Committee for Risk Assessment

RAC

Annex 2

Response to comments document (RCOM)

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

Octamethylcyclotetrasiloxane; [D4]

EC Number: 209-136-7
CAS Number: 556-67-2

CLH-O-0000001412-86-192/F

Adopted

9 March 2018

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON OCTAMETHYLCYCLOTETRASILOXANE; [D4]

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: Octamethylcyclotetrasiloxane; [D4]
EC number: 209-136-7
CAS number: 556-67-2
Dossier submitter: Germany

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
06.04.2017	Belgium		MemberState	1
Comment received				
BE CA regrets that the Repr.2, H361f*** (translation from dir. 67/548/EEC) wasn't tackled in this CLH report.				
Dossier Submitter's Response				
During the preparation of the CLH dossier the registration data and the 'Opinion on cyclomethicone D4/D5 (22 June 2010)' of the SCCS (Scientific Committee on Consumer Safety) (SCCS/1241/10, 2010) for carcinogenicity, mutagenicity, reproductive toxicity and respiratory sensitisation were checked which is evaluated with reliability 4 (secondary source). However, it was concluded that the registrants' and SCCS evaluation of the reliabilities of the studies is appropriate. As a result of this evaluation the dossier submitter concludes that no additional classification regarding human health or change of the current harmonized classification as Repr. 2, H361f is required. Therefore no data are presented in Section 10 'Evaluation of health hazards'.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
07.04.2017	United States		Individual	2
Comment received				
Table 12, page 14, proposes hazard classification 1 for siloxane D4. This hazard classification is based on the results of a 21-day reproduction study with Daphnia magna, and supported by the results of a 14-day prolonged acute study with rainbow trout. I believe that this proposal is not based on a thorough evaluation of the science and should be reconsidered.				

D4 is an extremely volatile compound with low water solubility and, as such, aquatic testing is a challenge. The studies described in the paper by Sousa et al. (1995), referenced in the Proposal, were conducted in completely enclosed systems in order to prevent loss of test material. This is not an environmentally-relevant test system; however, it was necessary in order to maintain measurable test concentrations. In the Daphnia magna reproduction study, there was a statistically significant increase in mortality at the highest measured test concentration of 15 µg/L. However, there was no impact on reproduction, and in fact, reproduction increased with increasing test concentrations. Thus, the no observable effect concentration (NOEC) for reproduction was > or equal to 15 µg/L. Reproduction is the population-relevant endpoint and should take precedence in the scientific evaluation of the study, especially given the extreme measures required just to keep D4 in solution.

The Proposal also points to the results of a 14-day prolonged acute rainbow trout study, with an acute NOEC for mortality of 4.4 µg/L, in support of the chronic hazard classification. It is unclear why an acute study is being used to support a chronic classification. Sousa et al. (1995) reported on the results of a 93-day early life-stage (ELS) study with rainbow trout that had no effects up to the highest dose tested of 4.4 µg/L. In order to evaluate the likely reliability of the results of the 14-day prolonged acute study, given the apparent inconsistency in the results of the two rainbow trout studies, modelling was employed to determine the critical body burden (CBB) required to elicit an adverse effect in both of the two studies using procedures described in Mackay et al. (2015). The CBB is defined as the lowest observed total body concentration of a chemical in an organism which is associated with the occurrence of adverse toxic effects. In the work of Mackay et al. (2015), a simple first order pharmacokinetic model (Cfish = K1/k2*Cw*(1-exp-(k2+km)*time)) is used to estimate fish CBB levels and compare those CBB levels to those associated with a narcotic mode of action, under which materials like D4 are proposed to operate (Redman et al., 2012).

The results of the 93-day trout ELS study at 12°C with a NOEC of 4.4 µg/L indicate that no adverse effects on embryos and larvae were noted at this dose/exposure time combination. As shown in Figure 1 (attached document), these empirical results are consistent with the results of the Mackay et al. (2015) simulation of the exposure, where fish averaged 1.6 g in weight by the end of the study. Five other dose regimes were modeled in addition to 4.4 µg/L: 6.9, 11, 12, 22, and 27 µg/L; the last modeled dose is the functional water solubility for D4 at 13°C (calculated). The graph in Figure 1 indicates that only at dose concentrations of 22 and 27 µg/L would the small trout accumulate sufficient D4 by day 90 of the simulation to exceed the CBB for a narcotic mode of action of 3 mmol/kg (Mackay et al., 2015). This suggests that concentrations of D4 up to and including 12 µg/L could have been used in the 93-day trout study without any adverse effects occurring.

The pharmacokinetic model of Mackay et al. (2015) was also used to examine the unexplained mortality noted in the D4 14-day prolonged acute study. As shown in Table 1, the Mackay et al. (2015) model was used to calculate the time to achieve CBB at a given D4 dose concentration of 6.9, 12, and 22 µg/L, concentrations that elicited mortality in the acute study. The 4.4 µg/L empirical dose level in the 93-day trout ELS study is also presented. The results show that the experimental results from the D4 14-day prolonged acute study are anomalous compared to the pharmacokinetic modeled results, which indicate that dose concentrations as high as 22 µg/L should not have produced the observed trout mortality in 14 days or less. It is unknown why the mortality occurred in the prolonged acute study. It is possible that since the water

accommodated fraction was established at room temperature (approximately 21°C) but the study was performed at 12°C, the decrease in temperature resulted in a super-saturated solution that might have introduced a precipitate into the test system causing a physical effect. Further work would be needed to confirm this hypothesis.

In summary, the 21-day Daphnia magna reproduction study resulted in a NOEC for reproduction of > or equal to 15 µg/L, a concentration above the hazard classification 1 criteria. In addition, modeling of the pharmacokinetic behavior of D4 has shown that the empirically-observed top dose of 4.4 µg/L, the NOEC in the D4 93-day trout ELS study, could conceivably have been as high as 12 µg/L without adverse impact. However, the mortality observed in the prolonged acute study is inconsistent with a narcotic mode of action and the pharmacokinetic behavior of D4. In addition, information in the literature on possible environmental exposures suggests that D4 would not achieve a concentration in surface water that would cause toxicity to aquatic organisms. Thus, a hazard classification of 1 is inappropriate given the available data.

ECHA note – An attachment was submitted with the comment above. Refer to public attachment Mihaich-CCB D4-4-7-2017.pdf

Dossier Submitter's Response

The tests described in Sousa et al. (1995) were conducted in completely closed systems. This is critically commented by Mihaich but recommended by CLP guidance (version 4.1 p.588ff), the respective OECD test guidelines and OECD guidance no. 23 (p.26ff) to minimise losses from test systems. The modifications to minimise the losses of volatile substances from test media are described amongst others in the cited guidance documents.

For the comment on the relevance of the effect on survival of adult daphnia in the *Daphnia* reproduction test: In OECD guidance 211, the survival of adults is also an endpoint to be documented as well as reproduction. In the guidance it is stated that "…if parental mortality occurs in exposed replicates, it should be considered whether or not the mortality follows a concentration-response pattern…". As the mortality occurred at the highest test concentration this could not be excluded. Therefore, the NOEC for long-term toxicity to *Daphnia* is 7.9 µg/L.

Concerning the comment on the 14-day prolonged acute fish study with a NOEC of 4.4 µg/L, the 93-day ELS study and a calculation of critical body burden (CBB) based on Mackay et al. (2015): The LOEC for the effect in the prolonged toxicity study was 6.9 µg/L. The highest test concentration in the FELS test was 4.4 µg/L. Using the equation from EU TGD calculating baseline toxicity the result fits very well to the result in the prolonged acute toxicity study (calculated 96h-LC_{50}= 0.122 µmol; the 14d-LOEC of 6.9 µg/L corresponds to 0.023 µmol). Additionally, the critical body burden (CBB) of 3 mmol/kg cited from Mackay et al. (2015) by Mihaich-CCB D4-4-7-2017.pdf is the critical body residue where 50 % mortality occure to the test organisms after an exposure time of 96 hours (96h-LC_{50}) (= CBR_{50}) (see Mackay et al. 2015, page 11916). The effect concentration of 6.9 µg/L in the prolonged acute fish toxicity test is a LOEC and 4.4 µg/L the corresponding NOEC. It is therefore not astonishing that there are differences in the calculation by Mihaich and the results in the experiment, as Mihaich refers to the LC_{50} and the result of the experimental study is a NOEC. Bearing in mind, that the calculated CBR_{50} (Mackay et al. 2015) is an estimation for a 5 g fish and the fish in Sousa et al. (1995) have a mean wet weight of 0.42 g. For a neutral narcotis it is not expected that the effect in a FELS test would be seen at considerably lower concentrations than in the prolonged acute toxicity test. These facts together reveal that the calculation by Mackay et al.

(2015) fits very well to the results of the prolonged acute fish toxicity study (Sousa et al. 1995) and the results of the FELS test (Sousa et al. 1995).

It is stated in the comment that due to the test medium preparation was done at approximately 21 °C and the test at 12 °C, it is possible that this decrease in temperature resulted in a super-saturated solution. This is a conjecture. During the analytical confirmation of the test concentration in the test nothing was conspicuous.

Therefore, in our opinion the 21d-$NOEC_{Daphnia,survival}$ of 7.9 µg/L (measured) and also the 14d-$NOEC_{fish}$ of 4.4 µ/L (measured) should be used for classification of D4.

RAC's response

RAC agrees with the Dossier Submitter response.

Date	Country	Organisation	Type of Organisation	Comment number
07.04.2017	Germany	Wacker Chemie AG	Company-Manufacturer	3

Comment received

Wacker Chemie AG disagrees with the proposed classification of octamethylcyclotetrasiloxane (D4) (CAS RN: 556-67-2) to modify the current entry in Annex VI of CLP regulation as follows: Aquatic Chronic 4, to Aquatic Chronic 1, M-factor=10.

ECHA note – An attachment was submitted with the comment above. Refer to public attachment Wacker Comments on D4 CLH dossier.zip

Dossier Submitter's Response

Please consider the response to comment number 8.

RAC's response

Please consider the response to comment number 8.

Date	Country	Organisation	Type of Organisation	Comment number
07.04.2017	Canada		Individual	4

Comment received

Please see the attached document which is formatted in a way that cannot be replicated here.

ECHA note – An attachment was submitted with the comment above. Refer to public attachment Comments from Solomon and Bridges on the classification of D4.docx

Dossier Submitter's Response

1.i) It is stated that the test interpretation using standard test-water solubility is challenging and that the degradability values are likely to be incorrect.
Response: We agree that the test concentration was well above the water solubility, but a sediment simulation study supports the conclusion that the substance is not rapidly biodegradable. Based on i.a. this study the substance was also identified as a vP substance according to REACH.

1.ii) It is stated that the tests for ecotoxicity are not realistic as they used sealed exposure systems. Response: It is recommended by the CLP guidance (version 4.1 p.588ff), the respective OECD test guidelines and OECD guidance no. 23 (p. 26ff) to minimise losses from test systems. The modifications to minimise the losses e.g. of

volatile substances from test media are described amongst others in the cited guidance documents.

1.iii) It is commented that the test used for classification were carried out under unrealistic conditions and the findings are thus incorrect. Response: As stated in the CLP guidance the tests should examine the intrinsic ecotoxicological properties of the test substance. The majority of tests used for classification of D4 were ranked with a relative score of zero because the result of the test is compared with measured concentrations in the environment and these results are higher than the concentrations found in the environment (Bridges and Solomon 2016 Table 7 and Figure 17). As this is not a risk assessment but a classification dossier this procedure is not expedient.

1. iv) Filed studies to assess bioaccumulative properties
Response: According to CLP regulation the potential for bioaccumulation shall normally be determined by using BCF or if not available by log Kow. The data which was used for classification and labelling, was also used and accepted for other regulations of the substance e.g. for identifying the substance as a vPvB-substance according to REACH. The data was not determined as inappropriate by the experts of the MSC.

RAC's response

i) RAC agrees that test concentration in the ready biodegradation study was well above the water solubility of D4. However, the OECD 310 is applicable also to insoluble test substances, though good dispersion of the substance should be ensured. This information is not, however available.

ii) RAC agrees with the Dossier Submitter

iii) RAC agrees with the Dossier Submitter

iv) RAC agree with the Dossier Submitter

Date	Country	Organisation	Type of Organisation	Comment number
07.04.2017	Belgium	Reconsile Reach Consortium	Industry or trade association	5

Comment received

Please find Reconsile comments in the attached XL commenting sheet and supporting papers.

ECHA note – An attachment was submitted with the comment above. Refer to public attachment Reconsile comments on D4 CLH proposal - 7Apr2017.zip

Dossier Submitter's Response

1: It is commented that the tests used for the assessment of the ecotoxicity properties of D4 excluded the intrinsic property of D4 – the volatility. Response: Please see also the response to comment number 4. It is recommended by the CLP guidance (version 4.1 p. 588ff), the respective OECD test guidelines and OECD guidance no. 23 (p. 26ff) to minimise losses from test systems due to intrinsic properties of the tested substance like volatility.

2+10: The comparison of measured concentrations in the environment with effect concentrations in the tests is used for risk assessment but not for classification purposes.

3: Thank you for the information.

4: Based on Annex II.1 (version 4.1, p.562) of the guidance on the application of the CLP criteria, the degree of degradation depends not only on the intrinsic degradability, but also on the environmental conditions. As indicated in Table 7 of the CLH report, the hydrolysis of D4 shows strong pH and temperature dependence. The average surface water temperature of 12°C is a more realistic environmental condition in Europe than 25°C.
We agree, that beside the relevant temperature also the relevant pH-value should be considered. As Reconsile mentioned the relevant pH for European surface water bodies range from 7.0 to 8.5. At this pH range the hydrolysis half-life of D4 decrease with increasing pH value. The half-life results in ≤16.7 days for pH 7 - 8.5 at 12°C. Hence, D4 should be considered as not rapidly degradable at relevant pH-values and relevant temperature of European surface water.

6 and 7: The same results can be found in the classification dossier.

8+11: It is correct that according to ECHA Guidance R.7b and also the CLP guidance the growth rate instead of biomass should be used for the derivation of the EC_{50} and NOEC. In the endpoint study record (ECHA, 2016), only the mean cell densities after 96 hours (cell/mL) but not the cell counts per replicate were reported. Therefore a recalculation of the growth rate based EC_{50} and NOEC was not possible.

9: It was commented that the ELS fish toxicity test showed no effects up to the highest concentration tested. The 14-day prolonged fish toxicity test (OECD 204) showed effects. The calculated critical body burden (CBB) was used to argue that the effect in the prolonged acute toxicity study is "anomalous with regard to the observed toxicity vs. the time…".
Response: The highest test concentration in the FELS test was 4.4 µg/L. At this concentration no effects occurred in the FELS test and neither in the prolonged toxicity test on fish. In the next higher test concentration (6.9 µg/L) 20 %, at 12 µg/L 75 % and at 22 µg/L 80 % of the organisms died at day 14. According to EU TGD, the QSAR baseline 96h-LC_{50} for D4 calculated with the LogKow of 6.49 is 0.122 µmol. The 14d-LOEC of 6.9 (from the prolonged fish toxicity test) corresponds to 0.023 µmol. As this is a LOEC and also after a longer exposure, the calculation fits well to the result obtained from the prolonged fish toxicity test. The CLP guidance and the ECHA guidance R.7b state that the OECD 204 is not considered suitable as a long-term toxicity test as only adults are exposed and maybe sensitive life stages are missed. But the OECD 204 test with D4 showed effects. These effects also fit to the cited calculations from Mackay et al. (2015). The critical body burden (CBB) of 3 mmol/kg cited from Mackay et al. (2015) by "Reconsile comments" and "Further considerations re CBB" is the critical body residue where 50 % mortality occure to the test organisms after an exposure time of 96 hours (96h-LC_{50}) (= CBR_{50}) (see Mackay et al. 2015, page 11916). The effect concentration of 6.9 µg/L in the prolonged acute fish toxicity test is a LOEC and 4.4 µg/L the corresponding NOEC. (The effects on mortality observed in the prolonged acute fish toxicity test are: 20 % at 6.9 µg/L, 75 % at 12 µg/L and 80 % at 22 µg/L.) It is therefore not astonishing that there are differences in the calculation by Reconsile and the results in the experiment, as Reconsile (the CBB of 3 mmol/kg) refers to the LC_{50} and the result of the experimental study is a NOEC. Bearing in mind, that the calculated CBR_{50} (Mackay et al. 2015) is an estimation for a 5-g fish (see Figure 2 of Mackay et al. 2015) and the fish in Sousa et al. (1995) have a mean wet weight of 0.42 g. For a neutral narcotis it is not expected that the effect in a FELS test would be seen at considerably lower concentrations than in the prolonged acute toxicity test. These facts together reveal that the calculation by Mackay et al. (2015) fits very well to the results of the prolonged acute

fish toxicity study (Sousa et al. 1995) and the results of the FELS test (Sousa et al. 1995).

10: addresses the long-term toxicity test on *Daphnia* and the closed system as well as the effect on adult survival.
Response: For the closed system please see response to point 1 of this comment. For the effects in the long-term toxicity test please see response to comment number 2: For the comment on the relevance of the effect on survival of adult daphnia in the *Daphnia* reproduction test: In OECD guidance 211, the survival of adults is also an endpoint to be documented as well as reproduction. In the guidance it is stated that "…if parental mortality occurs in exposed replicates, it should be considered whether or not the mortality follows a concentration-response pattern…". As the mortality occurred at the highest test concentration this could not be excluded. Therefore, the NOEC for long-term-toxicity to *Daphnia* is 7.9 µg/L.

12: Comparing the test results with the criteria for long-term aquatic hazards, the Reconsile Reach Consortium concludes the classification should be "Aquatic Chronic 2". As answered in the previous comments we do not concord.

RAC's response

1. RAC agrees with the Dossier Submitter.
2. + 10. RAC agrees with the Dossier Submitter.
3. Noted.
4. RAC agrees with the Dossier Submitter and in addition notes that at pH 6.99 and 9.5 °C the half-life was 542 hours (~ 23 days).
5. Noted.
6. Noted.
7. Noted.
8. RAC agrees with the DS and welcomes the new calculation.
9. RAC agrees with the DS.
10. RAC agrees with the DS.
12. RAC is of the opinion that the information available the classification of D4 should be "Aquatic Chronic 1".

Date	Country	Organisation	Type of Organisation	Comment number
16.03.2017	France		MemberState	6

Comment received

France supports the proposal to modify classification of Octamethylcyclotetrasiloxane (D4) (n° CAS: 556-67-2) of the current entry in Annex VI of CLP regulation: Aquatic Chronic 4, to Aquatic Chronic 1, M-factor=10.

Dossier Submitter's Response

Thank you for your support.

RAC's response

Noted.

OTHER HAZARDS AND ENDPOINTS – Hazardous to the Aquatic Environment

Date	Country	Organisation	Type of Organisation	Comment number
07.04.2017	United States		Individual	7

Comment received

Table 12, page 14, proposes hazard classification 1. However, the 21-day Daphnia magna reproduction study resulted in a NOEC for reproduction of > or equal to 15 µg/L, a concentration above the hazard classification 1 criteria. In addition, modeling of the pharmacokinetic behavior of D4 has shown that the empirically-observed top dose of 4.4 µg/L, the NOEC in the D4 93-day trout ELS study, could conceivably have been as high as 12 µg/L without adverse impact. The mortality observed in the prolonged acute study is inconsistent with a narcotic mode of action and the pharmacokinetic behavior of D4. In addition, information in the literature on possible environmental exposures suggests that D4 would not achieve a concentration in surface water that would cause toxicity to aquatic organisms. Thus, a hazard classification of 1 is inappropriate given the available data. The figure and table detailing this information are in the attached document.

ECHA note – An attachment was submitted with the comment above. Refer to public attachment Mihaich-CCB D4-4-7-2017.pdf

Dossier Submitter's Response

For the comment on the relevance of the effect on survival of adult daphnia in the *Daphnia* reproduction test: In OECD guidance 211, the survival of adults is also an endpoint to be documented as well as reproduction. In the guidance it is stated that "…if parental mortality occurs in exposed replicates, it should be considered whether or not the mortality follows a concentration-response pattern…". As the mortality occurred at the highest test concentration this could not be excluded. Therefore, the NOEC for long-term toxicity to *Daphnia* is 7.9 µg/L.
Concerning the comment on the 14-day prolonged acute fish study with a NOEC of 4.4 µg/L, the 93-day ELS study and a calculation based on Mackay et al. (2015): The LOEC for the effect in the prolonged toxicity study was 6.9 µg/L. The highest test concentration in the FELS test was 4.4 µg/L. Using the equation from EU TGD calculating baseline toxicity the result fits very well to the result in the prolonged acute toxicity study (calculated 96h-LC_{50}= 0.122 µmol; the 14d-LOEC of 6.9 µg/L corresponds to 0.023 µmol). See also responses to comments number 2 and 5.
The comparison of measured concentrations in the environment with effect concentrations in the tests is used for risk assessment but not classification purposes.

RAC's response

RAC agrees with the Dossier Submitter.

Date	Country	Organisation	Type of Organisation	Comment number
07.04.2017	Germany	Wacker Chemie AG	Company-Manufacturer	8

Comment received

Comments on 11.1.3 Hydrolysis

In the interpretation of the hydrolysis data for D4 risk assessment arguments have been applied in the hazard identification process. By doing so, the separation between hazard and risk was lifted only for cases where these risk assessment arguments are supportive for a stricter classification of D4. We argue that this approach is not appropriate. Either hazard identification must be performed based on CLP guidance or risk assessment arguments must be accepted for other relevant aspects as well (e.g. pH; monitoring data).

In the first case a temperature correction on the existing OECD 111 data for D4 is not appropriate. Otherwise, representative pH data for surface water bodies in the EU and monitoring data have to be considered as well. By applying the mean temperature of European surface waters of 12°C and the respective median pH value of 7.94 the hydrolysis half-life of D4 is far below 16 days, indicating that D4 clearly meets the criterion for rapid degradability.

In the attached document named "Wacker Comments on 11.1.3 Hydrolysis.docx" (contained in "Wacker Comments on D4 CLH dossier.zip") we provide evidence that authorities do not only use hazard but also risk-based arguments for hazard classification. We therefore argue that, in this context, the average pH value of European surface water bodies should be considered in the same manner. In the document, the dependence of the half-life in water versus the pH of the water body for D4 is presented.
It is further emphasized that monitoring data on effluents from waste water treatment plants reveal that water concentrations of D4 are orders of magnitude below the NOECs in aquatic organism tests.

Comments on 11.5.3 Acute (short-term) toxicity to algae or other aquatic plants

Evaluation of the algae study was based on yield/biomass only. As raw data have been reported in the study report, a re-analysis as recommended in the Guidance on IR & CSA R.7b has been conducted revealing an inhibition of the average specific growth rate in the treatment group by 6.8% and 6.4% after 72 h and 96 h, respectively, when compared to the control. Therefore, the ErC10 > 22 µg/L, which is the maximum water solubility level in the test medium.

In the attached document named "Wacker Comments on 11.5.3 Algae.docx" (contained in "Wacker Comments on D4 CLH dossier.zip") we provide arguments why average specific growth rate is preferred compared to biomass/yield. The embedded Excel sheet contains the full re-analysis of the raw data.

Comments on 11.6.1 Chronic toxicity to fish

Based on a personal communication with the study director of the 14-d prolonged acute toxicity study with Oncorhynchus mykiss, the stock solution was prepared at room temperature (approx. 20°C). However, the test solution temperature was 12°C. The effect of cooling down the test media to 12°C on D4 water solubility, however, was not investigated or considered in the study design. Consequently, it is possible that by the applied media preparation scheme a super-saturated solution was active during the study leading to mortality not relevant for C&L purposes. This observation is supported by calculations showing that a critical body burden for a narcosis mode of action cannot be achieved within the exposure periods used for all fish studies performed with D4.

In the attached document named "Wacker Comment on 11.6.1 Chronic toxicity to fish.docx" (contained in "Wacker Comments on D4 CLH dossier.zip") we provide the supporting calculations.

ECHA note – An attachment was submitted with the comment above. Refer to public attachment Wacker Comments on D4 CLH dossier.zip

Dossier Submitter's Response

Comments on 11.1.3 Hydrolysis

Response: Based on Annex II.1 of the guidance on the application of the CLP criteria (version 4.1, p. 562), the degree of degradation depends not only on the intrinsic degradability, but also on the environmental conditions. As indicated in Table 7 of the CLH report, the hydrolysis of D4 shows strong pH and temperature dependence. We agree, that beside the relevant temperature also the relevant pH-value should be considered.

Temperature correction:
12 °C is the mean temperature of surface water in Europe. Because of the strong pH and temperature dependence of the hydrolysis of D4, this environmentally relevant temperature should be used for the assessment of the classification and labelling of this substance.

Organic matter in natural waters:
As stated in the introduction of Annex II.1 (version 4.1, p.562), environmental conditions should be considered. This includes also the occurrence and concentration of other substrates. As Wacker commented, the sorption in natural waters in not part of the OECD 111 guideline. Therefore, it was only pointed out in the CLH report that the high adsorption potential of the substance (log Koc = 4.22) prevents the hydrolytic degradation in natural waters and was not included in the determination of the half-life.

Consideration of the pH range of surface water bodies in the EU:
We agree, that the relevant pH-value of surface water bodies in Europe should be used. Wacker commented that Bundschuh et al. (2016) identified the median pH-value for surface water bodies in Europe to be 7.94.
Bundschuh et al. evaluated water monitoring data from the European Environment Agency and peer-reviewed scientific literature to determine the pH range of surface water bodies in Europe. 2648 locations in European rivers and 427 locations in European lakes were derived. It should be remarked that the data set may have only a limited relevance for Scandinavia as only low number from Scandinavian sites were included in the evaluation. The authors identified a mean pH range of all European surface water bodies from 4.0 to 10.1, while the median was 7.9. 95 % of all mean values were between 7.0 and 8.5 (for rivers: 7.0-8.4, for lakes: 6.7-9.2). It was mentioned that the pH value can vary over the course of one day up to 1.2 pH units. The authors concluded that the narrow pH range from 7.0 to 8.5 may be suggested as representative for Europe. As at this pH range the hydrolysis half-life of D4 decrease with increasing pH value, the half-life results in ≤16.7 days for pH 7 - 8.5 at 12 °C. Hence, D4 should be considered as not rapidly degradable at relevant pH-values and relevant temperature of European surface water.

Consideration of monitoring data:
The guidance on the application of the CLP criteria allows the use of monitoring data only in the context of rapid degradation (removal of a substance from the aquatic environment, Annex II 2.3.3). In the context of aquatic toxicity the comparison of measured concentrations in the environment with effect concentrations in the tests is used for risk assessment but not classification purposes.

Comments on 11.5.3 Acute (short-term) toxicity to algae or other aquatic plants
Response: It is correct that according to ECHA Guidance R.7b and also the CLP guidance the growth rate instead of biomass should be used for the derivation of the EC_{50} and NOEC. In the endpoint study record (ECHA, 2016), only mean cell densities after 96 hours (cell/mL) but not the cell counts per replicate were reported. Therefore a recalculation of the growth rate based EC_{50} and NOEC was not possible.

Comments on 11.6.1 Chronic toxicity to fish
Response: It is stated in the comment that as the test medium preparation was done at approximately 21 °C and the test at 12 °C it is possible that this decrease in temperature resulted in a super-saturated solution. This is a conjecture. During the analytical confirmation of the test concentration in the test nothing was conspicuous. Concerning the prolonged acute fish toxicity test: At a test concentration of 6.9 µg/L 20 % of the fish died at day 14. According to EU TGD, the QSAR baseline 96h-LC_{50} for D4 calculated with the LogKow of 6.49 is 0.122 µmol. The 14d-LOEC of 6.9 (from the prolonged fish toxicity test) corresponds to 0.023 µmol. As this is a LOEC and also after a longer exposure, the calculation fits well to the result obtained from the prolonged fish toxicity test. The CLP guidance and the ECHA guidance R.7b states that the OECD 204 is not considered suitable as a long-term toxicity test as only adults are exposed and maybe sensitive life stages are missed. But the OECD 204 test with D4 showed effects. These effects also fit to the cited calculations from Mackay et al. (2015). The critical body burden (CBB) of 3 mmol/kg cited from Mackay et al. (2015) by Wacker is the critical body residue where 50 % mortality occure to the test organisms after an exposure time of 96 hours (96h-LC_{50}) (= CBR_{50}) (see Mackay et al. 2015, page 11916). The effect concentration of 6.9 µg/L in the prolonged acute fish toxicity test is a LOEC and 4.4 µg/L the corresponding NOEC. (The effects on mortality observed in the prolonged acute fish toxicity test are: 20 % at 6.9 µg/L, 75 % at 12 µg/L and 80 % at 22 µg/L.) It is therefore not astonishing that there are differences in the calculation by Wacker and the results in the experiment, as Wacker (the CBB of 3 mmol/kg) refers to the LC_{50} and the result of the experimental study is a NOEC. Bearing in mind, that the calculated CBR_{50} (Mackay et al. 2015) is a estimation for a 5-g fish (see Figure 2 of Mackay et al. 2015) and the fish in Sousa et al. (1995) have a mean wet weight of 0.42 g. For a neutral narcotis it is not expected that the effect in a FELS test would be seen at considerably lower concentrations than in the prolonged acute toxicity test. These facts together reveal that the calculation by Mackay et al. (2015) fits very well to the results of the prolonged acute fish toxicity study (Sousa et al. 1995) and the results of the FELS test (Sousa et al. 1995).

RAC's response

Temperature correction: RAC agrees with the Dossier Submitter.
Organic matter in natural waters: RAC agrees with the Dossier Submitter.
Consideration of the pH range of surface water bodies in the EU: RAC agrees with the Dossier Submitter and wants to point out that at pH 7 and 12°C the hydrolysis half-life for D4 is 16.7 days.
Consideration of monitoring data: RAC agrees with the Dossier Submitter.
Comments on 11.5.3 Acute (short-term) toxicity to algae or other aquatic plants: RAC agrees with the DS and welcomes the new calculation.
Comments on 11.6.1 Chronic toxicity to fish: RAC agrees with the Dossier Submitter.

Date	Country	Organisation	Type of Organisation	Comment number
07.04.2017	Canada		Individual	9

Comment received

We believe that the weight of evidence assessment of the physical, biological, and environmental data for D4 do not support its classification as acute and chronic toxicity category-1 under Regulation (EC) No 1272/2008

ECHA note – An attachment was submitted with the comment above. Refer to public attachment Comments from Solomon and Bridges on the classification of D4.docx

Dossier Submitter's Response
Please consider the response to comment number 4.
RAC's response
Please consider the response to comment number 4.

Date	Country	Organisation	Type of Organisation	Comment number
07.04.2017	Belgium	Reconsile Reach Consortium	Industry or trade association	10
Comment received				
Please find Reconsile comments in the attached XL commenting sheet and supporting papers. ECHA note – An attachment was submitted with the comment above. Refer to public attachment Reconsile comments on D4 CLH proposal - 7Apr2017.zip				
Dossier Submitter's Response				
Please consider the response to comment number 5.				
RAC's response				
Please consider the response to comment number 5.				

Date	Country	Organisation	Type of Organisation	Comment number
07.04.2017	Finland		MemberState	11
Comment received				
FI CA supports the proposal to modify the current harmonised classification of Aquatic Chronic 4 to Aquatic Chronic 1 with the M-factor of 10 for Octamethylcyclotetrasiloxane; D4.				
Dossier Submitter's Response				
Thank you for your support.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
07.04.2017	Belgium	CES-Silicones Europe	Industry or trade association	12
Comment received				
Public attachment has been uploaded. If internet/upload problems occur please email <confidential> ECHA note – An attachment was submitted with the comment above. Refer to public attachment CES Comments for D4 Classification.zip				
Dossier Submitter's Response				
Comments on Toxicity: The GHS Guidance states also that "[A9.3.5.1] Valid aquatic toxicity tests require the dissolution of the test substance in the water media under the test conditions recommended by the guideline. In addition, a bioavailable exposure concentration should be maintained for the duration of the test. Some substances are difficult to test in aquatic systems and guidance has been developed to assist in testing these materials (DoE 1996; ECETOC 1996; and US EPA 1996). The OECD Guidance document on aquatic toxicity				

testing of difficult substances and mixtures (OECD, 2000) is a good source of information on the types of substances that are difficult to test and the steps needed to ensure valid conclusions from tests with these materials." Similar in the CLP Guidance section 4.1.3.2.2.c volatile substances it is highlighted that "such substances that can clearly present testing problems when used in open systems should be evaluated to ensure adequate maintenance of exposure concentrations." In section 4.1.3.2.4.1 the use of weight of evidence is described and the cited sentence in the comment number 12 "There may be circumstances where the lowest toxicity value among taxa is not used for C&L where a WoE approach is used." is followed by the clarification "This will usually only arise where it is possible to define the sensitivity distribution with more accuracy than would normally be possible, such as when large datasets are available. Such large datasets should be evaluated with due caution." Therefore, the use of closed systems with zero head-space to minimise volatilisation and loss of D4 from aqueous solution is in accordance with OECD and CLP guidance.
For the comment on the relevance of the effect on survival of adult daphnia in the *Daphnia* reproduction test: In OECD guidance 211, the survival of adults is also an endpoint to be documented as well as reproduction. In the guidance it is stated that "…if parental mortality occurs in exposed replicates, it should be considered whether or not the mortality follows a concentration-response pattern…". As the mortality occurred at the highest test concentration this could not be excluded. Therefore, the NOEC for long-toxicity to *Daphnia* is 7.9 µg/L.
Concerning the maximum achievable solubility in the test media: It is correct and happens more often that substances with a low water solubility show a different solubility in the test media than in the water solubility test.
The comparison of measured concentrations in the environment with effect concentrations in the tests is used for risk assessment but not classification purposes.
Concerning the comment on the 14-day prolonged acute fish study with a NOEC of 4.4 µg/L, the 93-day ELS study and a calculation based on Mackay et al. (2015): The LOEC for the effect in the prolonged toxicity study was 6.9 µg/L. The highest test concentration in the FELS test was 4.4 µg/L. Using the equation from EU TGD calculating baseline toxicity the result fits very well to the result in the prolonged acute toxicity study (calculated 96h-LC_{50}= 0.122 µmol; the 14d-LOEC of 6.9 µg/L corresponds to 0.023 µmol). These effects also fit to the cited calculations from Mackay et al. (2015). The critical body burden (CBB) of 3 mmol/kg cited from Mackay et al. (2015) by CES is the critical body residue where 50 % mortality occure to the test organisms after an exposure time of 96 hours (96h-LC_{50}) (= CBR_{50}) (see Mackay et al. 2015, page 11916). The effect concentration of 6.9 µg/L in the prolonged acute fish toxicity test is a LOEC and 4.4 µg/L the corresponding NOEC. (The effects on mortality observed in the prolonged acute fish toxicity test are: 20 % at 6.9 µg/L, 75 % at 12 µg/L and 80 % at 22 µg/L.) It is therefore not astonishing that there are differences in the calculation by CES and the results in the experiment, as CES (the CBB of 3 mmol/kg) refers to the LC_{50} and the result of the experimental study is a NOEC. Bearing in mind, that the calculated CBR_{50} (Mackay et al. 2015) is a estimation for a 5-g fish (see Figure 2 of Mackay et al. 2015) and the fish in Sousa et al. (1995) have a mean wet weight of 0.42 g. For a neutral narcotis it is not expected that the effect in a FELS test would be seen at considerably lower concentrations than in the prolonged acute toxicity test. These facts together reveal that the calculation by Mackay et al. (2015) fits very well to the results of the prolonged acute fish toxicity study (Sousa et al. 1995) and the results of the FELS test (Sousa et al. 1995).
Concerning the algae test, it is correct that according to ECHA Guidance R.7b and also the CLP guidance the growth rate instead of biomass should be used for the derivation of the EC_{50} and NOEC. In the endpoint study record (ECHA, 2016), only mean cell densities after

96 hours (cell/mL) but not the cell counts per replicate were reported. Therefore a recalculation of the growth rate based EC_{50} and NOEC was not possible.

Comments on rapid degradability:
Based on Annex II.1 of the guidance on the application of the CLP criteria (version 4.1, p.562), the degree of degradation depends not only on the intrinsic degradability, but also on the environmental conditions. As indicated in Table 7 of the CLH report, the hydrolysis of D4 shows strong pH and temperature dependence. The average surface water temperature of 12 °C is a more realistic environmental condition in Europe than 25 °C.
Beside the relevant temperature also the relevant pH-value should be considered. The relevant pH range of European surface water range from 7.0 to 8.5 (for more details see response to comment number 8). At this pH range the hydrolysis half-life of D4 decrease with increasing pH value. The half-life results in ≤16.7 days for pH 7 - 8.5 at 12 °C. Hence, D4 should be considered as not rapidly degradable at relevant pH-values and relevant temperature of European surface water.

RAC's response

Comments on Toxicity: RAC agrees with the Dossier Submitter.
Comments on rapid degradability: RAC agrees with the Dossier Submitter.

Date	Country	Organisation	Type of Organisation	Comment number
16.03.2017	France		MemberState	13

Comment received

France supports the proposal to modify classification of D4 of the current entry in Annex VI of CLP regulation: Aquatic Chronic 4, H413 to Aquatic Chronic 1, H410.

According to data, D4 is not ready biodegradable, it meets the criteria for bioaccumulation and based on the long term test with Daphnia magna (21d-NOEC = 0.0079 mg/L), D4 fulfills the classification criteria for Aquatic chronic 1 (NOEC ≤ 0.1mg/L). Furthermore, France supports the M-factor of 10 presented in the proposition.

Dossier Submitter's Response

Thank you for your support.

RAC's response

Noted.

Date	Country	Organisation	Type of Organisation	Comment number
06.04.2017	Belgium		MemberState	14

Comment received

BE CA agrees with the conclusion that D4 is not rapid degradable and meets the CLP criteria for bioaccumulation (BCF = 14900L/kg>>500).

We agree with the classification for chronic aquatic toxicity : Aquatic chronic 1, H410 with a chronic M-factor = 10.

However we are of the opinion that it is not demonstrated that D4 shows no acute toxicity up to the water solubility. Based on the 96hLC50 for the mysid Americamysis bahia >9.1 µg/L(>0.0091 mg/L) which is < the water solubility of 0.0562 mg/l.

Dossier Submitter's Response
Thank you for your support. As at 9.1 µg/L no effects occurred in the 96h-acute toxicity test with *Americamysis bahia* it is not possible and necessary to classify D4 as acute toxic, but it is correct that there is an uncertainty if effects would occur at concentrations between 9.1 µg/L and the maximal water solubility. As this maximum achievable water solubility is often much lower in test medium than in distilled water, this would be lower than 56.2 µg/L. This was also seen in the other ecotoxicological tests, e.g. with *Daphnia magna* it was 15 µg/L.
RAC's response
Noted. RAC agrees with the Dossier Submitter.

Date	Country	Organisation	Type of Organisation	Comment number
04.04.2017	United Kingdom		Individual	15
Comment received				
I am making this contribution to the consultation process as an independent scientific consultant. As is well known, I have for some years worked with the silane and siloxanes producers and its submissions under REACH. However, I also provide consultancy to regulatory agencies and my company is part of a team approved to work for ECHA. Therefore within the necessary bounds of scientific objectivity, I offer a very few comments about the aquatic ecotoxicology of octamethylcyclotetrasiloxane, known as D4. I have access to the original study reports referred to in the REACH dossier. D4 is a substance of very low solubility in water (around 52 micrograms per litre), and its solubility in test media is likely to be lower than its solubility in pure water, due to the quantity of dissolved salts. The study reports for the most reliable long term studies show that the stock test media were prepared at ambient temperatures. The stock concentration, whether prepared by slow stirring or via solvent addition methods, was typically at saturation around 25 micrograms per litre. The lower solubility is consistent with laboratory-based experience with poorly-soluble substances. The slow-stir method to produce solutions used a very high excess of substance (far above the level used in the standard water solubility method) and the possibility for particulates to 'break off' and be present in the media cannot be excluded. The use of solvent addition can also produce over-saturation in the vicinity of the added concentrate. The stock was then taken to a test system operating at the lower temperature of around 12 degrees C, and used in flow through systems with dilution. It can be anticipated that the solubility of D4 is significantly lower at 12 degrees than it was under ambient conditions. However, there is no information on that. Therefore it is possible that the aqueous media had (before dilution) an amount of substance present that exceeded the saturated solubility at the test temperature. Several points need to be made concerning this test system: • Any undissolved D4 would not have been visible • The speed of change from dissolved to partially undissolved is not known; organisms could provide a substrate for the excess to adhere to. However, whatever the mechanism, given the high lipophilicity of D4 it can be anticipated that the excess could coat the test organisms with a layer of D4.				

• The analytical methods used would have analysed all the D4 present, whether dissolved or undissolved. The basic thorough work in the key studies is not questioned; indeed it is the complete reporting that allows concerns to be delineated carefully. However, the efforts to achieve saturation under ambient conditions could have produced a supersaturated system under the test conditions. My recommendation would be that the solubility at 12 degrees C in the test water could be investigated, to help interpret the studies. That should be done with a minimal excess of substance, in line with the standard OECD water solubility method for mobile liquids. I consider it necessary to base a significant classification decision on clear sound data, and that there are some doubts over the key studies.
Dossier Submitter's Response
The test media were prepared according to OECD guidance and the test concentrations were analytically confirmed. In the test protocol there is no hint on undissolved material but it would be possible that these were as little as it could not be observed. The measured concentration was lower than the maximum water solubility in the standard OECD test. But this is not unusual. Taking the results from the tests and also the measured concentrations together, the tests are conclusive.
RAC's response
RAC agrees with the Dossier Submitter.

OTHER HAZARDS AND ENDPOINTS – Hazardous to the Ozone Layer

Date	Country	Organisation	Type of Organisation	Comment number
07.04.2017	Canada		Individual	16
Comment received				
NA ECHA note – An attachment was submitted with the comment above. Refer to public attachment Comments from Solomon and Bridges on the classification of D4.docx				
Dossier Submitter's Response				
This endpoint was not subject of the CLH dossier. For response of the comments in the attachment please consider response to comment number 4.				
RAC's response				

PUBLIC ATTACHMENTS
1. Mihaich-CCB D4-4-7-2017.pdf [Please refer to comment No. 2, 7]
2. Wacker Comments on D4 CLH dossier.zip [Please refer to comment No. 3, 8]
3. Comments from Solomon and Bridges on the classification of D4.docx [Please refer to comment No. 4, 9, 16]
4. Reconsile comments on D4 CLH proposal - 7Apr2017.zip [Please refer to comment No. 5, 10]
5. CES Comments for D4 Classification.zip [Please refer to comment No. 12]