Committee for Risk Assessment

RAC

Opinion

proposing harmonised classification and labelling
at EU level of

cypermethrin (ISO); α-cyano-3-phenoxybenzyl 3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylate; cypermethrin cis/trans +/- 40/60

EC Number: 257-842-9
CAS Number: 52315-07-8

CLH-O-0000006733-71-01/F

Adopted

5 December 2019

5 December 2019

CLH-O-0000006733-71-01/F

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

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

Chemical name: **cypermethrin (ISO); α-cyano-3-phenoxybenzyl 3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylate; cypermethrin cis/trans +/- 40/60**

EC Number: **257-842-9**

CAS Number: **52315-07-8**

The proposal was submitted by **Belgium** and received by RAC on **13 November 2018.**

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

PROCESS FOR ADOPTION OF THE OPINION

Belgium has submitted a CLH dossier containing a proposal together with the justification and background information documented in a CLH report. The CLH report was made publicly available in accordance with the requirements of the CLP Regulation at ***http://echa.europa.eu/harmonised-classification-and-labelling-consultation/*** on **21 January 2019**. Concerned parties and Member State Competent Authorities (MSCA) were invited to submit comments and contributions by **22 March 2019**.

ADOPTION OF THE OPINION OF RAC

Rapporteur, appointed by RAC: **Miguel A. Sogorb**

Co-Rapporteur, appointed by RAC: **Katalin Gruiz**

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

The RAC opinion on the proposed harmonised classification and labelling was adopted on **5 December 2019** by **consensus**.

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

	Index No	Chemical name	EC No	CAS No	Classification		Labelling			Specific Conc. Limits, M-factors and ATE	Notes
					Hazard Class and Category Code(s)	Hazard statement Code(s)	Pictogram, Signal Word Code(s)	Hazard statement Code(s)	Suppl. Hazard statement Code(s)		
Current Annex VI entry	607-421-00-4	cypermethrin (ISO); α-cyano-3-phenoxybenzyl 3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylate; cypermethrin cis/trans +/- 40/60	257-842-9	52315-07-8	Acute Tox. 4* Acute Tox. 4* STOT SE 3 Aquatic Acute 1 Aquatic Chronic 1	H332 H302 H335 H400 H410	GHS07 GHS09 Wng	H332 H302 H335 H410			
Dossier submitters proposal	607-421-00-4	cypermethrin (ISO); α-cyano-3-phenoxybenzyl 3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylate; cypermethrin cis/trans +/- 40/60	257-842-9	52315-07-8	**Retain** Aquatic Acute 1 Aquatic Chronic 1 **Add** STOT RE 2 **Modify** Acute Tox. 4 Acute Tox. 4	**Retain** H400 H410 **Add** H373 (nervous system) **Modify** H332 H302	**Retain** GHS07 GHS09 Wng **Add** GHS08	**Retain** H410 **Add** H373 (nervous system) **Modify** H332 H302		**Add** M=100 M=1000	
RAC opinion	607-421-00-4	cypermethrin (ISO); α-cyano-3-phenoxybenzyl 3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylate; cypermethrin cis/trans +/- 40/60	257-842-9	52315-07-8	**Retain** Aquatic Acute 1 Aquatic Chronic 1 **Add** STOT RE 2 **Modify** Acute Tox. 4 Acute Tox. 4	**Retain** H400 H410 **Add** H373 (nervous system) **Modify** H332 H302	**Retain** GHS07 GHS09 Wng **Add** GHS08	**Retain** H410 **Add** H373 (nervous system) **Modify** H332 H302		**Add** oral; ATE = 500 mg/kg bw inhal; ATE = 3.3 mg/L M=100 000 M=100 000	
Resulting Annex VI entry if agreed by COM	607-421-00-4	cypermethrin (ISO); α-cyano-3-phenoxybenzyl 3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylate; cypermethrin cis/trans +/- 40/60	257-842-9	52315-07-8	Acute Tox. 4 Acute Tox. 4 STOT SE 3 STOT RE 2 Aquatic Acute 1 Aquatic Chronic 1	H332 H302 H335 H373 (nervous system) H400 H410	GHS07 GHS08 GHS09 Wng	H332 H302 H335 H373 (nervous system) H410		oral; ATE = 500 mg/kg bw inhal; ATE = 3.3 mg/L M=100 000 M=100 000	

GROUNDS FOR ADOPTION OF THE OPINION

RAC general comment

Cypermethrin (ISO) is an active substance used in plant protection and in biocidal products as an insecticide and has been evaluated in the framework of the former Directive 98/8/CE for PT8 (wood preservatives) and under the current Biocide Regulation 528/2012 for PT18 (insecticides, acaricides and products to control other arthropods). The current CLH proposal is focused on the revision of the existing acute toxicity classification, assessment of the available data relevant to STOT RE, and on the setting of M factors for the environment classification.

In response to a comment received during the consultation of the CLH report, the Dossier Submitter (DS) has confirmed that **the classification proposal of this CLH-report applies exclusively to the cis/trans +/- 40/60 isomeric mixture**.

HUMAN HEALTH HAZARD EVALUATION

RAC evaluation of acute toxicity

Summary of the Dossier Submitter's proposal

The CLH-report summarised data from 3 acute oral toxicity studies: (1) A study with a Klimisch (1997) reliability score of 1 yielded an LD_{50} of 500 mg/kg bw; (2) a study with a reliability score of 2 yielded an LD_{50} in males of 1732 mg/kg bw; and (3) a study with a reliability score of 3, using a cypermethrin with a cis:trans composition slightly different from the 40/60 considered in this proposal, yielded an LD_{50} of 250 mg/kg bw. The DS did not consider the information provided in the third study in its assessment due to its low reliability. The DS proposed classification of cypermethrin for acute oral toxicity category 4 H302 (Harmful if swallowed). No ATE was proposed.

The CLH-report summarised data from 2 acute inhalation toxicity studies: (1) a study with a reliability score of 1 producing no mortalities at 3.56 mg/L of cypermethrin with a cis:trans composition slightly different from the 40/60 considered in this proposal; and (2) an acute inhalation toxicity study with a reliability score of 2 yielding an LC_{50} in males of 3.281 mg/L. The DS proposed classification of cypermethrin within acute inhalation toxicity category 4 H332 (Harmful if inhaled). No ATE was proposed by the DS.

Comments received during public consultation

Two MSCA agreed with the proposals for classification for acute oral and inhalation toxicity. A third MSCA considered that the classification for acute oral toxicity should be set using the LD_{50} of 250 mg/kg bw because the difference with other studies reporting higher LD_{50} values might be due to the higher susceptibility of the young animals used in this study. The DS agreed with the proposal and changed their position to classification as acute oral toxicity category 3.

Assessment and comparison with the classification criteria

The tables below summarise the available acute toxicity studies by oral and inhalation routes with cypermethrin, respectively. The tables were built from information provided in the CLH-report.

***Table**: Summary of animal studies on acute oral toxicity with cypermethrin*

<table>
<tr><th>Study</th><th>Dose level</th><th>Results</th><th>Reference</th></tr>
<tr><td>OECD 423

GLP

Reliability 1

Wistar rats
3 females/group

15 days post exposure period</td><td>Cypermethrin cis:trans 40:60

Purity 94 %

300, 2000 mg/Kg bw in refined groundnut oil</td><td>No clinical signs of toxicity and no mortalities at 300 mg/kg bw

Slight/severe salivation, tremors, lethargy, ataxia and perineum wet with urine at 2000 mg/kg bw

One rat died on day 2 without abnormalities detected at necropsy and the other 2 died on day 3 with lung congestion

LD_{50} = 500 mg/kg bw (using the converted acute toxicity point estimate from table 3.1.2 of Annex I to CLP)</td><td>Study dated in 2005, author not available to RAC</td></tr>
<tr><td>Protocol partially consistent with OECD 401

Pre-GLP

Reliability 2

Tif:RAIf (SPF) rats

Male/female

5/sex/group

14 days post exposure period</td><td>Cypermethrin cis:trans 40:60

Purity 92.6 %

300, 600, 1 200, 2 500, 5 000 mg/Kg bw in arachis oil</td><td>Dyspnoea, exophthalmos, ruffled fur, diarrhoea, tremor and curved body in all test groups

Tonic clonic convulsions were observed from 600 mg/kg bw and onwards

At 1200, 2500 and 5000 mg/kg bw salivation, sedation and lateral/ventral body position

Surviving animals recovered within 10-12 days

Number and day of deaths
Dose (mg/kg bw) / Number dead / Time
Males
300: 0/5
600: 0/5
1200: 1/5 D1
2500: 3/5 D1
5000: 5/5 D1 (3) and D3 (2)
Females
300: 0/5
600: 0/5
1 200: 0/5
2 500: 4/5 D1
5 000: 5/5 D1 (4) and D3 (1)

LD_{50} in males = 1732 mg/kg bw
LD_{50} in females = 2150 mg/kg bw
LD_{50} in both sexes = 1945 mg/kg bw</td><td>Study dated in 1984, author not available to RAC</td></tr>
<tr><td>No guideline

No GLP

Wistar rats

Reliability 3

10 males/group</td><td>Cypermethrin cis:trans 37:63

Purity 92.4 %

Dose levels not mentioned

Vehicle: corn oil</td><td>LD_{50} = 250 mg/kg bw</td><td>Cantalamessa , 1993 Arch Toxicol 67:510-513</td></tr>
</table>

***Table**: Summary of animal studies on acute inhalation toxicity with cypermethrin*

<table>
<tr><th>Study</th><th>Dose level</th><th>Results</th><th>Reference</th></tr>
<tr><td>OECD 403

GLP

Reliability 1

5 Wistar rats/sex/group

Mist

4 hours

Head and nose

15 days post exposure period</td><td>Technical cypermethrin
cis:trans 53:47

Purity 94 %

0, 3.56 mg/L in DMSO

Mean particle size: 1.11±0.67 µm (0 mg/L) and 1.23±0.70 µm (3.56 mg/L)</td><td>Lethargy, slight/severe salivation, eye and nasal discharge and tremors on day 1

Lethargy on day 2

No animals died during the test period

LC_{50} > 3.56 mg/L</td><td>Study dated in 2005, author not available to RAC</td></tr>
<tr><td>OECD 403

No GLP

Reliability 2

Tif:RAIf (SPF) rats

5/sex/group

Aerosol

4 hours

Nose only

15 days post exposure period</td><td>Cypermethrin
cis:trans 40:60

Purity 92.6 %

0, 0.97, 1.926, 3.462 and 5.328 mg/L in ethanol</td><td>Control group: sedation, dyspnea, exophthalmos and ruffled fur at the day of the exposure

Test groups: dyspnea, ruffled fur, curved body and convulsions in both sexes with dose-dependent increase in intensity and duration

At the top dose extreme irritability and hyperkinetic behaviour

Surviving animals recovered within 9 days. All deaths occurred during exposure or within 2 hours thereafter

Half of the animals in the two higher dose groups showed mottled haemorrhagic or oedematous lungs, as well as dilatation of the stomach

<table><tr><td colspan="2">Occurrence of mortalities</td></tr><tr><td>mg/L</td><td>Number dead</td></tr><tr><td>0
0.970
1.926
3.462
5.328</td><td>0/10
0/10
1/10 (1/5 female)
3/10 (2/5 males + 1/5 females)
8/10 (5/5 males + 3/5 females)</td></tr></table>
LC_{50} males = 3.281 mg/L
LC_{50} female = 5.038 mg/L
LC_{50} both sexes = 3.894 mg/L</td><td>Study dated in 1985, author not available to RAC</td></tr>
</table>

Comparison with the criteria

Three different acute oral toxicity studies were presented in the CLH-report (Table " Summary of animal studies on acute oral toxicity with cypermethrin", above) showing a LD_{50} higher than 300 but lower than 2000 mg/kg bw and RAC considered the LD_{50} values of 500 mg/kg bw (i.e. the converted acute toxicity point estimate; reliability score = 1), 1732 mg/kg bw (reliability = 2)

and 250 mg/kg bw (reliability = 3). The two first studies supported classification in category 4, while the third would support a classification in category 3. However, RAC notes the lower reliability of the third study due mainly to deficiencies in reporting and because it was not performed in accordance with standard technical guidelines and GLP. Moreover, the dose levels in this study were not reported and the isomeric composition of the sample was slightly different from the composition of the substance as defined in the CLH-report. Taking all this into consideration, RAC accepted the results of the studies with reliability scores of 1 and 2 for classification. For these two studies, the lowest LD_{50} corresponds to a converted acute toxicity point estimate of 500 mg/kg bw (derived from the 2005 study). Therefore, RAC supports the **classification of cypermethrin cis:trans 40:60 +/- as acute oral toxicity category 4; H302 (Harmful if swallowed), with an ATE of 500 mg/kg bw.**

Two different acute inhalation toxicity studies with reliability scores of 2 and 1 reported LC_{50} of 3.28 mg/L and higher than 3.56 mg/L, respectively. The differences between these two LC_{50} values could be due to differences in the rat strain used or even to slightly different isomeric compositions of the tested cypermethrin. RAC focussed on the results of the first study, which gives the lowest ATE value. Thus, the Committee supports the DS's proposal for **classification of cypermethrin cis:trans +/- 40:60 for acute inhalation toxicity in category 4; H332 (Harmful if inhaled), with an ATE of 3.3 mg/L (dusts and mists).**

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

Summary of the Dossier Submitter's proposal

The DS proposed classification of cypermethrin cis:trans +/- 40:60 as STOT RE category 2; H373 (May cause damage to the nervous system through prolonged or repeated exposure) on the basis of the results of the short- and medium-term oral repeated dose toxicity studies in dogs with support from the chronic studies in rats and studies in the open scientific literature. According the DS, the neurotoxic effects considered for supporting the classification were clinical signs (piloerection, nervousness and uncoordinated movements, ataxia, splayed gait and hyperesthesia) together with relevant histopathological findings and evidence for peripheral nerve damage in rats.

Comments received during public consultation

Three different MSCAs supported the DS's proposal for classification as STOT RE 2 (nervous system). One MSCA highlighted the existence of a neurodevelopmental toxicity study available under Regulation EC Nº 1107/2009 supporting the proposal of classification. This same MSCA also considered that other studies performed with other isomer mixtures (for example beta-cypermethrin or zeta-cypermethrin) might also strengthen the assessment through read-across. The DS agreed with these comments but pointed out the lack of access to these studies since the rapporteur MSCAs of the different cypermethrin formulations under different EC regulations were different and therefore the complete data packages were not available to all MSCAs. Other comments highlighted the toxicity on the liver and immune systems, although they agreed that there are not sufficient data to draw classification conclusions on these. The DS responded that immunotoxicity was not consistently shown among regulatory studies while the open-literature studies did not raise particular concern since the information is scarce and of low reliability.

Assessment and comparison with the classification criteria

The tables below summarise overall the available sub-acute, sub-chronic and chronic toxicity studies with cypermethrin, respectively. All the tables were built from information provided in the CLH-report.

Table: *Summary of the short-term repeated dose toxicity studies with cypermethrin*

Method	Results	Reference
5 weeks oral feed Method B7 with deviations No GLP Absence of raw data Reliability 3 Cypermethrin cis:trans 1:1 Unknown purity Charles River rats 6/sex/group 1.25, 5, 12.5, 37.5, 75 mg/Kg bw/day	No test substance-related mortalities. 1.25, 5, 12.5, and 37.5 mg/Kg bw/day No test substance-related changes 75 mg/Kg bw/day Clinical signs: piloerection, nervousness, uncoordinated movements from 2 weeks onwards in 4/6 males and 1/6 females Body weight gain, food intake, terminal bw: reduced for males and females (no details) Organ weight: ↑ absolute and relative liver weight in females (no details) Clinical chemistry: ↑ haemoglobin and blood urea in males; ↑ plasma alkaline phosphatase in females (no details) NOAEL = 37.5 mg/kg bw/day LOAEL = 75 mg/kg bw/day	Study dated in 1976, author not available to RAC
5 weeks oral feed Method B7 with deviations No GLP Absence of raw data Reliability 3 Cypermethrin cis:trans 1:1 Unknown purity Beagle dogs 3/sex/group 0, 0.375, 3.75 and 37.5 mg/Kg bw/day	No test substance-related mortalities. 0, 0.375 and 3.75 mg/kg bw/day No test substance-related changes 37.5 mg/Kg bw/day Clinical signs: apprehension, diarrhoea, vomiting, licking and chewing of the paws, whole body tremors and stiff exaggerated hind leg gait, ataxia, convulsions during week 1 and 5 in 1 male and 1 female ↓ body weight gain (no details) Organ weight (males and females): relative thyroid weight (no details) Clinical chemistry: ↑ WBC and KCCT at week 5 in males; ↑ blood urea levels, ↓ blood glucose levels at week 5 in females (no details) NOAEL = 3.75 mg/kg bw/day LOAEL = 37.5 mg/kg bw/day	Study dated in 1976, author not available to RAC
3-week oral No guideline Reliability 3 Cypermethrin	Liver: cytoplasmatic hypertrophy with intracytoplasmatic droplets Mitochondrial ATPase activity: inhibitory effect	el-Toukhy and Girgis, (1993) J Environ Sci Health B 28: 599-619

Unknown purity Unknown isomer composition Male albino rats 0, 31.5 mg/Kg bw/day Vehicle: corn oil		
5 days oral No guideline Reliability 3 Cypermethrin Purity >91 % Unknown isomer composition Male Wistar rats 0, 75 mg/Kg bw/day Vehicle: corn oil	No mortalities and clinical signs Hepatic and cerebral tissues: enhanced peroxidation	Giray et al., (2001) Toxicology Letters 118: 139-146
3-week dermal 6 hours/day Method B.9 with deviations Performed on abraded skin, under occluded patch, Limited clinical description Reliability 3 Cypermethrin cis:trans 53:47 Purity 91.5 % New Zealand White rabbits 10/sex/group 0, 2, 20, 200 mg/Kg bw/day Vehicle: PEG300	<u>2 and 20 mg/Kg bw/day</u> Local effects: slight to mild erythema, dose dependent, slight to moderate oedema, dose dependent <u>200 mg/Kg bw/day</u> ↓significant food intake, bw gain, weight of gonads (no further detail provided) Local effects: slight to severe erythema, slight to severe oedema Focal liver necrosis	Study dated in 1981, author not available to RAC
7-days i.p. (daily) No guideline	No test substance-related mortalities Clinical signs: scratching, salivation, somnolence, ataxia, convulsion and hind limb paralysis noted at every time point, on a daily basis during 7 days	Aldana et al., (1998) Toxicology Letters 95: 31-39

Reliability 3 Cypermethrin cis:trans 49.9:50.1 Purity 91 % Wistar rats --- 7 males 0, 300 mg/Kg bw/day Vehicle: Pluronic F-68	Body weight reduced by 11 % at day 7 Organ weight: 20 % ↑ relative liver weight Clinical chemistry: ↓ 19 % serum albumin; AST and ALT variation with statistically significant increase on day 2. AST increase maintained up to day 6. Liver histology at 72 h post-exposure: hepatocytes with ovoid nucleus; intracytoplasmic droplets; small mitochondria with electron dense inclusions. Proliferation and swelling of smooth endoplasmic reticulum more evident on day 5 and subsequently	

Table: *Summary of the subchronic toxicity studies with cypermethrin*

Method	**Results**	**Reference**
90-days oral feed OECD 408 with deviations (histopathology not performed on all organs) No GLP Reliability 2 CD rats 12/sex/group Cypermethrin cis:trans ratio not reported, 98.5 % purity 0, 1.25, 5, 20, 80 mg/Kg bw/day	<u>0, 1.25, 5 and 20 mg/Kg bw/day</u> No test substance-related changes except ↑ 5 % in male kidney weight (without histological changes) at 20 mg/kg bw/day <u>80 mg/Kg bw/day</u> Clinical signs: ataxia, hypersensitivity and abnormal gait during the first 5 weeks (9/12 males ;7/12 females) Mortality: 1 male died, 3 were killed (2 of these rats showed axon breaks and Vacuolation of myelin in the sciatic nerve) Males and females: ↓body weight (males 17 %, females 10 % ($p < 0,01$)), ↓ Hb (males 4 %, females 6 % ($p < 0,05$)), ↑ urea (males 20 %, females 39 % ($p < 0,01$)), ↑ kidney weight (males 7 % ($p < 0,05$), females 14 % ($p < 0,01$)) Males: ↓KCCT (11 %, $p< 0,01$), ↑ K+ (13 %, $p< 0.05$) Females: ↓ RBC (6 %, sign $p < 0,01$), ↑ AP (40 %, $p < 0,01$), ↑ liver weight (10 %, $p < 0,01$), ↑ spleen weight (17 %, $p <0,01$) NOAEL = 20 mg/Kg bw/day <u>LOAEL = 80 mg/Kg bw/day</u>	Study dated in 1979, author not available to RAC
90-days oral feed OECD 408 with deviations No GLP Reliability 3 Beagle dogs 4/sex/group Cypermethrin cis:trans ratio not reported,	<u>0, 0.125, 1.25 and 12.5 mg/Kg bw/day</u> No overt signs of intoxication and no other test compound related effects were found <u>37.5 mg/Kg bw/day</u> Clinical signs: diarrhoea, licking and chewing of the paws, whole body tremors, stiff exaggerated hind leg gait, ataxia, incoordination and hyperaesthesia. Data were not verifiable since the summary table was not included in the full report.	Study dated in 1977, author not available to RAC

98 % purity 0, 0.125, 1.25, 12.5, 37.5 mg/Kg bw/day Vehicle: acetone	Mortality: 2 males and 2 females were sacrificed during week 6 and 10, 10 and 12, respectively, for humane reasons. Haematology: females ↓ RBC (6 %, $p < 0,05$), ↓ KCCT (21 %, $p < 0,01$) Pathology: focal bronchopneumonia in several animals. NOAEL = 12.5 mg/Kg bw/day LOAEL = 37.5 mg/Kg bw/day	
90-days oral No guideline No GLP Reliability 3 Cypermethrin Unknown purity and isomer composition Albino rats 35 males 0, 5, 10, 20, 40 mg/Kg bw/day Vehicle: ground nut oil	Dose-dependent decrease in delayed type hypersensitivity reaction on day 61 post-treatment <u>20 mg/Kg bw/day</u> ↑ adrenal weight (56 %, $p < 0.05$) <u>40 mg/Kg bw/day</u> ↓spleen weight (25 %, $p < 0.05$), ↑ adrenal weight (62 %, $p < 0.05$), leukopenia on day 90 (↓35 %, $p < 0.05$) NOAEL = 10 mg/Kg bw/day LOAEL = 20 mg/kg bw/day	Varshneya et al. (1992) Indian J Physiol Pharmacol 36: 123-126
12-week oral No guideline No GLP Reliability 3 Cypermethrin Purity 25 % Unknown isomer composition New Zealand White rabbits 6 males 0, 24 mg/Kg bw/day	↓ body weight gain ↑ relative liver, spleen, kidney weight ↑ plasma glucose, urea, creatinine, total bilirubin ↓ plasma total protein, albumin ↑ plasma total lipid, cholesterol, TG, LDL, VLDL ↓ HDL ↓ Hb, RBC, PCV, ↑ total leucocyte count NOAEL < 24 mg/Kg bw/day LOAEL = 24 mg/Kg bw/day	Yousef et al. (2003a) Toxicology 189: 223-234

Table: *Summary of the chronic toxicity study with cypermethrin*

Method	Results	Reference
2-year oral feeding OECD 453 with deviations (low number of rats; blood, albumin, glucose, glucose, GGT, ornithine decarboxylase not measured; urinalysis not performed No GLP Reliability 2 Cypermethrin cis:trans 1:1 98 % purity Wistar rats 24/sex/group 0, 0.05, 0.5, 5, 50 mg/Kg bw/day	No substance related mortalities or signs of clinical toxicity in any of the treatment groups Histopathology sciatic nerves: at 1 year and later sciatic nerves showed very small numbers of nerve fibres exhibiting the changes of Wallerian degeneration. Lesions consisted of swelling and fragmentation of axons and myelin. There was no clear and consistent differences in incidences between dose groups <u>50 mg/kg bw/day</u> Food consumption: ↓ (males 7 %, females 10 %) Body weight: ↓ (males 7 %, females 7 %) Haematology: platelets ↑ (males 4 %) Clinical chemistry: ↑ liver PNOD (both males and females), ↑ urea (males 58 %), AP ↓ (males 33 %) Other (minor) changes in haematological and clinical chemical parameters were not considered of toxicological significance, as they were not supported by histopathological or other evidence of tissue damage Relative testes weight:↓ 10 % (6 months) Liver weight: ↑ absolute 18 % and relative 12 % in males at 18 months Heart weight: relative ↑ 6 % (males, 6 months) Heart weight: 28 % ↓ absolute (males 12 months) Relative kidney weight: ↑ 8 % (males 12 month); ↑ 9 % (females 6 months) Absolute kidney weight: 7 % ↑ (males 18 months) NOAEL = 5 mg/kg bw/day LOAEL = 50 mg/Kg bw/day	Study dated in 1978, author not available to RAC

RAC notes that the database contains only studies scored with reliability 2 and 3. Studies published in the open literature were scored with reliability 3 due to lack of raw data, and missing statements about purity and the cis:trans ratio. The reasons for the reliability score assigned in regulatory studies were summarised in the respective tables but the reasons for scoring these as 2 or 3 were the lack of raw data and statistical analysis, that they were not GLP compliant and were performed with a product with a cis:trans ratio varying from 50:50 to 40:60. Overall, RAC notes that the reasons supporting the reliability scores of the studies contained in the database do not prevent these from being used for setting a classification using a weight of evidence approach.

The analysis of the information provided in the Tables above revealed that the main reported effects in the repeated dose toxicity studies with animals were: i) reductions in body weight; ii) alterations in clinical chemistry; iii) hepatotoxicity; iv) neurotoxicity; and, v) mortality. All these

five toxic effects appeared always at doses that might potentially warrant a classification as STOT RE.

Reductions in body weight

Reductions in body weight were reported in the 5-week oral toxicity studies in rats and dogs, 3-week dermal toxicity study in rabbits, 7-day toxicity study by the intraperitoneal (ip) route; 12-week oral study in rabbits and in the 2-year oral toxicity study in rats. However, these reductions in body weight and body weight gain were in general of moderate severity, were in most of the cases poorly reported or appeared (in one study) via a route which is not relevant for classification purposes. Therefore, RAC does not consider that the reductions in body weight provided sufficient evidence to support classification.

Clinical chemistry

Most of the regulatory studies analysed in the three Tables above reported changes in clinical chemistry. However, these changes were not consistently reported across these studies and the severity was in most of the cases low or was poorly reported. Therefore, RAC does not consider that the alterations in clinical chemistry were sufficient or robust enough to support classification.

Hepatotoxicity

Effects on the liver were reported in the following studies: i) increases of unknown magnitude in absolute and relative liver weight in the 5-week oral study in rats; ii) cytoplasmic hypertrophy with intracytoplasmic droplets in the 3-week study in rats; iii) oxidative stress in the 5-day study in rats; iv) focal necrosis in the 3-week dermal study in rabbits; v) histological alterations in the 7-day ip study in rats; and, vi) increases of 12 % (absolute) and 18 % (relative) liver weight in the 2-year oral study in rats. Most of these data were from studies of low reliability with poor reporting, which precluded an in depth assessment by RAC. Therefore, RAC notes that the information about potential hepatotoxicity of cypermethrin is inconclusive for supporting classification.

Immunotoxicity

RAC noted that the CLH-report refers to two sub-chronic rat studies from the open scientific literature reporting immunotoxicity indicated by effects on spleen weight, adrenal weight, leucocyte number and on delayed type hypersensitivity (Table ”Summary of the subchronic toxicity studies with cypermethrin”, above). The results were partly conflicting and the organ weight changes could not be confirmed in a rat guideline study of comparable duration, testing comparable doses (anonymous 1979) (Table ”Summary of the subchronic toxicity studies with cypermethrin”, above) and were not seen in a chronic rat study at comparable doses (1978, author not available) (Table ”Summary of the chronic toxicity study with cypermethrin”, above). On that basis, RAC does not consider the available data robust enough to support classification.

Neurotoxicity

The table below provides an overview of neurotoxic effects relevant for STOT-RE classification that were consistently observed in available repeated toxicity studies.

Table: *Neurotoxic effects of cypermethrin relevant for STOT-RE classification. Data were taken from the studies summarised in the preceding three Tables (above).*

Effect	Study	Lowest reported effect dose (mg/kg bw/day)	Guidance value for STOT-RE Cat 2 (mg/kg bw/day)
Clinical signs: piloerection, nervousness, uncoordinated movements from 2 weeks onwards in 4/6 males and 1/6 females	5-week oral in rats	75	250
Clinical signs: apprehension, whole body tremors and stiff exaggerated hind leg gait, ataxia, convulsions during week 1 and 5 in 1 male and 1 female	5-week oral in dogs	37.5	250
Clinical signs: ataxia, hypersensitivity and abnormal gait during the first 5 weeks (9/12 males; 7/12 females) and axon breaks and vacuolation of myelin in the sciatic nerve of 4 rats.	90-days oral in rats	80	100
Clinical signs: whole body tremors, a stiff exaggerated hind leg gait, ataxia, incoordination and hyperaesthesia	90-days oral in dogs	37.5	100
Histopathology sciatic nerves: at 1 year and later sciatic nerves showed very small numbers of nerve fibres exhibiting the changes of Wallerian degeneration. Swelling and 'fragmentation of axons and myelin	2-year oral in rats	0.05, 0.5, 5, 50*	12.5

**there was no difference in the severity of the effect between these dose groups.*

In addition to the information summarised in the Table above, entitled "Neurotoxic effects of cypermethrin relevant for STOT-RE classification", other non-regulatory studies published in the open scientific literature have described cypermethrin as also having been able to induce oxidative stress in cerebral tissues after oral administration as well as clinical signs such as scratching, salivation, somnolence, ataxia, convulsion and hind limb paralysis after ip administration.

RAC notes that, despite the unclear dose-response relationship for the histopathological effects, the weight of evidence supports the conclusion that the nervous system is the target organ for toxicity of cypermethrin.

Mortality

Four dogs had to be sacrificed for humane reasons after 6, 10, 10 and 12 weeks of exposure to 37.5 mg cypermethrin/kg bw/day. The state of the sacrificed animals were not reported, although neurotoxic clinical signs were experienced by the dosed animals. On the other hand, the exposure of rats to 80 mg cypermethrin/kg bw/day also caused neurotoxic clinical sings and four mortalities, but in this case it is reported that 2 of these rats showed axon breaks and vacuolation of myelin in the sciatic nerve. This suggests that mortalities were due to neurotoxicity and therefore this effect should not be used for classification as STOT RE.

Comparison with the criteria

The short- and medium-term toxicity studies with cypermethrin identified the nervous system as the target for adverse effects. Neurotoxicity was characterised by clinical signs including piloerection, nervousness and uncoordinated movements, ataxia, splayed gait and hyperesthesia. The neurotoxicity-related clinical signs were observed in two different species (rats and dogs) at dose levels warranting classification as STOT RE 2. Open literature studies confirmed neurotoxicity through clinical signs and oxidative stress in rats. Overall, RAC supports the DS's proposal for **classification of cypermethrin cis/trans +/- 40/60 as STOT RE 2; H373 (May cause damage to the nervous system through prolonged or repeated exposure).**

ENVIRONMENTAL HAZARD EVALUATION

RAC evaluation of aquatic hazards (acute and chronic)

Summary of the Dossier Submitter's proposal

The Dossier Submitter (DS) concluded that cypermethrin fulfils the criteria for classification as Aquatic Acute 1 with an M-factor of 100 and also fulfils the criteria as Aquatic Chronic 1 with an M-factor of 1000.

Degradation

Photodegradation

The DS assessed photodegradation in water and soil (EC directive, 94/37/EC and 94/36/EC)

Data on distribution of radioactivity and the DT_{50} indicate that photolysis is a minor route of degradation of the active substance.

Hydrolysis

Hydrolytic degradation of cypermethrin is temperature and pH dependent (Schneider, 1997 – GLP, reliability 1). Measured DT_{50} values (EEC method C.7):

pH 4, 50°C: >1 yr pH 7, 50°C: 4.73 d

pH 9, 50°C: 1.9 h pH 7, 25°C: >29 d

For conversion to 12°C, the equation of $DT_{50}(X°C) = DT_{50}(t)* e (0.08\cdot(T - X)$ was used by DS (TGD on RA, 2003). The respective half life values are:

pH 7, 12°C: 98.8 d pH 9, 12°C: 1.65 d

Biodegradation

The DS presented a detailed overview of biodegradation studies on ready, inherent and ultimate biodegradation, as well as biodegradation in water/sediment systems and in soil.

Ready biodegradability (OECD TG 301B)

0.6–1.4% at 33 d (Klein, 1990 – GLP, reliability 1).

Inherent biodegradability (OECD TG 301B & 302C)

0% in 28 d (Burwood, 2005 – GLP, reliability 1).

Ultimate anaerobic biodegradability (ISO 11734, 1995)

17% in 60 d (Barnes, 2005 – GLP, reliability 1).

Degradation in water/sediment system (OECD TG 308) of two different lakes (Brice, 2006a – GLP, Rel 1). ^{14}C labelled cypermethrin was used.

Dissipation rate in the water/sediment system: DT_{50} = 3.5–9.8 d;

Dissipation from the water phase: DT_{50} = 0.5 d;

Dissipation from the sediment phase: DT_{50} = 10.9–14.3 d;

Metabolites: 25–69% degradation within 100 days (based on evolved CO_2), but the concentration of one unidentified metabolite was above10%, and increased still after 100 days.

Degradation in soil (OECD TG 307) – in five soil types (Brice & Cooke, 2006c)

Primary extracts contained 6–35% of applied radioactivity after 120 days;

Volatile radioactivity (CO_2) = 49–78% of applied radioactivity on day 120;

DT_{50} in five soil types (corrected to 12°C): 12.13–45.9 d;

Total cypermethrin geometrical mean DT_{50} = 17.2 days.

Three degradation products were identified: 3-PBA, CDCVC and TDCVC.

Degradation half-life of the metabolites (corrected to 12°C)

3-PBA DT_{50} = 8.4–25 d; geometrical mean DT_{50} = 20.52 d;

CDCVC DT_{50} = 16.9–33.4 d; geometrical mean DT_{50} = 22.24 d;

TDCVC DT_{50} = 23.13 to 65.0 d; geometrical mean DT_{50} =34.66 d;

Cypermethrin arithmetical mean:

DT_{50} (20°C) = 13.45 d;

DT_{50} (12°C) = 25 days.

Anaerobic degradation in soil (OECD TG 307) (Brice & Cooke, 2006c):

DT_{50} for total cypermethrin (12°C): 87.2 d

Three degradation products were identified: 3-PBA, CDCVC and TDCVC.

Based on the above information on cypermethrin degradation, the Dossier Submitter proposed that cypermethrin does not meet the CLP criteria and is considered as non rapidly degradable for classification purposes.

Aquatic Bioaccumulation

The DS included in the CLH Report a fish bioaccumulation study and two model calculations.

Fish bioaccumulation (OECD TG 305E): BCF_{fish}= 373.4 (± 45.35) L/kgww (Anonymous, 1990).

Based on log K_{ow}: the applied equation: $BCF_{fish} = 0.85 \times \log K_{ow} - 0.7$ (TGD on RA, 2003)

$BCF_{fish,Kow} = 0.85 \times 5.6 - 0.7 = 11\,481.53$ L/kgww (Anonymous, 2002)

Based on QSAR: $BCF_{fish,QSAR}$ = 417 L/kgww (RMS by EPISuite)

The DS prioritised the BCF value derived from the measured fish bioaccumulation study over the respective one from the octanol–water partition coefficient, for classification purposes.

Based on the measured BCF_{fish} of 373.4 L/kg ww, the DS considered cypermethrin as being non bioaccumulative for classification purposes.

Aquatic Toxicity

The DS included 6 acute and 8 chronic studies on three trophic levels, as well as activated sludge and multi-species mesocosm studies.

***Table**: Acute aquatic toxicity results included in the CLH report*

Method	Result	Reliability	Reference
1. Fish acute toxicity (96h) *Onchorhynchus mykyss* OECD TG 210 Semi-static	LC_{50} = 2.83 µg/L (mean measured)	GLP reliability 1	Industry report 1669/018-D2149
2. Invertebrates acute toxicity (48h) *Dapnia magna* OECD TG 202 Static	EC_{50} = 4.7 µg/L (mean measured)	GLP reliability 1	Manson, 2005b Industry report 1669/019-D2149
3. Invertebrates acute toxicity *Dapnia magna* OECD TG 202 Semi-static	EC_{50} = 0.3 µg/L (nominal)	NOT GLP reliability 3	Review report/RAR (PPP) Stephenson, 1981
4. Toxicity to aquatic algae (96h) *Pseudokirchneriella subcapitata* OECD TG 201 Static	E_bC_{50} >33.0 µg/L E_rC_{50} >33.0 µg/L (mean measured)	GLP reliability 1	Industry report 1669/018-D2149
5. Toxicity to aquatic algae (96h) *Selenastrum capricornutum* OECD TG 201 Static	E_rC_{50} >100 µg a.s./L (nominal)	NOT GLP reliability 3	Stephenson, 1981
6. Inhibition of microbial activity (3h) Activated sludge OECD TG 209	EC_{50} = 163 mg/L	GLP reliability 1	Bealing, 2002, Industry study 40/46-D2149

The acute daphnia toxicity value of EC_{50} = 0.3 µg a.s./L (Stephenson, 1981) has not been taken into account by the DS for CLH purposes, as this study is not GLP, the methodology is poorly documented in the report, the guideline used (OECD TG 202) has been revised and the identity of the substance as regards to the isomeric composition is not reported. According to the DS opinion, this study by Stephenson (1981) should not be used for classification purposes.

After exclusion of the Stephenson study, the lowest valid acute toxicity result (with fish) is: EC_{50} = 2.83 µg/L (study 1). Based on acute toxicity results, the DS proposed: Aquatic Acute 1, H400, with an M factor of 100.

***Table**: Chronic aquatic toxicity results included in the CLH report*

Method	Result	Reliability	Author
1. Fish chronic toxicity, hatching success (ELS) *Pimephales promelas* OECD TG 210	28d NOEC = 0.463 µg/L (mean measured) LOEC = 0.463 µg/L	GLP reliability 1 **Key study**	2012 Industry study 8252888

Flow through			
2. Fish chronic toxicity (ELS) *Pimephales promelas* OECD TG 210 Flow through	28d NOEC = 0.03 µg/L (nominal)	NO GLP reliability 2	1983 Review report/RAR (PPP)
3. Fish chronic toxicity (ELS) *Pimephales promelas* OECD TG 210 Flow through	NOEC = 0.25 µg/L (nominal)	NO GLP reliability 2	1980 Review report/RAR (PPP)
4. Fish chronic toxicity, hatching success, fry survival & growth *Pimephales promelas* OECD TG 210 (ELS) Flow through	28d NOEL = 0.01 µg/L (nominal) Empirical NOEC 0.32 µg/L (nominal)	reliability 3	2005 Charles River Lab., 805972
5. Invertebrates reproduction *Daphnia magna* OECD TG 202 Semi-static	21d NOEC = 0.04 µg/L (nominal)	GLP reliability 1	Dickhaus, 1990 Pharmatox Report E.H./B. 2-7-44-90 (CYP/T143)
6. Invertebrates reproduction *Daphnia magna* OECD TG 211 Semi-static	21d NOEC = 0.053 µg/L (time weighted average)	GLP reliability 1	Simon, 2015
7. Toxicity to aquatic algae *Pseudokirchneriella subcapitata* OECD TG 201 Static limit test	96h NOE_bC ≥33.0 µg/L (mean measured)	GLP reliability 1	Manson, 2005c, Industry report 1669/020- D2149
8. Mesocosm study Multispecies	6m Min. NOAEC= 0.05 µg/L		Schnoder, 2003 Industry Lab. study 0040/045 (CYP/T331)

The fish study (4) from 2005 (RAR) with the lowest NOEC (0.01 µg/L) has been assessed by the DS as having a low reliability study (Rel 3). Based on probable additional adverse biological impact on fry (most likely a fungal infection), the NOEL of 0.01 µg/L based on hatching success was, thus, considered too conservative by the authors. Instead, an empirically derived NOEC of 0.32 µg/L was recommended by the authors.

The overall lowest NOEC value of 0.03 µg/L from study 2 on *Pimephales promelas* (1983 Review report/RAR, PPP) has been considered by the DS as the basis for classification. Another two reliable invertebrates studies resulted in NOEC values within the same range (NOEC = 0.04 and 0.053 µg/L). According to these NOEC values and the fact that the substance was considered non rapidly degradable for classification purposes, the DS proposed: Aquatic Chronic 1, H410 and an M factor of 1 000.

Comments received during public consultation

Five comments have been received from Member States. All comments refer to the selection and rating of one acute aquatic toxicity study, one bioaccumulation study, and their acceptance for classification purposes. The inclusion of additional bioaccumulation, acute and chronic aquatic toxicity study endpoints was recommended by the commenters. The additional studies were

identified during the EFSA peer review for the renewal of the active substance cypermethrin (EFSA Journal 2018, 16(8):5402 and efs25402-sup-0001-Appendix-A.pdf) and have been subjected to a targeted public consultation (see Section below). A comprehensive reporting of the different comments during the consultation on bioaccumulation, acute and chronic toxicity can be found in the RCOM and Background Document, together with the Dossier Submitter responses and RAC evaluation.

Assessment and comparison with the classification criteria

Abiotic Degradation

Photodegradation: Light accelerates the degradation of cypermethrin (cis:trans/40:60) in air, water and on soil surfaces, however these data are not relevant for classification.

Hydrolysis (Hydrolysis; EEC method C.7): Cypermethrin hydrolyses more rapidly under alkaline than under acidic conditions. Under neutral pH (7) at temperature of 25 °C it is stable for at least 29 days, at 12 °C for 98.8 days (Schneider, 1997). Cypermethrin is hydrolytically not degradable as the longest half-life determined within the pH range 4–9 is more than 16 days.

Biodegradation

Cypermethrin is not readily biodegradable (based on the OECD TG 301B ready biodegradability study of Klein, 1990), as only 0.6–1.4% degraded within a 33 day period, instead of the minimum criterion of 70% in 28days.

Cypermethrin was degraded in both the water and the sediment phase (OECD TG 308) with $DT_{50water}$ = 0.95 day and DT_{50sed} = 4.7–18.5 days (12°C), meaning that cypermethrin is (bio)degradable in a water/sediment system (more than 70% was degraded, i.e. the half-life is less than 16 days). However, the two main degradation products – TDCVC and CDCVC – have to be considered persistent with the typical DT_{50} values >40 days, which exceeds the DT_{50} = 16 days (equivalent to the criterion of 70% within a 28 days period). (RAC notes here that the pH values of the lake waters (5.85 and 8.22) indicate the possible contribution of hydrolysis to dissipation rates.)

In addition to the known degradants of TDCVC and CDCVC, a third, unknown degradation product was also present in the test solution in a concentration of above 10%.

Some doubts arose during the RAC consultation regarding the evidence from the biodegradation studies: (i) the test material concentrations were orders of magnitude higher than the water solubility limit in the screening test; (ii) the suspected microbial toxicity in the inherent biodegradation study and (iii) the interpretation of the results of the primary degradation study in a water-sediment system.

RAC evaluated the biodegradation studies and their results.

(i) The ready biodegradability study (Klein, 1990) in the CLH dossier is GLP, rated as reliability 1, using the OECD TG 301 B test method. The biodegradation of cypermethrin was 0.6 to 1.4% after 33 days incubation, whereas the biodegradation of aniline (positive control) was 94.4 to 100.7% after 28 days incubation, indicating that the inoculum was effective. RAC cannot see any reason to regard this tudy as unreliable.

(ii) The inherent biodegradation study (Burwood, 2005) applied a medium composition and test substance and inoculum concentrations according to OECD TG 302 C, but the CO_2 measurement method was adapted from OECD TG 301 B. The study is classified as GLP and reliability 1. Degradation of the reference substance (sodium benzoate), exceeded 60% on day 6, and was 89% at the end of the test. These data show that the inoculum was viable, exerting normal

degradative activity. A slight toxicity of cypermethrin on the activated sludge microbes can be supposed due to lower CO_2 production compared to the negative control.

OECD TGs 301 and 302 test methods work with high inoculum and high substance concentrations (to get measurable CO_2 concentrations); the referred studies were executed accordingly, RAC can accept their results as valid.

(iii) The primary degradation in a water–sediment system (Brice, 2006) was measured by using the OECD TG 308 test guideline. The study showed rapid dissipation both from the water-phase (DT_{50} = 0.5 d) and sediment (DT_{50} = 10.9–14.3 d) for cypermethrin.

According to these results, cypermethrin itself could be considered degradable in a water-sediment system, but the two main degradants – TDCVC and CDCVC – are persistent with measured DT_{50} values above 40 days (Table 39 of the CLH report). 20–44% radioactivity was measured in the sediment assigned to TDCVC and 15–9% for CDCVC after 58 days. A third, unknown degradation product was also present in the test solution in a concentration above 10%.

In such cases, the CLP Guidance says: "*Primary biodegradation does not normally suffice in the assessment of rapid degradability unless it can be demonstrated that the degradation products do not fulfil the criteria for classification as hazardous to the aquatic environment.....In case of rapid primary degradation, information shall be given whether the degradation products can be classified as hazardous to the aquatic environment or not; ....In the absence of toxicity information on the degradation products, they can be considered as hazardous to the aquatic environment*".

Due to the results of the ready biodegradation study and as it cannot be satisfactorily demonstrated that the unknown degradation product does not fulfil the criteria for classification as hazardous to the aquatic environment, cypermethrin should be considered as **non-rapidly degradable**.

RAC also notes that cypermethrin has not been assessed as rapidly degradable under any previous regulatory assessment.

Summary of degradation

Cypermethrin should be considered as ***non-rapidly degradable*** for classification purposes.

Bioaccumulation

The study of Anon. (1993) following OECD TG 305, is considered reliable, the endpoint for fish bioaccumulation has been normalised for lipid content and for growth during the test. Giving priority to measured BCF over the model values, the Anon. (1993) study is considered by both the DS and RAC as a key study and provides the basis for the classification conclusion. The measured bioaccumulation factor in fish is 266–331 L/kg, i.e. below the trigger value of 500 L/kg. The other studies mentioned in previous sections are no longer considered reliable, according to the RAR (Vol. 3 B.9 AS).

Based on this measured BCF value, therefore, cypermethrin has ***no bioaccumulative potential*** for classification purposes.

Acute toxicity and M-factor

An additional study (Rapley and Hamer, 1996) was indicated during the EFSA review programme (EFSA Journal 2018, 16(8):5402) on the invertebrates *Hyalella azteca* and *Chironomus riparius*, resulting in EC_{50}s of 0.0053 µg/L and an EC_{50} of 0.0069 µg/L, respectively. These were carried out under GLP and the test and analytical methods are adequately described and documented, so can be considered reliable for classification purposes.

The test material purity (920 g/kg) and isomeric composition (alpha cis/trans +/- 40/60) comply with the FAO specification (332/TC/S/F, 1993): min. 900 g/kg and the cis-isomer content shall be declared and shall be between 40% minimum and 60% maximum of the declared cypermethrin content. The minimum purity of the active substance as manufactured agreed by the EU is also 900 g/kg (Com. Dir. 2005/53/EC, 2005), and cis:trans: 40/60 to 60/40. As the substances responsible for toxicity are almost completely the 2-alpha isomers from the total of eight isomers, purity is the key condition. Toxicity of the alpha cis- and trans-cypermethrin does not differ significantly (Liu et al, 2005).

Table: *Acute studies recommended for inclusion*

Method	Result	Reliability	Source
Acute, toxicity, mortality *Hyalella azteca* Standard method: not mentioned Similar to OECD TG 202	EC_{50} = 0.0053 µg//L (mean measured)	GLP reliability 1	Rapley and Hamer, 1996
Acute, toxicity, mortality, 1st instar *Chironomus riparius* Standard method: not mentioned Similar to OECD TG 202	EC_{50} = 0.0069 µg//L (mean measured)	GLP reliability1	Rapley and Hamer, 1996

Both the DS and RAC agree on the use of the *Hyalella* study endpoint (Rapley & Hamer, 1996) as the most conservative EC_{50} value (= 0.0053 µg/L) for acute aquatic classification and M-factor derivation.

Based on this smallest EC_{50} value the proposed classification is ***Aquatic Acute 1*****, H400,** as EC_{50} = 0.0053 µg/L <1 mg/L.

This results in an ***M-factor of 100 000*** based on the criterion of:

0.000001 mg/L < EC_{50} = 0.0000053 mg/L ≤ 0.00001 mg/L

Chronic toxicity and M-factor

Due to the assessment of cypermethrin in the context of the PPP renewal program, the previously considered key study in the CLH Report used for aquatic chronic classification was found to not be adequate for classification purposes.

Three additional, valid chronic aquatic studies were identified in the EFSA Journal 2018, 16(8):5402; Appendix A: p. 112 and 113 but not contained in the CLH report. These are considered relevant for cypermethrin classification: a fish, a daphnia and a midge study, see the table below.

Method	Result	Relia-bility	Source
Pimephales promelas Chronic (300 d) Full life cycle (flow through)	NOEC = 0.077 µg/L (mean measured)	GLP REL1	Anonymous, 1988 EFSA Journal 2018, 16(8):5402; Appendix A: p. 112 efs25402-sup-0001-Appendix-A.pdf
Daphnia magna (21 d) Reproduction, development (semi-static)	NOEC = 0.05 µg//L (mean measured)	?	EFSA Journal 2018, 16(8):5402; Appendix A: p. 113 efs25402-sup-0001-Appendix-A.pdf
Chironomus riparius (28 d) (midge) Emergence (static)	NOEC = 0.064 µg//L (mean measured)	?	EFSA Journal 2018, 16(8):5402; Appendix A: p. 113 efs25402-sup-0001-Appendix-A.pdf

The studies of Anon. (1988) and Simon (2015) were evaluated by RAC and were both found to be GLP-compliant and reliable (reliability 1), i.e. suitable for classification purposes. The full study reports for the chronic *Daphnia* and *Chironomus* studies (as in the Table above) were not accessible to RAC, so could not be evaluated and were therefore excluded these two studies from further evaluation.

The chronic *Daphnia* study of Simon (2015) has already been included into the CLH Report, with the endpoint of NOEC = 0.053 µg/L. It is in good agreement with the fish NOEC = 0.077 µg/L from the study of Anonymous (1988) which should also be considered for classification purposes as well as the Dickhaus, 1990 study deriving an NOEC value of 0.04 µg/L. These three toxicity studies indicate a classification as *Aquatic Chronic 1, H410,* with an M-factor of 1000 (0.00001 mg/L < NOEC $\leqslant$ 0.0001 mg/L).

However, RAC noted the absence of chronic data for the most sensitive species from the acute aquatic toxicity studies (*Hyalella azteca*). In such cases, the CLP Regulation is proposing the derivation of an environmental classification based on the results of both chronic and acute toxicity studies (surrogate approach). Application of the latter leads to a derived classification of **Aquatic Chronic 1, H410**, with an M-factor of **100 000**, based on the lowest EC_{50} value of 0.0053 µg/L for Hyalella Azteca. This was the chronic classification agreed by the RAC.

Conclusion
RAC agreed to classify the substance as **Aquatic Acute 1, H400**, **with an acute M-factor of 100 000 and Aquatic Chronic 1, H410, with a chronic M-factor of 100 000.**

Additional references

Liu, W., Gan, J.J. & Qin, S. (2005) Separation and aquatic toxicity of enantiomers of synthetic pyrethroid insecticides. Chirality 17:127–133.

EFSA Review (2018) EFSA Journal 16(8):5402.

ANNEXES:

Annex 1 The Background Document (BD) gives the detailed scientific grounds for the opinion. The BD is based on the CLH report prepared by the Dossier Submitter; the evaluation performed by RAC is contained in 'RAC boxes'.

Annex 2 Comments received on the CLH report, response to comments provided by the Dossier Submitter and RAC (excluding confidential information).

Annex 3 Records of the targeted consultation following the submission of additional information on the hazard to the aquatic environment.