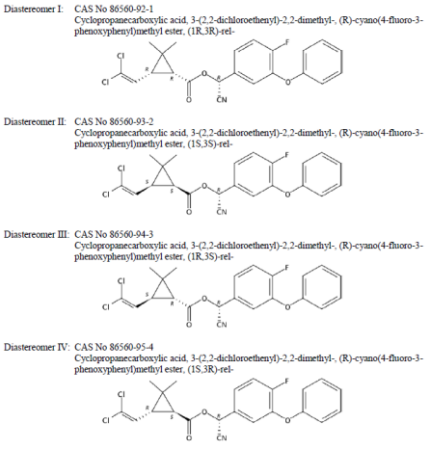
The DS concluded that as cyfluthrin does not ultimately degrade to greater than 70% in aquatic systems and undergoes to primary degradation to classifiable products, cyfluthrin does not fulfil the criteria to be considered as rapidly degradable in the aquatic environment. This is based on data for cyfluthrin.

<u>Justification of read-across of data to cyfluthrin from beta-cyfluthrin for bioaccumulation and aquatic toxicity</u>

Cyfluthrin and beta-cyfluthrin are mixtures of eight isomers, four of the isomers are considered active. The proportion of diastereoisomer pairs and their structures in cyfluthrin and beta-cyfluthrin is 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**.



Cyfluthrin consists of approximately 40% beta-cyfluthrin, therefore representing a major constituent. Cyfluthrin and beta-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) and plant protection evaluation (beta-cyfluthrin) that both substances share a similar toxicological profile.

There are indications from scientific literature that diastereomers I and III could be regarded as around one order of magnitude less active than isomers II and IV (Leicht, 1996). If only diastereomers II and IV would be biologically active, cyfluthrin would be approximately 2.4 times less toxic as beta-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 levels of relevance of data for both substances can be concluded and effect studies with beta-cyfluthrin are considered for the hazard assessment of cyfluthrin.

Bioaccumulation

Cyfluthrin consists of four diastereoisomers I-IV with log K_{OW} values ranging from 5.91 for diastereoisomer IV to 6.04 for diastereoisomer III. 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 ranged between 27164 L/kg_{wet} in fish, for diastereoisomer III, and 21062 L/kg_{wet} in fish, for diastereoisomer IV.

From a study similar to OECD TG 305 of reduced reliability with Bluegill sunfish, a BCF of 854 L/kg_{wet} fish for cyfluthrin has been derived, which represents the highest value from the study, despite no stable steady state plateau being reached within the uptake period of 28 days.

Another bioaccumulation study following a flow-through test design according to OECD TG 305 with *Lepomis macrochirus* and radio-labelled beta-cyfluthrin has been provided. A reliable BCF_k of 1822 L/kg_{wet} fish was derived. The DS adds that in the case of bioaccumulation it is appropriate to conclude that data for beta-cyfluthrin is relevant for cyfluthrin, especially because the study available for cyfluthrin exhibits significant shortcomings (see section on justification of read-across of data to cyfluthrin from beta-cyfluthrin).

The DS considers cyfluthrin as having a high potential for bioaccumulation based on reliable Log K_{ow}s > 4 for diastereomers of cyfluthrin and a BCF_k > 500 for beta-cyfluthrin.

Aquatic toxicity

Summary of relevant information on aquatic toxicity of cyfluthrin

Test	Test species	Result **µg/L**	Reference
Fish			

cyfluthrin (purity 97.6%) US EPA FIFRA G. 72-1 equivalent to OECD TG 203 flow-through, 96 h	*Oncorhynchus mykiss*	LC_{50} = 0.302 based on mean measured concentrations	Anonymous (1994) Report 106652 A 7.4.1.1/01
cyfluthrin (purity 97.6%) FIFRA G. 72-1 equivalent to OECD TG 203 flow-through, 96 h	*Lepomis macrochirus*	LC_{50} = 0.998 based on mean measured concentrations	Anonymous (1994) Report 106774 A 7.4.1.1/02
cyfluthrin (purity 96.6%) OECD TG 203 flow-through, 96 h	*Cyprinus carpio*	LC_{50} = 5.57 based on mean measured concentrations	Anonymous (2004) Report EBBDU004 A 7.4.1.1/03
cyfluthrin (purity 96%) Test laboratory's internal method, equivalent to EPA - FIFRA § 72-4 and OECD TG 210 flow-through, 58 d	*Oncorhynchus mykiss*	NOEC = 0.01 based on mean measured concentrations	Anonymous (1985) Report 683 A 7.4.3.2/01
^{14}C-cyfluthrin (purity 99%) US-EPA FIFRA § 72-4 guideline, 40 CFR, Section 158.145 flow-through, 307 d	*Pimephales promelas*	NOEC = 0.14 based on mean measured concentrations	Anonymous (1990) Report 100097
Invertebrates			
cyfluthrin (purity 98.6%) EPA G. 72-2 (1982) equivalent to OECD TG 202 flow-through, 48 h	*Daphnia magna*	LC_{50} = 0.16 based on mean measured concentrations	Burgess, D. (1990) A 7.4.1.2/01
cyfluthrin (purity 97%) ASTM, 1980 flow-through, 96 h	*Procambarus clarkii*	LC_{50} = 0.062 based on mean measured concentrations	Suprenant, D.C. (1990) A 7.4.1.2/02
cyfluthrin (purity 95.8%) OCSPP draft 850.1020 flow-through, 96 h	*Hyalella azteca*	**LC_{50} = 0.00055** based on mean measured concentrations	Bradley, M.J. (2013) A7.4.1.2/05
cyfluthrin (purity 94.7%) ASTM Draft No. 3 (1981) equivalent to OECD TG 211 flow-through, 21 d	*Daphnia magna*	NOEC = 0.02 (reproduction and adult length) based on mean measured concentrations	Forbis, A. D. (1984) A 7.4.3.4
beta-cyfluthrin (purity 99.2%) OCSPP draft 850.1350 flow-through, 28 d	*Americamysis bahia*	**NOEC = 0.00041** based on mean measured concentrations	Schwader, A.L. (2013) A7.4.3.4/02
Algae/Other aquatic organisms			
cyfluthrin (purity 96.6%) Draft Proposal for Updating OECD Guideline 201 (2004), JMAFF guideline (2000) static, 72 h	*Pseudokirchneriella subcapitata*	NOE_rC = 4.45 mg/L E_rC_{50} > 8.05 based on initial mean measured concentrations	Dorgerloh, M. (2004) A 7.4.1.3
cyfluthrin (purity 99%) EPA - Springborn Smithers Protocol No.: 051704	*Chironomus tentans*	LC_{50} = 280 µg/kg dw	Putt, A (2005) A7.4.3.5.1/01

spiked sediment with renewal of overlying water per day, 10 d		based on mean measured sediment concentrations	
cyfluthrin (purity 95.8%) EPA 100.5, 850.SUP and SS-1069 spiked sediment with renewal of overlying water, 63 d	*Chironomus dilutus*	Emergence: 6.2 µg/kg dw based on mean measured sediment concentrations	Picard, C.R. (2013a) A 7.4.3.5.1/02
cyfluthrin (purity 95.8%) EPA 100.5, 850.SUP and SS-1069 spiked sediment with renewal of overlying water, 42 d	*Hyalella azteca*	NOEC = 20 µg/kg dw based on mean measured sediment concentrations	Picard C.R. (2013b) A 7.4.3.5.1/03
cyfluthrin (purity 93.3%) EPA Guideline series 850 spiked sediment with renewal of overlying water, 28 d	*Leptocheirus plumulosus*	NOEC = 13 µg/kg dw based on mean measured sediment concentrations	Putt, A.E. (2005a) A 7.4.3.5.1/04

Acute Aquatic Toxicity

Acute toxicity of cyfluthrin to fish was investigated in studies that were considered reliable and equivalent to OECD TG 203. Three different fish species (Rainbow trout, Bluegill sunfish and Common carp) were exposed under flow-through conditions for 96 h. The LC_{50} values ranged from 0.000302 mg/L to 5.57 µg/L. The lowest no observed effect level out of the three acute fish toxicity tests was 0.105 µg/L. The results are based on mean measured concentrations.

The acute toxicity of cyfluthrin to invertebrates was investigated in flow-through tests with Daphnia, crayfish, and *Hyalella azteca* according to ASTM and EPA methods, which can be considered as equivalent to the corresponding OECD test guidelines. The tests results were all based on mean measured concentrations and considered reliable. The most sensitive species was *Hyalella azteca*, the 96 h study was performed without sediment with nominal concentrations of 0.20, 0.40, 0.80, 1.6 and 3.2 ng/L (measured concentrations: 0.17, 0.32, 0.60, 1.2 and 2.6 ng/L). Based on mortality, a **LC_{50} = 0.00055 µg/L** was derived.

The acute toxicity of cyfluthrin to midge in a water-sediment system was also determined, resulting in an LC_{50} of 280 µg/kg dw based on mean measured sediment concentrations and survival as the most sensitive parameter.

Chronic Aquatic Toxicity

The chronic toxicity of cyfluthrin to two fish species (Rainbow trout and Fathead minnow) was investigated according to a flow-through test procedures, 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.

The presented acceptable Daphnia chronic study was conducted in accordance with an ASTM method in principle comparable to OECD TG 211. The 21-d NOEC value for reproduction and adult length was 0.02 µg/L based on mean measured concentration and for adult survival 0.041 µg/L, 100% mortality occurred at the highest mean measured concentration of 0.22 µg/L.

Considering the acute effect data for invertebrates, *Daphnia magna* has been shown to be two orders of magnitude less sensitive than the most sensitive species tested, *H. azteca*. Long-term data for cyfluthrin is only available for *D. magna*, which would not cover the differences in species sensitivity observed in the acute dataset. However, for beta-cyfluthrin a relevant additional chronic study with the marine mysid *A. bahia* is available and has been considered for hazard assessment (see above section on justification of read-across of data to cyfluthrin from beta-cyfluthrin).

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** for beta-cyfluthrin (mean measured) was derived.

Three tests presented that studied the long-term toxicity of cyfluthrin on benthic organisms *C. dilutus*, *H. azteca* and *L. plumulosus* resulted in a 63-d NOEC of 6.2 µg/kg dw (emergence), 42-d NOEC of 20 µg/kg dw (survival, growth and emergence) and in a 28-d NOEC of 13 µg/kg dw (survival and growth), respectively, based on mean measured sediment concentrations.

Toxicity in Algae

A study with *P. subcapitata* in accordance with the draft proposal for updating OECD TG 201 has been presented. There are discrepancies between the nominal and the measured concentrations of cyfluthrin in the test medium and the algae growth in the control and solvent control cultures do not follow a monotonal exponential growth. In addition, the effect value exceeds the water solubility of cyfluthrin by several orders of magnitude. However, the test is considered acceptable for hazard assessment, especially as algae are not the critical species for the aquatic hazard assessment.

Comments received during public consultation

Two MSCAs supported the proposed environmental classification of Aquatic Acute 1, H400 (M = 1000000) and Aquatic Chronic 1, (M = 100000) based on the available data for the most sensitive species (Invertebrates: *H. Azteca*; 96-h LC_{50}= 0.55 ng/L and *A. bahia* 28-d NOEC=0.41 ng/L), respectively.

One MSCA commented that the study on which the acute classification is based (Bradley, 2013) can be considered valid and reliable for hazard classification. Regarding using the available chronic endpoint 28-d NOEC of 0.00000041 mg/L (mm) for *A. bahia*, it was noted that beta-cyfluthrin is anticipated to be more toxic than cyfluthrin and the surrogate approach using the *H. Azteca* acute endpoint for cyfluthrin chronic classification results in an M-factor of 1000000. It was further noted that *H. Azteca* appears to be more sensitive to the active isomers in cyfluthrin and beta-cyfluthrin on the basis of a less sensitive acute 96-h LC_{50} of 0.0000022 mg/L (mm) for *A. bahia* using beta-cyfluthrin.

The same MSCA also agreed that algae are not likely to be the most sensitive species for hazard assessment but did not agree that the presented acute toxicity study with *P. subcapitata* is suitable for definitive hazard classification as the study controls were not valid.

Assessment and comparison with the classification criteria

Taking into account the argumentation for read-across of aquatic toxicity data from beta-cyfluthrin to cyfluthrin based on cyfluthrin consisting of approximately 40% beta-cyfluthrin (II + IV) and sharing the same chemical structure as well as the corresponding diastereomers, RAC agrees with the DS that read-across from beta-cyfluthrin to cyfluthrin can be made for bioaccumulation and aquatic toxicity in algae.

RAC agrees with the DS submitter that based on data for cyfluthrin, there is no evidence that cyfluthrin degrades to a degree greater 70% over 28 days. Cyfluthrin is subject to rapid primary degradation (DT_{50} < 16 days) via photodegradation and in water/sediment systems. However, as some of the degradation metabolites appear to meet the criteria for hazardous to the aquatic environment under CLP, cyfluthrin cannot be considered as rapidly degradable in the aquatic environment. Therefore, RAC agrees with the DS to consider 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 diastereomers of cyfluthrin. Consequently, RAC agrees with the DS that cyfluthrin is bioaccumulative in the aquatic environment.

There are reliable experimental data on acute toxicity on fish and invertebrates available for cyfluthrin, the lowest value being a 96-h LC_{50} for *H. azteca* of 0.00055 µg/L.

There is reliable experimental data on chronic toxicity for fish and invertebrates for cyfluthrin. However, RAC does not consider the algal data for cyfluthrin reliable for classification purposes due to the previously mentioned issues (regarding monitoring data and algal control growth). RAC considers the read-across acceptable and uses aquatic toxicity data for algae using beta-cyfluthrin to complete the data set, even though this makes no difference to the classification outcome. In the read-across algae study, beta-cyfluthrin was tested at one concentration of 0.01 mg as/L as higher test concentrations could not be examined due to low water solubility. No effects were seen at this concentration (NOEC ≥ 0.01 mg/L for biomass and the growth rate).

Having accepted the read-across from beta-cyfluthrin, the lowest available chronic toxicity value is a 28-d NOEC for *A. bahia* 0.00041 µg/L based on a study with beta-cyfluthrin. However, it can be expected that, based on the content of biological active isomers, beta-cyfluthrin is possibly up to 2.4 or 1.3 times more toxic than cyfluthrin. Therefore, classifying cyfluthrin using beta-cyfluthrin data as proposed by the DS may underestimate the chronic effects of cyfluthrin on the most sensitive species (*H. azteca*). As there is no chronic data for the most sensitive species under acute testing for cyfluthrin, RAC considers it appropriate to use acute data with cyfluthrin under the surrogate approach to derive a chronic classification for cyfluthrin.

The chronic classification derived using the 28-d NOEC for *A. bahia* of 0.00000041 mg/L using beta-cyfluthrin, results in a classification of Aquatic Chronic 1, M=100000, for a not rapidly degradable substance. Although RAC considers the read-across acceptable, the acute 96-h LC_{50} for *H. azteca* of 0.00000055 mg/L with cyfluthrin results in a more stringent classification of Aquatic Chronic 1, M = 1000000, following CLP table 4.1.0(b)(iii) and 4.1.3.

Data that RAC considers for comparison with the CLP criteria are summarised in the table below.

Table: *Summary of data for classification of cyfluthrin*

Results	Test substance	Remarks
Fish		
96-h LC_{50} = 0.000302 mg/L *Onchorhynchus mykiss*	cyfluthrin	
58-d NOEC = 0.000010 mg/L *Oncorhynchus mykiss*	cyfluthrin	growth
Invertebrates		
96-h LC_{50} = 0.00000055 mg/L *Hyalella azteca*	cyfluthrin	
21-d NOEC = 0.000020 mg/L *Daphnia magna*	cyfluthrin	
Algae/Aquatic plants		
E_rC_{50} = > 10 µg/L NOE_rC = 10 µg/L *Scenedesmus subspicatus*	beta-cyfluthrin	read-across from beta-cyfluthrin

Note – following use of the surrogate approach, chronic data for beta-cyfluthrin is no longer used.

In conclusion, RAC agrees with the DS that based on an LC_{50} of 0.00000055 mg/L for *H. azteca*, cyfluthrin warrants classification as **Aquatic Acute 1 (H400), M=1000000**.

However, for chronic classification RAC disagrees with the DS and proposes to classify cyfluthrin as **Aquatic Chronic 1 (H410), M=1000000** based on the surrogate approach using the LC_{50} of 0.00000055 mg/L for *H. Azteca*, as no chronic data is available for this species.

RAC notes that if long-term data on *H. Azteca* becomes available, the classification could be reconsidered.

6 OTHER INFORMATION

None.

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8 ANNEXES

Confidential Annex