Committee for Risk Assessment

RAC

Annex 2

Response to comments document (RCOM)

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

2,2'-methylenebis(6-(2H-benzotriazol-2-yl) -4-(1,1,3,3-tetramethylbutyl)phenol)

EC Number: 403-800-1
CAS Number: 103597-45-1

CLH-O-0000001412-86-177/F

Adopted
5 December 2017

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON 2,2'-METHYLENEBIS(6-(2H-BENZOTRIAZOL-2-YL)-4-(1,1,3,3-TETRAMETHYLBUTYL)PHENOL)

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.

ECHA accepts no responsibility or liability for the content of this table.

Substance name: 2,2'-methylenebis(6-(2H-benzotriazol-2-yl)-4-(1,1,3,3-tetramethylbutyl)phenol)
EC number: 403-800-1
CAS number: 103597-45-1
Dossier submitter: Germany

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
06.02.2017	France		MemberState	1
Comment received				
France does not support the proposal to remove classification of 2,2'-methylenebis(6-(2H-benzotriazol-2-yl)-4-(1,1,3,3-tetramethylbutyl)phenol) (n° CAS: 103597-45-1) from the current entry Aquatic Chronic 4.				
Dossier Submitter's Response				
See response to comment 4.				
RAC's response				
See response to comment 4.				

OTHER HAZARDS AND ENDPOINTS – Hazardous to the Aquatic Environment

Date	Country	Organisation	Type of Organisation	Comment number
09.02.2017	Belgium		MemberState	2
Comment received				
Besides the joint submitted registration dossier, 7 individual registration dossiers are currently available for this substance and as mentioned in the CLH report, all registration dossiers were taken into account. We do regret however that not all studies of the different registration dossiers were recorded in the CLH report in order to have an overview of the available data, an insight in the quality of those data and weight of each study (WoE). How were studies from the different registration dossiers selected for this CLH dossier? Were the most reliable studies selected for CLH purpose? The CLH dossier does not contain all the studies/results reported in the different publically available registration dossiers f.i. also other log Kows than 12.7 (20°C)-KI2 are reported : Log Kow = 4.2 (23°C)-KI2, QSAR : log Kow =14.48 (25°C), QSAR log Kow = 12.5 (25°C).				

F.i. hydrolysis, only 1 registration dossier records experimental data on hydrolysis at pH 4,7 and 9 at 25°C and is considered as Key study but no reliability was mentioned. However in the CLH report this study was attributed KI4. Please mention why this study was not reliable. In the other registration dossiers also data at 50,60 and 70°C are available with KI2.

Some results for a certain endpoint were not reported in the CLH report : f.i. data on surface tension : 2 results on surface tensions are available in the registration dossiers : 72N/m (20°C) at a conc. of 10.000mg/L (KI2) and 71.6N/m (20°C) at a conc. of 0.007 mg/L, indicating that the substance is not surface active.

Aquatic toxicity
All LC50 values >1 mg/L. No toxicity was seen up to the water solubility.
No chronic data are available for all 3 trophic levels (only for algae and invertebrates). The lowest NOEC algae was ≥2 mg/L and no toxicity was seen up to the water solubility.

It is mentioned in Table 16 that no long term toxicity study with fish is available. However in the joint submitted registration dossier a 56 d NOEC (>1 mg/L, mortality) is available for Cyprinus carpio. This study should have been described in the CLH report (even if it is not reliable, together with the reason why).
As it is not clear whether there is a valid and reliable NOEC for fish, a conclusion on chronic toxicity for all 3 trophic levels can't be drawn (all NOECs>1mg/L?). >THAN SOLUBILITY

Bioaccumulation
The classification criteria use the BCF or in the absence of it the Log Kow as the measure of potential for bioaccumulation. No reliable BCF (KI3) is available.
Following the guidance "R.11 :PBT/vPvB assessment" a substance may be considered as not B, based on Weight-of-Evidence and expert judgement, if Log Kow > 10 : calculated value, preferably by several estimation programs, for substances for which Log Kow can be calculated and the model is reliable).
For this substance many QSAR predictions are reported however not reliable (not in the applicability domain, not in the structural domain, low similarity found in molecule, low confidence due to mean average error, …). It is therefore not sufficiently demonstrated that the substance will not bioaccumulate over an extended period.

In case no valid BCF is available, the determination is thus based on the reliable log Kow. Log Kow for this substance is >4, meeting the criterion for potential bioaccumulation. However, a substance or mixture need not be classified when it can be shown by conclusive experimental data from internationally acceptable test methods that the substance or mixture is not biologically available.

Some factors indicate that there is limited potential for the substance to be taken up by biota.
It should however be noted that the only conclusion drawn based on these factors is that the substance is not (very) bioaccumulative, and not that the substance can't be taken up at all. The supplementary information to confirm this limited uptake may comprise data from a chronic toxicity study with mammals (≥ 90 days, showing no toxicity), a toxicokinetic study with mammals or birds, a bioconcentration study with invertebrates, or reliable read-across from a structurally similar compound (all showing no uptake) (R.11 PBT/vPvB assessment).

I. Factors :
1. An average maximum diameter (Dmax aver) of greater than 1.7 nm plus a molecular

weight of greater than 1100 : MW = 658.89 g/mol : not meeting the criterion
2. a maximum molecular length (MML) of greater than 4.3 nm : not reported
3. Octanol-water partition coefficient as Log10 (Log Kow) > 10 : Log Kow=12.7 >10 : meeting the criterion
4. measured octanol solubility (mg/L) < 0.002 mmol/L × MW (g/mol) (without observed toxicity or other indicators of bioaccumulation) Calculated from log Kow =12.75, WS : 0.000005 mg/L and MW= 658.89 g/mol.=> octanol solubility 2.8117x107 mg/L >> 1.317 : not meeting the criterion

II.Toxicokinetics with mammalians
Toxicokinetic study in rats with dermal treatment was performed with the commercial formulation and not with the active substance as such. Therefore we consider it not relevant for this purpose.
Toxicokinetic data for a single oral administration of the substance in rats following OECD417/427 demonstrate that absorption is unlikely, that the substance is quickly and almost completely excreted (96-97% parent compound in faeces) The residual concentration in carcass was very low and under the detection limit in blood and plasma. The achieved mass balance was acceptable.

"It is assumed that the substance will either be absorbed by the organisms through passive diffusion or taken up actively by a specific mechanism. Bioavailability may, therefore, vary between different organisms" (Guidance on CLP criteria, 1.3.2.2).

Moreover the substance has a very low water solubility and a high adsorption potential. The estimated half live in water is 180d (4320 h)[Level III Fugacity Model (Episuite 4.1)] and it will partition from the water merely to soil and sediment most probably by adsorption. Because the substance is not readily degradable it will therefore also be available for a longer period to organism living in soil and sediment.

Because of the above findings and uncertainties, we are of the opinion that the safety net is still of application and declassification for the environment is not considered appropriate.

Dossier Submitter's Response

For all physico chemical endpoints only the most reliable and relevant result is stated in the CLH Report. Further information – also most of the cited Log Pow values – are included in the corresponding section in the IUCLID Dossier.
In the case of the Log Pow the stated value is the one used by the company who asked for the CLH Dossier. Additionally two of the calculated values are in the same range (with 12.5 using Kowwin (v1.68) and 12.7 using CLOGP Release 3.42). Furthermore, also a value of >> 4.6 is stated in the IUCLID dossier as result of a preliminary test.
As we have no further information regarding the exact methods used for the stated published values we decided that the Log Pow of 12.7 is the most reliable one.
In the case of the surface tension values we got the proposed information that "not applicable - The water solubility is < 1 mg/L". Based on this, we first checked the water solubility, which is <0.000005 mg/L at 20 °C (and therefore < 1 mg/L). Additionally, we checked the other surface tension studies, where concentrations of <0.13 mg/L, 10000.0 mg/L and 0.007 mg/L were used. The given water solubility is below below the value < 1mg/L, which is the trigger value of EG 440/2008 A.5 to waive the test. Additional the values are all above the requested concentration of 90% of the water solubility or 90% saturated solution. Therefore, we could not evaluate without doubt that the values are correct and decided to adopt the justification.
Hydrolysis:
Only one study on hydrolysis is available. This study was included in three of the seven

registration dossiers. In two registration dossiers only data at 50°C, 60°C and 70°C were mentioned (with reliability 2). The data on 25°C are only mentioned in one dossier with reliability 4. For the half-life values for the higher temperature see the following table:

Temperature [°C]	pH	Half-life [h]
50	4	276
	7	341
	9	888
60	4	218
	7	152
70	4	185
	7	76.1

Screening tests biodegradation:
The reliability for the study based on 84/499/EEC C.5 in table 12 of the CLH report should be changed from 4 (secondary literature) to 2 (reliable with restriction).

Aquatic toxicity:
There is no long-term toxicity study with fish available. The 56d-study mentioned by BE MS found on the dissemination site is a bioaccumulation study according to OECD 305. According to the registrant this study has the reliability 2 (Klimisch). Juvenile *Cyprinus carpio* was exposed to nominal 1 and 0.1 mg/L of the test substance. No toxic effects were observed. This is the same study used for the assessment of the bioaccumulation. We assessed this study with reliability 3.
Bioaccumulation:
Your reasoning is very comprehensible and conclusive. We agree that there are some uncertainties on measured and estimated bioaccumulation data. But a toxicokinetic study demonstrated that the substance is not bioavailable and does not significantly cross biological membranes. Additionally, the very low water solubility argues against the presence of the substance in the water.

RAC's response

RAC can only partly accept the procedure used by the DS for selecting the most relevant and appropriate data and information from the seven registration dossiers, because the lack of detailed characterisation of the decisive study results in high uncertainty on the field of study quality and the acceptability of their results. Such studies are the fish bioaccumulation study and the physicochemical study, reporting a log Kow of 12.7. Neither does the qualification of the QSAR BCF studies by the DS result in a clear evidence.

The chronic toxicity value, mentioned by the commenting MS derives from the bioaccumulation study as an indirect conclusion. RAC assessed this 56 days fish study, applied for measuring bioaccumulation, and found that it is not suitable to substitute a chronic fish study: there are no toxicity data included, the only sentence suggesting that no toxic effect was posed on juvenile carp in the test using two concentrations (0.1 and 2.0 mg/L) from the substance is *"No abnormal appearance was observed in test fishes",* what does not adequately substitute a NOEC.

RAC shares the opinion with the commenting MS that this study should have been mentioned in the CLH report, and argues that it is not suitable for the purpose of aquatic chronic toxicity assessment.

RAC agrees with the commenting MS that in case no valid BCF is available, the determination is thus based on the reliable log Kow. However the use of log Kow >4 criterion for this substance is not adequate, because, as the CLP Guidance says: *"For highly*

lipophilic substances, e.g. with log Kow above 6, experimentally derived BCF values tend to decrease with increasing log Kow."

RAC agrees that the high uncertainties do not allow the removal of the safety net classification.

Date	Country	Organisation	Type of Organisation	Comment number
30.12.2016	United Kingdom		MemberState	3

Comment received

We do not support removal of the current Aquatic chronic 4 classification.
There are no data for the chronic toxicity to fish endpoint and relative chronic toxicity to fish is unclear.
While the dossier includes details for predicted and measured BCFs, none of the values are considered reliable. Therefore, it is not possible to conclude the substance is not bioaccumulative.
This approach is consistent with the RAC conclusion for substance EC: 401-680-5 adopted on 4 December 2015 (Ref: CLH-O-0000001412-86-88/F).

Dossier Submitter's Response

Thank you for your comment.
We agree that no long-term toxicity data for fish is available.
We agree that there are some uncertainties on measured and estimated bioaccumulation data. But a toxicokinetic study demonstrated that the substance is not bioavailable and does not significantly cross biological membranes. Based on the limited bioavailability, combined with the very low water solubility (<5 ng/L) and the very high log Kow (12.7) bioaccumulation in organisms is not expected. Hence, the substance does not fulfil the criteria for Aquatic Chronic 4.

RAC's response

After assessing the original bioaccumulation study RAC agrees that there are too many uncertainties in this study (e.g. the solvent is not a recommended one and the substance concentration was not in an environmentally realistic range). Furthermore, this study cannot substitute a chronic toxicity test as measured chronic mortality results have not been included into the study report.
The QSAR estimates of BCFs cannot be considered as reliable based on the information included in the dossier. In addition, the value of log Kow of 12.7 also carries uncertainties, which further weakens the quality of the estimated BCF. Thus, RAC agrees with the commenting MS that the evidence is not sufficient to remove the classification of 2,2'-methylenebis(6-(2H-benzotriazol-2-yl)-4-(1,1,3,3-tetramethylbutyl)phenol) as Aquatic Chronic 4.

Date	Country	Organisation	Type of Organisation	Comment number
06.02.2017	France		MemberState	4

Comment received

France does not support the proposal to remove classification of 2,2'-methylenebis(6-(2H-benzotriazol-2-yl)-4-(1,1,3,3-tetramethylbutyl)phenol) (n° CAS: 103597-45-1) from the current entry Aquatic Chronic 4.

According to data presented in the dossier, the substance exhibits a very low water solubility, is not ready biodegradable and a bioaccumulation potential is still expected (log Pow=12.7). The predicted BCF values from QSAR models are considered not valid because

the substance does not fulfil the requirements of the applicability domain (AD) of the model. The substance complied with the AD restrictions of the US EPA TEST v4.1 QSAR model but the confidence in the estimated BCF are low (page 18). Thus, there are still uncertainties about bioaccumulation potential. Considering all the information, we believe that the classification of the substance must be remained Aquatic chronic 4.
Dossier Submitter's Response
Thank you for your comment. We agree that only one QSAR model fulfil the requirements of applicability domain and that there are some uncertainties on measured and estimated bioaccumulation data. However, due to the low bioavailability, poor water solubility and high log Kow, bioaccumulation in organisms is not expected. Therefore, the substance does not fulfil the criteria for Aquatic Chronic 4.
RAC's response
RAC does not agree with the general statement that a bioaccumulation potential is still expected at log Kow of 12.7. The BCF decreases above log Kow of 6 due to hydrophobicity, reduced membrane permeation kinetics or reduced biotic lipid solubility (CLP guidance, Annex III.2.1, 2015). On the other hand the estimated log Kow value of 12.7 carries uncertainties and the QSAR estimates included in the CLH dossier are based on this log Kow value. In addition a large number of QSAR based BCF values are presented in the CLH dossier without proper evaluation and selection, which makes the opinion formulation difficult and causes further uncertainties. Altogether the bioaccumulation potential of the substance cannot be sufficiently judged, based on the presented QSAR estimates or any other evidence in the dossier. RAC agrees with the commenting MS that due to the high level of uncertainties in bioaccumulation potential the removal of the safety net classification is not sufficiently substantiated.

Date	Country	Organisation	Type of Organisation	Comment number
31.01.2017	Netherlands	RIVM/BR	National Authority	5
Comment received				
Conclusion on proposal: The removal of the classification of the substance with Aquatic Chronic 4 is supported. Proposed comments: Justification of removal Chronic 4 classification is mainly based on the information of aquatic toxicity results and bioaccumulation predication. Although the QSAR predications are not valid, the limited bioavailability suggests that the bioaccumulation may be very low. In addition, the limited water solubility of <5 ng/L suggests that toxicity to aquatic organisms is likely to occur at low concentrations than the water solubility. However, the daphnia study shows that this is not the case. Although a chronic fish toxicity test is absent, it is expected that the substance may not be toxic to fish at the limit of the water solubility because such potent chemicals have been only demonstrated in a few chemicals like endocrine disruptors. As a general remark, we would like to point out the study summaries for bioaccumulation and ecotoxicity tests were quite limited. Bioaccumulation Page 16: "This assumption is supported by the QSAR calculations which have been performed using different models". The QSAR predications are not valid and varied with				

great differences. Such information with great variations does not support the conclusion of low bioavailability and low bioaccumulation.

Ecotoxicity
Page 5, Section 2.2
We do not agree with the dossier submitter's statement "according to the acute aquatic toxicity data, neither fish nor aquatic invertebrates seem to be more sensitive. A chronic fish toxicity test is therefore not necessary to assess the toxicity towards aquatic organisms." This is not completely correct and is misleading. Based on the available results of acute toxicity tests, it is not possible to draw a conclusion that neither fish nor aquatic invertebrates seem to be more sensitive. Therefore, there is no basis for the conclusion that chronic fish toxicity test is not needed

Dossier Submitter's Response

Thank you for your support.

Bioaccumulation:
We agree that the QSAR data are not valid and that there are some uncertainties on measured and estimated bioaccumulation data. Nevertheless, due to the low bioavailability bioaccumulation on organisms is not expected.

Ecotoxocity:
We agree that for substances with a low water solubility no conclusion can be drawn from acute toxicity testing whether fish or daphnia are more sensitive, especially when there are no effects observed in the acute toxicity tests.

RAC's response

RAC understands the MS's comments and general conclusions and does not deny that the safety net could have even been removed from 2,2'-methylenebis(6-(2H-benzotriazol-2-yl)-4-(1,1,3,3-tetramethylbutyl)phenol) if the information in the dossier was sufficiently substantiated. But there are neither sufficiently reliable study results for the Kow itself, nor for the bioaccumulation potential or for chronic aquatic toxicity, as well as a well grounded list of evidence to follow the WoE approach. Therefore RAC advises to retain the classification of **Aquatic Chronic 4** for 2,2'-methylenebis(6-(2H-benzotriazol-2-yl)-4-(1,1,3,3-tetramethyl butyl)phenol).