COMMENTS AND RESPONSE TO COMMENTS ON CLH: PROPOSAL AND JUSTIFICATION

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Substance name: cypermethrin (ISO); α-cyano-3-phenoxybenzyl 3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylate; cypermethrin cis/trans +/- 40/60
CAS number: 52315-07-8
EC number: 257-842-9
Dossier submitter: Belgium

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
20.03.2019	Germany		MemberState	1
Comment received				
Substance ID The used CAS and EC numbers are for the cis/trans isomer in accordance to the regulation (EU) 2018/1130. In case all individual isomers, which have a specific CAS and (maybe also) EC number, should be covered by the CLH proposal this needs to be clearly stated in chapter 1 of the report and also on the front page of the report. Otherwise the classification will apply only to the cis:trans 40:60 isomeric mixture. Carcinogenicity: Carcinogenicity was not evaluated in the dossier. DE suggests to evaluate this endpoint in the CLH dossier, as testicular tumours were observed in the Forbes study (1982) and classifi-cation for carcinogenicity was discussed in the Pesticide Peer Review meeting 175 (even if the majority of experts did not agree). There was a higher incidence of testicular interstitial neoplasia (11/11/11/20% at 0/20/150/1500 ppm active substance in feed) and an indication of an earlier onset of tumour formation in the top dose group. Reference is made to the re-cent RAC opinion (September 2016) recommending classification of tetramethrin with Carc 2 based on interstitial testicular tumours. Specific target organ toxicity – single exposure: The discussion about classification for narcotic effects (in animals and humans), STOT SE 3 H336, should also be further evaluated in the dossier to allow RAC its own consideration. At the moment, this point is not addressed at all. The following was discussed during PPR 175: "Lethargy was observed in rats in acute oral toxicity studies (B.6.2.1.1 –with ataxia-, B.6.2.1.2), acute inhalation toxicity study (B.6.2.3.1), in the reproduction/development tox-icity study, and in a neurotoxicity study (B.6.7.1.1.4 –with ataxia). Ataxia is also described in B.6.3.1.2, B.6.3.1.4.2, B.6.3.2.1.2, B.6.3.2.3.1 –with incoordination, B.6.4.4.2.6 (Comet assay), B.6.6.1.2 -with incoordination-, B.6.7.1.1.2 (acute neurotoxicity study), and in metabolite studies B.6.8.1.1 (acute oral toxicity of DCCA), B.6.8.1.3 (acute oral toxicity of 3-Phenoxybenzaldehyde). Most of these effects were observed at high doses and they could maybe due to general toxicity. However, in the CLP, there is no mention of any threshold value for this classifica-tion. More importantly, as underlined by the MSNL, dizziness is mentioned in humans in				

B.6.9.2 (Data collected on humans), B.6.9.3 (Direct observation), B.6.9.4 (Epidemiological data) and B.6.9.5 (Diagnosis of poisoning). However, no other effect related to narcosis, except, sometimes, fatigue, is observed."

Skin corrosion/irritation:
It should be also discussed in the dossier whether classification for skin effects might be appropriate (based on strong skin irritation in subacute dermal study in rabbits, Handerson and Parkinson 1981). During Pesticide Peer Review, the following arguments were brought for-ward: "Five dermal irritation/corrosion studies were reported in the acute toxicity studies section B.6.2.4:
- in the most recent of these, from Yogeesh, B.S., 2005, which is GLP and in compliance with EC Method B.4 of Regulation (EU) no 440/2008, "Cypermethrin needs not to be classified for skin irritation".
- in the Seifert (1984a) study, not GLP but compliant with the method B.4 of Directive 92/69/EEC, "Cypermethrin is a moderate skinirritant, but needs not to be classified". in three other less relevant studies, Cypermethrin was mentioned as being not a skin irritant or producing moderate to severe erythema and slight edema. The Henderson and Parkinson (1981) short term dermal toxicity study was not GLP and was only partially compliant with method B.9 of directive 92/69/EEC. As the study was still available in a paper form, but with-out several original tables reporting on individual data, it was only possible to provide the related study text, as follows: In "Experimental procedures" …Immediately before the first application of Cypermethrin, half the animals (i.e. five males and five females at each dose level) were further prepared by making epidermal abrasions in a 5x5 lattice arrangement over the area of exposure. The abrasions were made using the back of a scalpel blade and they were sufficienly deep to penetrate the stratum corneum, but not to disturb the dermis (that is, they did not cause bleeding). The abrasions were carried out weekly. Half the con-trol rabbits were also abraded as above. In "Results" Signs of local irritation: At 2 mg/kg/day slight to mild erythema was observed in three males and one female (RMSBE: 10 ani-mals/sex/dose), while slight to moderate oedema was noted in three male rabbits and slight to mild oedema was observed in two female rabbits. Other observations included desqua-mation and thickening. At 20 mg/kg/day slight erythema was observed in five male and six female rabbits, while slight oedema was observed in three male rabbits and slight to moder-ate oedema was observed in five female rabbits. Other observations included desquamation, bruising and scabbing. At 200 mg/kg/day slight to severe erythema and oedema were seen in most male rabbits, and slight to mild erythema and slight to severe oedema were ob-served in most female rabbits. Other observations included desquamation, scabbing, flaking, cracking, thickening and wrinkling. In the control animals, slight erythema was observed in two male and two female animals, while slight to moderate oedema was seen in three male rabbits and slight to mild oedema was seen in five female rabbits. Other observations in-cluded thickening, bruising and slight scabbing. Thus, from the study as it is available now (without individual data), it is impossible to know when (i.e., after how many doses) irritation became apparent, nor which rabbits (abraded or not) were affected. RMS-BE is of the opinion that the study is "supplemental information" in what concerns "skin irritation" and may be contributive in determining the global irritation performance of Cypermethrin. In consequence, while RMS-BE concluded that Cypermethrin should not be classified as skin irritant, despite the fact that some signs of irritation were occasionally observed, this may be further discussed."

Date	Country	Organisation	Type of Organisation	Comment number
22.03.2019	France		MemberState	2
Comment received				
FR:				

- p.14: Identity of the substance, Table 4: Unit (g/mol) of the molecular weight is missing.

- p.15 : Table 7 should be amended as follow:
Row 2: [1S-(1α(S*),3α)] should be replaced by [1S-(1α(R*),3α)]
Row 2: 72204-44-5 should be replaced by 72204-43-4
Row 4: 1S-(1α(R*),3α)] should be replaced by [1S-(1α(S*),3α)]
Row 4: 72204-43-4 should be replaced by 72204-44-5
Row 6: [1S-(1α(S*),3β)] should be replaced by [1S-(1α(R*),3β)]
Row 6: 83860-32-6 should be replaced by 83860-31-5
Row 8: [1S-(1α(R*),3β)] should be replaced by [1S-(1α(S*),3β)]
Row 8: 83860-31-5 should be replaced by 83860-32-6

OTHER HAZARDS AND ENDPOINTS – Acute Toxicity

Date	Country	Organisation	Type of Organisation	Comment number
22.03.2019	France		MemberState	3
Comment received				
FR: Acute toxicity: 4.2.3 Conclusions on classification and labelling acute toxicity findings relevant for classification as ACUTE TOX. The proposal for classification Acute Tox. 4; H302 and Acute Tox. 4; H332, is supported.				

Date	Country	Organisation	Type of Organisation	Comment number
22.03.2019	Denmark		MemberState	4
Comment received				
A minor typo in section 4.2.3 in the report was found, 1894 should be changed to 1984. Acute tox oral: DK agrees with this assessment, and the classification of Cypermethrin as (oral) Acute tox 4. Acute tox inhalation: DK agrees with this assessment, and classification as (inhalation) Acute tox 4.				

Date	Country	Organisation	Type of Organisation	Comment number
20.03.2019	Germany		MemberState	5
Comment received				
Acute toxicity: Acute Tox 3 (H301) should be considered based on the LD50 value of 250 mg/kg bw (confidence interval 233-277) in male rats reported by Cantalamessa (1993). The difference to the results of Anonymous 2005 with an ATE of 500 mg/kg bw may be due to sex differences in sensitivity (see also Anonymous 1984a with LD50 values of 1732 vs. 2150 in males vs. fe-males). Notably, young animals were significantly more sensitive than adults as reported by Cantalamessa (LD50=15/27/49/250 mg/kg bw at age of 8d/16d/21d/adult). This may support stronger classification into Cat.3. The same conclusion was reached by majority of experts at PPR 175 (refer to LOEP of EFSA conclusion). However, according ATE values should be discussed and harmonised.				

OTHER HAZARDS AND ENDPOINTS – Specific Target Organ Toxicity Repeated Exposure

Date	Country	Organisation	Type of Organisation	Comment number
22.03.2019	Denmark		MemberState	6
Comment received				
DK: Agrees that STOT RE2 (nervous system) is justified. However, we find that a number of studies mentioned in the RAR volume 3-B6 table B.6.3.4.1 (2018) could also be relevant for the assessment of STOT RE in the CLH report. Also in the RAR, section B.6.3.2., corrections according to food consumption data have been made. As noted by the RMS, indications of liver toxicity was seen in several studies, and in one also indications of immunotoxicity, however, we agree that there is not sufficient data to draw conclusions on this.				

Date	Country	Organisation	Type of Organisation	Comment number
22.03.2019	France		MemberState	7
Comment received				
FR: STOT RE: It is agreed that a classification STOT RE 2 H373 (nervous system) is warranted. However, further information is available and may be considered : - A DNT study is available in the dossier for the renewal of cypermethrin (cis:trans/40:60) under Regulation (EC) No1107/2009 and is reported in the dDAR. While the level at which FOB changes in offspring were observed according to pesticide peer review (25 mg/kg bw/day) do not challenge the proposed cat2, this study should also be considered in this CLH report in respect to neurotoxicity. - Page 51, it is "stated that no regulatory and reliable studies are available of which it is 100% clear that they are performed with cypermethrin cis:trans/40:60 as no studies were performed with the pure". Since GLP reliable repeated dose studies are available with other isomers mixtures (beta-cypermethrin, zeta-cypermethrin,…), in order to strengthen neurotoxic potential assessment read-across from other cypermethrin (isomer composition) taking into account the isomer activity (1R cis αS and 1R trans αS being the more active ones) would be of value. Classification for neurotoxicity is also supported by the insecticidal mode of action of cypermethrin, which acts on the central, and peripheral nervous system of target insects. It acts on sodium channels (also present in nervous system of mammals), by modulating the opening and the closing of the channels, leading to synaptic discharge, repetitive discharge and depolarisation.				

Date	Country	Organisation	Type of Organisation	Comment number
22.03.2019	Sweden		MemberState	8
Comment received				
The Swedish Chemicals Agency agrees with the proposal to classify cypermethrin as STOT RE 2, H373 (nervous system) mainly based on evidence from short and medium term oral toxicity studies in rats and dogs. In the 90-day oral toxicity study in dogs, clinical signs of neurotoxicity were observed at 37.5 mg/kg bw/day (including diarrhea, licking and chewing of the paws, whole body tremors, a stiff exagegerated hind leg gait, ataxia, incoordination and hypereasthesia). The 5-week oral study in dogs resulted in similar symptoms at 37.5 mg/kg bw/day. The				

neurotoxicity effects observed at 37.5 mg/kg bw/day in the 90-day and 5-week study in dogs are below the guidance values to assist in Category 2 classification, established for rat, for STOT RE 2(10<C ≤100 mg/kg bw/day and 25<C≤250 mg/kg bw/day, respectively).

In comparable studies of rats, clinical signs of neurotoxicity were observed at 80 mg/kg bw/day with hypersensitivity and abnormal gait during the first 5 weeks of the experiment in the 90-day oral toxicity study. Moreover, neurotoxicity was confirmed by histopathology as peripheral nerve damage at this dose level: two rats showed axon breaks and vacuolation of myelin in the sciatic nerve. In the 5-week oral toxicity study, a dose of 75 mg/kg bw/day resulted in clinical signs of neurotoxicity including piloerection, nervousness and uncoordinated movements from week 2 onwards. Thus, also in rats there are supporting evidence of neurotoxicity observed at dose levels below the guidance values for classification in Category 2.

OTHER HAZARDS AND ENDPOINTS – Hazardous to the Aquatic Environment

Date	Country	Organisation	Type of Organisation	Comment number
22.03.2019	France		MemberState	9
Comment received				
FR: - Please note that from the List of endpoint published by EFSA in 2018 (EFSA Journal 2018;16(8):5402) a worst-case acute endpoint for Hyalella azteca is available, 48h-EC50 = 0.0053 µg a.s./L. This allows to calculate a new acute M-Factor of 100000 instead of the one of 100 proposed in the CLH report. From the EFSA journal, the following classification is proposed for cypermethrin : Category Acute 1 | Endpoint: 0.0053 µg a.s./L [48h EC50 Hyalella azteca] H400 (M-factor = 100000) Category Chronic 1 | Endpoint: 0.03 µg a.s./L [Chronic NOEC Pimephales promelas] H410 (M-factor = 1000) - Beside the new endpoint available for Hyalella azteca, new chronic endpoints are also available in the EFSA journal for Daphnia magna and Chironomus riparius. It is FR opinion that for completeness, these endpoints should appear in the list of available data in the CLH report.				

Date	Country	Organisation	Type of Organisation	Comment number
22.03.2019	Denmark		MemberState	10
Comment received				
The acute environmental hazard should be based on LC50 = 0.0000055 mg/L for Hyalella azteca. Now there is a zero too much in the LC50 mentioned in the first section of 5.5 in the CLH report (LC50 = 0.00000055 mg/L for Hyalella Azteca). Consequently M = 100000 (not 1000000 as stated now).				

Date	Country	Organisation	Type of Organisation	Comment number
21.03.2019	Netherlands		MemberState	11
Comment received				
Agreed with comments				

Proposed comments
The Dossier Submitter has drawn conclusions on the potential to bioaccumulate on the basis of a BCF of 373 L/kg. From the summary proved it is unclear if the BCF value is normalised to 5% lipid and if it has been corrected for growth. Furthermore, the age of the fish and their lipid content is unclear. Since the reported value is close tho the criterion of 500 L/kg, growth correction and normalisation for the lipid content of the fish may very well result in a BCF exceeding thecriterion. If the available information in the study report does not allow for growth correction and lipid normalisation it can not be excluded that the lipid and growth corrected BCF could exceed 500 L/kg. The calculated value suggests a slightly higher BCF , but experimental BCF values reported for cypermethrine in literature report BCF values as high as 758 (Baldwin and Lad, 1978) and 821 L/kg (Bennet, 1981). These studies should be checked for availability and validity. Overall based on the available data, the conclusion should be that it can not be excluded that the substance has a potential to bioaccumulate.
For the chronic classification, the Dossier Submitter selected the NOEC of 0.04 µg/L for D. magna as the key study. For fish however, a NOEC of 0.03 µg/L is available for O. mykiss. It is unclear why the latter value has not been selected as key study for the chronic classification.
Considering that the substance is not rapidly biodegradable, and that both chronic effect concentrations are in the same range, the above comments do not affect the proposed chronic classivcation.

References:
BALDWIN, M.K. & LAD, D.D. (1978b) The accumulation and elimination of WL 43467 by the Rainbow trout (Salmo gairdneri), Sittingbourne, Shell Research (TLGR.0041.78).

BENNETT, D. (198la) The accumulation, distribution, and elimination of RIPCORD b Rainbow trout using a continuousflow procedure, Sittingbourne, Shell Research SBGR.81.026 and Addendum).

Reported in:
• Reviews of Environmental Contamination and Toxicology: Continuation of Residue Reviews Vol. 174 – ISBN 9781475742602
• IPCS - Environmental Health Criteria 82 Cypermethrine (https://apps.who.int/iris/bitstream/handle/10665/40017/9241542829-eng.pdf;jsessionid=97CB0A2B02736DB78339FAB90B09F920?sequence=1)

Date	Country	Organisation	Type of Organisation	Comment number
21.03.2019	United Kingdom		MemberState	12

Comment received

Cypermethrin (EC: 257-842-9; CAS: 52315-07-8)
Bioaccumulation:
Please can you confirm test method details, study reliability and GLP status for the octanol-water partition coefficient endpoint (Bates, 2002a). This is relevant to assess suitable inputs for bioaccumulation estimates.

We note the EPIWIN database / model training set includes the following relevant data which indicate the cypermethrin logKow may be >6:
1) experimental logKow of 6.6 for cypermethrin (CAS: 523`5-07-8).
2) experimental logKow of 6.94 for alpha-cypermethrin (CAS: 67375-30-8) and relatively close agreement between the predicted BCF of 254.9 and measured BCF of 275

3) experimental log Kow values of 6.05 and 6.06 for beta-cypermethrin (CAS: 065731-84-2).

We think further details are required to consider the suitability of the presented EPIWIN QSAR result. This should include full model output, consideration of the model domain and applicability of analogues in the training set analogues. It could also include a QMRF (QSAR model reporting format).

We think further details should be provided to consider the reliability of the bioaccumulation in fish study. The DS considers that the study reached a 'quasi steady state' – it is unclear if the quoted BCF is based on steady-state or kinetic evaluation. It would be useful to clarify if fish lipid data are available to present a lipid normalised BCF.

Overall, the above information is relevant to interpret if cypermethrin meets the bioaccumulation criteria.

Ecotoxicity:
Please can you confirm if ecotoxicity data used to derive current Water Framework Directive EQSs have been considered? For example the Annual Average AA-EQS is based on a 32-d NOEC of 0.0041 µg/l (≡0.0000041 mg/l) for the marine organism Acartia tonsa (reference 1) and the Maximum Allowable Concentration MAC-EQS reflects acute ecotoxicity to multiple invertebrate species.

1. Barata C, Medina M, Telfer T and Baird D, 2002 Determining demographic effects of cypermethrin in the marine copepod Acartia tonsa: stage specific short tests verses life-table tests. Archives of Environmental Contamination and Toxicology, 43, 373–378.

Date	Country	Organisation	Type of Organisation	Comment number
20.03.2019	Germany		MemberState	13

Comment received

Hazardous to the aquatic environment:
page 9, point 1.2 Proposed harmonised classification and labelling (Table 2):
We agree with the proposal of classification for environmental hazards as Aquatic acute 1 (H400), Aquatic chronic 1 (H410) and chronic M-factor of 1000. We would propose to change the acute M-factor to 100000.
Page 121 ff, point 5.4.2.1 Short-term toxicity to aquatic invertebrates:
There are additional acute data available for cypermethrin with the aquatic invertebrate species Hyalella azteca and Chironomus riparius (Rapley, J.H. and Hamer, M.J. 1996). These data (report CA 8.2.4.2/01) were provided at DAR Volume3, B.9 (2017). The study fulfil valid-ity criteria and is considered acceptable and suitable for classification purposes. The lowest EC50 (48 hours) is 0.0000053 mg/l (mean measured) for Hyalella Azteca and 0.0000069 mg/l (mean measured) for Chironomus riprius.
Page 137, point 5.5 Comparison with the CLP-criteria for environmental hazards:
The lowest acute EC50 (48 hours) is 0.0000053 mg/l (mean measured) for Hyalella azteca. This result would confirm an acute M-factor of 100000, instead of 100 based on acute end-points in the range of 0.000001 to 0.00001 mg/L.
Page 92: In chapter 5.1.1 "Stability" the sub item "Photochemical degradation in air" is missing. Please add this sub item in chapter 5.1.1 and provide the results of the relevant study. A reference to this study is even listed in chapter 6.1 "Hazardous to the ozone layer" of the CLP report of cypermethrin.