Committee for Risk Assessment

RAC

Annex 2

Response to comments document (RCOM)

to the 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

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON CYPERMETHRIN (ISO); A-CYANO-3-PHENOXYBENZYL 3-(2,2-DICHLOROVINYL)-2,2-DIMETHYLCYCLOPROPANECARBOXYLATE; CYPERMETHRIN CIS/TRANS +/- 40/60

COMMENTS AND RESPONSE TO COMMENTS ON CLH: PROPOSAL AND JUSTIFICATION

Comments provided during public consultation are made available in the table below as submitted through the web form. Any attachments received are referred to in this table and listed underneath, or have been copied directly into the table.

All comments and attachments including confidential information received during the public consultation have been provided in full to the dossier submitter (Member State Competent Authority), the Committees and to the European Commission. Non-confidential attachments that have not been copied into the table directly are published after the public consultation and are also published together with the opinion (after adoption) on ECHA's website. Dossier submitters who are manufacturers, importers or downstream users, will only receive the comments and non-confidential attachments, and not the confidential information received from other parties.

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Substance 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
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, ex-cept, sometimes, fatigue, is observed."

Skin corrosion/irritation:
It should be also discussed in the dossier whether classification for skin effects might be ap-propriate (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."

Dossier Submitter's Response

Substance ID

RMS BE Cypermethrin agrees that the evaluation only holds for the racemate. It is however of note that a number of non-neurotoxic endpoints may be considered in a read-across. Exception is thus made for the neurotoxicity effects, which are the most sensitive and the most critical ones, and which may to a certain extend be influenced by variable proportions of enantiomeric subcomponents (the reference values may thus well be different for the racemate, alpha-, beta, zeta cypermethrin).

Carcinogenicity:

Carcinogenicity was not evaluated in the biocide dossier, but the information is available in the PPP dossier, which was recently peer-reviewed, and for which an EFSA conclusion is available.

(i) Regarding the Forbes, 1982 study, notifier provided the HCD, indicating that at termination, the spontaneous incidence in this lab and around this period was up to 17-25% (intermittent-final phase).

(ii) It is however even more important to keep in mind that in this study, the finding at termination is unremarkable (in the presence of an incidence of 29% in one control group). Since there is no increase of mortality (♂:45.8%-50%-59.8%-47.9% at 0-20-150-1500ppm), no less animals were at target in the final phase of the study.

The overall incidence of testicular interstitial cell adenoma was apparently increased (13-11-11-20%), but only because of an increase at 52 weeks (8-0-7-25%), which did not confirm when the incidences were registered at termination (29-27-24-26%). If the increase at top-dose at intermittent kill would really have been a treatment-related observation, it is difficult to understand the absence of effect when the terminal cohort was examined (taking into account the approximately equal number of animals in each phase).

(iii) In the Mc Ausland study (1978), there was no evidence of interstitial cell tumours either.

(iv) In an analysis of carcinogenic outcome, RMS agrees that a possible class-effect should be taken into account. However, in the case of the cypermethrins, substance-specific data are present, taking precedence over a hypothesised class effect. In addition, while top-dose effects were noted in terms of testicular toxicity in a number of experilmental conditions (most likely explained by systemic toxicity), both alpha-cypermethrin and the racemate cypermethrtin were considered no endocrine disturbing substances on a WoE basis. Therefore, there is very weak biological plausibility that this class of pyrethroids would induce testicular adenoma based on an endiocroine mechanism

In conclusion, RMS BE considers the finding not eligible for carcinogenicity classification.

Specific target organ toxicity – single exposure:

STOT SE 3 for narcotic effects was finally NOT recommended in the case of Cypermethrin at the outcome of the EFSA PRAS pexpert consultation.

While several animal studies were mentioned to report narcotic effects and, also in several human studies relevant effects related to narcosis were listed, it is unclear whether the effects are simply a result of the acute neurotoxic action of the a.s. rather than an other mechanism, not covered by the neurotoxicity effect.
The nature of all these effects was reported to be transient.
Regarding narcotic effects (in animal but also in human studies) observed among studies, the majority of the experts were of the opinion that this was related to the neurotoxicity.
Therefore, no classification is proposed based on these effects.

Skin corrosion/irritation:
It was 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).
It is useful to keep in mind that in human, cypermethrin as other pyrethroids are known to induce cutaneous paresthesia which is distinct from the classical irritation. Results from experimental studies do not trigger classification for skin irritation. Therefore no classification is considered warranted.
BE still supports this position, and considers that (like most other pyrethroids, including the very similar alpha-cypermethrin), cypermethrin is devoid of primary irritating properties towards the skin.

RAC's response

Thank you very much for your comments. RAC agrees with the comment and the dossier submitter that this CLH-report applies exclusively to cypermethrin preparations with isomeric composition cis/trans +/- 40/60.

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

Dossier Submitter's Response

DS fully agrees with the comments made. The two proposals are accepted and report is modified accordingly.

RAC's response

Thank you very much for your comments. Noted.

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.				
Dossier Submitter's Response				
(related to comment 4 and 5 below) The following acute toxicity classification was agreed during the PRAS expert consultation: • Acute Tox (oral) Cat 3, (H301, toxic if swallowed) • Acute Cat 4 (H332, Harmful if inhaled) • STOT-SE3 (H335, May cause respiratory irritation) RMS **BE** still agrees with this proposal.				
RAC's response				
Thank you very much for your comments. Noted.				

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.				
Dossier Submitter's Response				
(related to comment 3 and 5) The following acute toxicity classification was agreed during the PRAS expert consultation: • Acute Tox (oral) Cat 3, (H301, toxic if swallowed) • Acute Cat 4 (H332, Harmful if inhaled) • STOT-SE3 (H335, May cause respiratory irritation) RMS **BE** still agrees with this proposal. Typos have been considered (thank you)				
RAC's response				
Thank you very much for your comments.				

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 LD_{50} 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 LD_{50} values of 1732 vs. 2150 in males vs. females). Notably, young animals were significantly more sensitive than adults as reported by Cantalamessa (LD_{50}=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.

Dossier Submitter's Response

The following acute toxicity classification was agreed during the PRAS expert consultation:
- Acute Tox (oral) Cat 3, (H301, toxic if swallowed)
- Acute Cat 4 (H332, Harmful if inhaled)
- STOT-SE3 (H335, May cause respiratory irritation)

RMS BE still agrees with this proposal, and we thank DE for his support.

RAC's response

Thank you very much for your comments. RAC notes that the LC_{50} of 250 mg/kg bw was proposed in the Cantalamessa (1993) paper for adult (and not for young) animals.

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.

Dossier Submitter's Response

(1) We indeed think that the allocation of STOT RE2 for neurotoxicity of cypermethrin is justified. Thank you for your support.

(2) Cypermethrin immunotoxicity is not consistently shown among regulatory studies. On the other hand, the open literature describing potential adverse immune effects of cypermethrin in mammalians is scarce, of limited reliability, and provide no particular concern. It is concluded that the immune system is not a sensitive target organ regarding the toxicity of cypermethrin.

It may be useful, as a raed-across consideration, to mention that in the peer review of alpha-cypermethrin it was concluded that the a.s. did not reveal any signs of immunotoxicity when administered via the diet over a period of 4 weeks to male Wistar rats. The NOAEL for the immunotoxicologically relevant endpoints was set to 450 ppm (34 mg/kg bw/day), the highest dose tested. **In conclusion, the overall WoE seems to indicate that the cypermethrins are not specifically immunotoxic**.
RAC's response
Thank you very much for your comments. Noted.

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.				
Dossier Submitter's Response				
We indeed think that the allocation of STOT RE2 for neurotoxicity of cypermethrin is justified. Thank you for your support. We agree that all neurotoxicity studies evaluated in the DRAR Cypermethrin under Reg (EC) no 1107/2009 could be of use in the CLH dossier. Please note that applicant for cypermethrin under Biocide regulation is different that those for alpha-cyp. and have no access to it. As the data analysis suggested by MS Denmark does neither lead to other conclusions than the already suggested classification for STOT RE2 (nervous system), nor does it allow to draw new conclusions, the suggested re-evaluations are unnecessary for Cypermethrin.				
RAC's response				
Thank you very much for your comments. Noted.				

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.				
Dossier Submitter's Response				
We indeed think that the allocation of STOT RE2 for neurotoxicity of cypermethrin is justified. Thank you for your support.				
RAC's response				
Thank you very much for your comments. Noted.				

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.

Dossier Submitter's Response

We agree with the remark, since this study is critical as regards the ecotoxicological C&L. Please note that:
-The CLH report was initially based on data available/submitted in the context of biocide registration and dat from the first Cypermethrin evaluation in the context of PPP were included. For Cypermethrin renewal in the context of PPP registration, the existing data package was re-assessed and new state of the art studies were submitted. This will be reflected in the CLH report.
The acute 48 h EC_{50} of 0.0053 µg a.s./L for *Hyalella azteca* is correct. The new acute M-factor should be 100000

-For the Chronic End point, the conclusion of the renewal of the substance in the context of the PPP was that the chronic fish NOEC of 0.03 µg a.s./L is not relevant as this endpoint is based on a study which is not suitable to derive a reliable an endpoint anymore (please refer to DRAR 11 volume 3 B11 page 131-132) . The relevant chronic NOEC is 0.077 µg a.s./L for fish is based on a Fish Full Life-Cycle study **(Tapp J.F. et al. (1988) Cypermethrin: Determination of Chronic Toxicity to Fathead Minnow (Pimephales promelas) Full Lifecycle).** The NOEC of 0.077 µg a.s./L has no impact on the classification (chronic 1) and derivation of the M-factor (1000).

-RMS agree to list the additional studies in the list of available data in the CLH report.

Please note that for the sake of clarity, since you already know the study and the conclusions an d since other commenting party agrees on that point we do not add the study in this RCOM

RAC's response

- RAC agrees with the inclusion of the *Hyalella* study with the endpoint value of ED_{50} = 0.0053 µg a.s./L (Rapley and Hamer, 1996). This study has been re-assessed and included into the peer-reviewed EFSA list of valid endpoints for cypermethrin (Annex of the EFSA review: efs25402-sup-0001-Appendix-A.pdf). RAC itself assessed the study, and found that it is executed in compliance with GLP, test conditions are correctly documented and proper testing method and analytics has been used: it can be classified as GLP and REL 1. RAC agrees with the new aquatic acute classification recommended by DS in line with the commenter:
Aquatic acute 1, H400, M= 100,000.

- Regarding acute endpoints in the study of Rapley and Hamer (1996), the midge *Chironomus riaprius* has also been tested, both in the first and fouth instars. As the study has been rated GLP and REL1, the EC_{50} value for the midge should also be included: EC50 = 0.0069 µg a.s./L. The *Hyalella* and the *Chironomus* EC_{50} values are very close, so both support the Aquatic acute 1 classification, and the new M factor of 100,000.

- As regards the remark of MS to include all valid chronic endpoints coming up in the EFSA Review, RAC agrees, assuming that the studies can be acquired and assessed by RAC. It is necessary also because the chronic fish NOEC of 0.03 µg a.s./L, – applied as far as key study for classification – should be ignored, because it does not fulfil quality criteria, as DS also noted referring to DRAR 11 volume 3 B11 page 131–132.

- RAC made a search in the EFSA Appendix and could identify four valid chronic studies, relevant for classification: one fish, two daphnia, and a midge study (EFSA Journal 2018, 16(8):5402; Appendix A: pages 112 and 113). Two chronic Daphnia studies (Dickhaus, 1990 and Simon, 2015) – with GLP and REL1 rating – has already been included into the CLH Report. The relevant endpoint from the Dickhause (1990) study is NOEC=0.04 µg/L and from theSimon (2015) study is NOEC = 0.053 µg/L, very close to the NOEC = 0.077 µg/L from the fish study of Tapp, et al. (1988). The other two studies (one more Daphnia and the midge study) resulted NOEC values in the same order of magnitude (0.05 µg/L and 0.0.64 µg/L respectively) as the valid studies, but has not been evaluated by RAC because the original studies are not available. Therefore RAC would include the Tapp et al. study only.

- Final opinion of RAC reagarding aquatic chronic classification is that the Tapp et al. (1988) study should be included additionally into the ODD and together with the studies of Dickhaus (1991), Simon (2015) (which hava already been included into the HCL report) consider these three studies as basis for aquatic chronic classification. The studies of Dickhaus (1990) and Simon (2015) with the result of NOEC = 0.04 µg/L and 0.053 µg/L support the classification based on the newly included Tapp et al. (1988) study, and all three results would indicate a classification of Aquatic chronic 1 with H410 and M = 1000.

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).				
Dossier Submitter's Response				
RMS BE Cypermethrin agrees : see response to FR comment above The Correct EC50 for hyalella Azteca is 0.0053µg/L M= 100000				
RAC's response				
Thank you for the comment.				

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)

Dossier Submitter's Response

With reference to the CLH report chapter 5.3, the study by Szeleczky (1990) was used to assess the potential for bioaccumulation of Cypermethrin. With reference to the Cypermethrin RAR (Vol. 3 B.9 AS) the studies by Szeleczky (1990), Baldwin (1978) and Bennett (1981) are not acceptable anymore.
In the Cypermethrin RAR, the assessment for bioaccumulation of Cypermethrin in fish is based on the valid study by Giroir and Stuerman (1993) which was re-evaluated to comply with state of the art requirements (OECD TG 305, 2012). The re-calculated BCF value of 266 – 331 for Cypermethrin as given in the EFSA Conclusion (2018) were corrected for lipid content and fish growth, for details please refer to the Cypermethrin RAR B.9 AS. (See annex I below)
The CLH report should be updated with the BCF values calculated considering state of the art guidance based on the study by Giroir and Stuerman (1993). The results of the non-acceptable study by Szeleczky (1990) should be deleted from the report. As measured BCF data are available for Cypermethrin (corrected for lipid content and growth), one could also skip the BCFwin estimated BCF value for Cypermethrin.

The chronic *Daphnia magna* study by Dickhaus and Heisler (1990) which resulted in a NOEC of 0.04 µg a.s./L is considered not acceptable in the Cypermethrin RAR (Vol. 3 B.9 AS). The current EU agree *Daphnia magna* NOEC is 0.05 µg a.s./L (see EFSA Conclusion, List of endpoints)
The chronic fish NOEC of 0.03 µg a.s./L is not relevant as this endpoint is based on a study which is not suitable to derive a reliable endpoint anymore, for details please refer to the

Cypermethrin EFSA Conclusion (2018, List of endpoints, page 112 and footnote 3). Please also note that the Fish Early Life Stage NOEC of 0.25 µg a.s./L as given in chapter 5.4 of the CLH report is also not valid anymore based on the assessment given in the Cypermethrin RAR B.9 AS.
The relevant chronic NOEC is 0.077 µg a.s./L for fish is based on an FFLC study. The NOEC of 0.077 µg a.s./L has no impact on the classification (chronic 1) and derivation of the M-factor (1000).

RAC's response

- Bioaccumulation: According to the the newly included study of Giroir and Steuerman (1993) the lipid and growth normalized BCF = 266–331 L/kg is a valid result.
A supportive information can be found in the EFSA Review: "based on toxicokinetic studies there is no evidence on bioaccumulation in humans and animals" (EFSA Journal 2018, 16(8):5402; Appendix A, p. 13.). Therefore based on the newly included fish bioaccumulation study result RAC opinion is, that cypermethrin has no potential for bioaccumulation.
- Chronic toxity: due to GLP and realiability issues, the most relevant and by RAC also assessed study results are
for fish: NOEC = 0.077 µg a.s./L (Todd et al, 1988)
for invertebrates NOEC = 0.004 µg a.s./L (Dickhaus, 1990) and NOEC = 0.053 µg a.s./L (Simon, 2015)
According to the EFSA list in Appendix A: EFSA Journal 2018, 16(8):5402; Appendix A: p. 113.) there are two more valid studies, one for Daphnia with a NOEC = 0.05 µg/L and a chronic study for midge with a NOEC = 0.064 µg/L. These results do not impact the proposed classification. Depending on the accessibility of the studies and the result of the evaluation of their realiability by RAC their inclusion will be decided by RAC.

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.

Dossier Submitter's Response

Bates 2002a: Test method: EECA8 (HPLC-method)
Purified a.s. 98.3% w/w (cis:trans/40-60) Batch n° AH902
GLP: yes; Reliability 1

As regards to epiwin we agree that these information are usefull. The model was run by a former colleague. The only output model document is provided in annex II. However due to recent developpement, the EPIWIn evaluation could pententially be skipped.

We would like to refers you to the response made to NL regarding the BCF

As regards to the Ecotoxicity endpoint, the data use in the WFD to derive where not used because these mixed data for which it is not possible to clearly identified the purity or bacthes and for different cypemethrin, not the specific cis:trans/40:60 which is of consideration in this report. We do not have in Biocide framework or in the PPP framework the study from Barata and al 2002. It is therefore not possible to clearly state whether this study is suitable and correspond to the the chemical specification of the cypermethrine considered in this report.

RAC's response

- Bioaccumulation: RAC gives priority to the measured BCF from the valid study of Giroir and Steuerman (1993) and rejects both the former bioaccumulation studies of Szeleczky (1990), Baldwin (1978) and Bennett (1981), as well as the model calculations of Bates (2002) based on log K_{ow} and the one prepared the RMS by using EPISuite.
- Ecotoxicity: RAC agrees with DS argumentation for not to include WFD information.

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON CYPERMETHRIN (ISO); A-CYANO-3-PHENOXYBENZYL 3-(2,2-DICHLOROVINYL)-2,2-DIMETHYLCYCLOPROPANECARBOXYLATE; CYPERMETHRIN CIS/TRANS +/- 40/60

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.

Dossier Submitter's Response

DS agree with DE. Please refers to above responses.

As regards to chapter 5.1.1 Due to the low vapour pressure of $< 1 \times 10^{-5}$ Pa, the exposure via air is negligible. Furthermore, the photochemical degradation with a DT_{50} of 6 h is far below the trigger of 2 days for consideration of the long-range transport.

The references to chapter 5.1.1 in 61. Should be removed

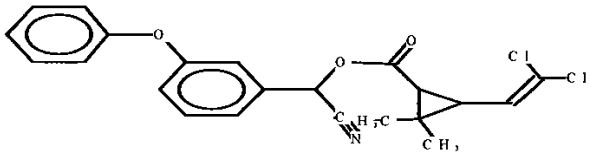
RAC's response

Thank you for your support in aquatic acute classification and your other comments. See the previous sections for answers and discussion.

Annex I:

See confidential annex

Annex II



```
SMILES : CLC(CL)=CC1C(C)(C)C1C(=O)OC(C(#N))c2cccc(Oc3ccccc3)c2
CHEM   : Cypermethrin
MOL FOR: C22 H19 CL2 N1 O3
MOL WT : 416.31
---------- BCFBAF v3.00 ----------
Summary Results:
  Log BCF (regression-based estimate):  1.73  (BCF = 54.1 L/kg wet-wt)
  Biotransformation Half-Life (days) :  0.605  (normalized to 10 g fish)
  Log BAF (Arnot-Gobas upper trophic):  3.28  (BAF = 1.89e+003 L/kg wet-wt)

Experimental BCF-kM Database Structure Match:
---------------------------------------------
  Name       :  Cypermethrin
  CAS Num    :  052315-07-8
  Log BCF    :  2.62  (BCF = 417 L/kg wet-wt)
  BCF Data   :  BCF Validation Set
  Log Bio HL:  ---
  Bio Data   :  ---

Experimental BCF-kM Database Structure Match:
---------------------------------------------
  Name       :  [1 alpha(S*), 3 alpha]-(+-)-3-(2,2-Dichloroethenyl)-2,2-dime
  CAS Num    :  067375-30-8
  Log BCF    :  2.444  (BCF = 278 L/kg wet-wt)
  BCF Data   :  BCF NonIonic Training Set
  Log Bio HL:  0.701  (Bio Half-life = 5.02 days)
  Bio Data   :  kM Training Set

============================
BCF (Bioconcentration Factor):
============================

Log Kow (experimental):  6.06
Log Kow used by BCF estimates:  5.04 (user entered)

Equation Used to Make BCF estimate:
   Log BCF = 0.6598 log Kow - 0.333 + Correction

      Correction(s):                  Value
       Cyclopropyl-C(=O)-O- ester    -1.259

   Estimated Log BCF =  1.733  (BCF = 54.11 L/kg wet-wt)

=========================================================
Whole Body Primary Biotransformation Rate Estimate for Fish:
=========================================================
------+-----+-------------------------------------------+---------+---------
 TYPE | NUM | LOG BIOTRANSFORMATION FRAGMENT DESCRIPTION |  COEFF  |  VALUE
------+-----+-------------------------------------------+---------+---------
 Frag |  1  |  Ester   [-C(=O)-O-C]                     | -0.7605 | -0.7605
 Frag |  2  |  Aliphatic chloride   [-CL]               |  0.3608 |  0.7215
 Frag |  1  |  Carbon with 4 single bonds & no hydrogens| -0.2984 | -0.2984
 Frag |  1  |  Cyanide / Nitriles   [-C#N]              |  0.1542 |  0.1542
 Frag |  1  |  Aromatic ether  [-O-aromatic carbon]     | -0.0694 | -0.0694
 Frag |  1  |  Unsubstituted phenyl group (C6H5-)       | -0.6032 | -0.6032
 Frag |  1  |  Aromatic-CH                              | -0.4629 | -0.4629
 Frag |  9  |  Aromatic-H                               |  0.2664 |  2.3974
 Frag |  2  |  Methyl  [-CH3]                           |  0.2451 |  0.4902
```

Frag	2	-CH - [cyclic]	0.0126	0.0252
Frag	1	-C=CH [alkenyl hydrogen]	0.0988	0.0988
Frag	1	-C=CH [alkenyl hydrogen]	0.0000	0.0000
Frag	2	Benzene	-0.4277	-0.8555
L Kow	*	Log Kow = 5.04 (user-entered)	0.3073	1.5490
MolWt	*	Molecular Weight Parameter		-1.0675
Const	*	Equation Constant		-1.5058
RESULT		LOG Bio Half-Life (days)		-0.2181
RESULT		Bio Half-Life (days)		0.6051
NOTE		Bio Half-Life Normalized to 10 g fish at 15 deg C		

Biotransformation Rate Constant:
kM (Rate Constant): 1.145 /day (10 gram fish)
kM (Rate Constant): 0.6441 /day (100 gram fish)
kM (Rate Constant): 0.3622 /day (1 kg fish)
kM (Rate Constant): 0.2037 /day (10 kg fish)

Note: For Arnot-Gobas BCF & BAF Methods, Experimental Km Half-Life Used:
Exp Km Half-Life = 0.701 days (Rate Constant = 0.138/ day)
Arnot-Gobas BCF & BAF Methods (including biotransformation rate estimates):
Estimated Log BCF (upper trophic) = 3.226 (BCF = 1681 L/kg wet-wt)
Estimated Log BAF (upper trophic) = 3.277 (BAF = 1893 L/kg wet-wt)
Estimated Log BCF (mid trophic) = 3.300 (BCF = 1993 L/kg wet-wt)
Estimated Log BAF (mid trophic) = 3.427 (BAF = 2675 L/kg wet-wt)
Estimated Log BCF (lower trophic) = 3.313 (BCF = 2055 L/kg wet-wt)
Estimated Log BAF (lower trophic) = 3.535 (BAF = 3430 L/kg wet-wt)

Arnot-Gobas BCF & BAF Methods (assuming a biotransformation rate of zero):
Estimated Log BCF (upper trophic) = 3.926 (BCF = 8424 L/kg wet-wt)
Estimated Log BAF (upper trophic) = 5.099 (BAF = 1.256e+005 L/kg wet-wt)