COMPILED COMMENTS ON CLH CONSULTATION

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Substance name: 2,2',6,6'-tetra-tert-butyl-4,4'-methylenediphenol
CAS number: 118-82-1
EC number: 204-279-1
Dossier submitter: Austria

OTHER HAZARDS AND ENDPOINTS – Hazardous to the Aquatic Environment

Date	Country	Organisation	Type of Organisation	Comment number
24.07.2023	France		MemberState	1
Comment received				
- FR agrees that the substance should be considered as not rapidly biodegradable. - FR agrees that the substance has a potential for bioaccumulation based on the estimated log Kow value and the measured bioaccumulation test data. - In the description of the available aquatic toxicity tests, it is indicated in the fish short-term toxicity study (Anonymous, 1988) that undissolved test material was observed. Could you please indicate whether this information was available for the other studies? - Regarding acute toxicity, data was available for the 3 trophic levels. Nevertheless, most of the tests were performed with concentrations exceeding the water solubility of the substance (0.032 µg/L) resulting in difficulties in defining the L(E)C50. Moreover, no analytical verification of the test concentrations was performed in most of them. Only the tests on algae were conducted with concentrations below the water solubility of the substance and with analytical verification. As all available acute toxicity tests show no acute toxicity at levels in excess of the water solubility, FR agree with DS that the L(E)C50 for classification purposes may be considered to be greater than the measured water solubility. According to these results, FR agree that no classification for aquatic acute toxicity can be warranted. - Classification for long-term aquatic hazard is based on OECD TG 211 (Anonymous, 2012b). This study is rated as reliable with restrictions. Mortality in the negative control is higher than recommended by the OECD TG, probably due to a handling mistake. The amount of feeding exceeds the recommended amount probably in consideration of the number of daphnids per compartment (5/compartment). Nevertheless FR consider that the study should be used for classification purposes. - This key study shows no observed effect on reproduction. A statistically significant reduction on growth is observed, although it is not concentration-responsive and treatment related and is not supported by statistically significant difference observed for the weight. Nevertheless, the effects on growth and a dose-related discoloration of the daphnids are indicative of an adverse effect. Thus, as the substance is not rapidly degradable and based on the NOEC of 1.4 ng/L for body length according to OECD TG 211 on daphnids, FR agree with the DS' proposal of classification Aquatic Chronic 1 with a chronic M-factor of 10 000.				

- The first day of brood in the control groups and treatment groups was indicated to be on day 7, 8 or 9. More detailed information on this endpoint could be added, if available, to highlight a potential difference between control and treated groups. Additionally, it is not clear if statistics were applied for the data in table 20. The effects observed on the treated group at 2.4 ng/L raise concern and are consistent with the effect observed in growth reduction.

Date	Country	Organisation	Type of Organisation	Comment number
01.07.2023	Netherlands		MemberState	2

Comment received

We agree with the proposed classification as Aquatic chronic 1 with an M-factor of 10 000.

Considering the classification for aquatic acute toxicity, in the acute short-term toxicity test with Salmo gardneiri an LC50 of 820 mg/L was found for TBMD, which is far above the solubility of the test compound (0.032 µg/L). These test results are considered relevant by the dossier submitter as the study is given and scored Klimisch 2.
We question whether these test results are relevant. In the guidance on application of the CLP criteria, Annex section I.4.2. on poorly soluble substances it is stated that "excess undissolved substance may have given rise to physical effects on the test organisms" and "Where this is considered the likely cause of the effects observed, the test should be considered as invalid for classification purposes"'. We gently request the dossier submitter to elaborate why the derived LC50 is relevant for the expected effects of TBMD in the environment and for the classification of TBMD.

In case these test results are considered relevant, we disagree that an Acute Category 1 classification for TBMD is not warranted. In the introduction of the guidance on the application of the CLP criteria is stated that "It is usually assumed that toxic effects are only measured following exposure to the dissolved fraction" and in the Annex section I.4.2 it is stated that "where the acute toxicity is recorded at levels in excess of the water solubility, the L(E)C50 for classification purposes may be considered to be equal to or below the measured water solubility". A nominal LC50 of 820 mg/L indicates that the LC50 based on the dissolved fraction will be ≤ 0.032 µg/L and this value results in an Aquatic acute 1 classification with an M-factor of 10 000.

Date	Country	Organisation	Type of Organisation	Comment number
21.07.2023	United Kingdom	Health and Safety Executive	National Authority	3

Comment received

We are unclear on the application of the OECD TG 211 (Anon., 2012b) Daphnia magna 21-day NOEC(length) of 0.0000014 mg/L (mm) for hazard classification purposes in this instance for the following reasons:

- No significant effects were observed in acute toxicity studies with fish, Daphnia, algae up to the limit of solubility.
- No significant effects were observed in long-term toxicity tests with algae and available fish data (QSAR and surrogate approach) do not support chronic hazard classification.
- No statistically significant effects on mortality, reproduction or weight were observed in the TG 211 Daphnia study up to the highest treatment of 0.000043 mg/l (mm). In general,

mortality and reproduction are key endpoints for hazard classification based on potential biological relevance at a population level. In this instance, while small but statistically significant reductions in length were reported, it did not impact on reproductive success.
- One procedural control replicate included high mortality (>20% test guideline validity criterion) which was considered likely (although not confirmed) due to inadvertent mortality such as handling. This resulted in a reduced number of procedural control test organisms - 15 instead of 20. Given the procedural and solvent control were pooled, this is not considered to impact statistical power of the control. However, the solvent control (and consequently the combined pooled control) did not meet normal distribution criteria - it would be useful for the DS to provide individual organism measurements for controls (and treatments) to consider outliers and, if relevant, any influence they may have.
- The length measurements are extremely small for example there is only 0.23 mm difference in mean length measurements between the combined control and LOEC. Are there further details on the measurement analysis and error? Ideally this should report when the measurements were made, which part of the organism was measured (OECD TG refers to body length excluding the anal spine) and supporting information on measurement method precision and accuracy.
- A clear dose-response was not observed for length and all statistically significant differences are low with a maximum of 5.05% reduction observed at the LOEC. In addition, the % reduction decreases with increasing concentration and while a 2.63% reduction in length is considered statistically significant in the 0.000021 mg/L treatment, we are unclear how biologically relevant this is. Given ECx endpoints are generally considered preferable to NOECs for hazard classification, please can the DS confirm if such low observed effects mean it is not possible to derive a robust EC10(length) with confidence limits.
- All treatment length measurements are within the historical control range of 3.6-6.3 mm for this test, which demonstrates test organism variability for the length endpoint which is notably greater than the reported difference in this case.
- Some test organisms were observed to be 'pale'. While the DS notes 'discolouration seems to indicate an adverse effect on the organisms' the reason for the paleness and its population relevance are unclear and the registration notes that some stock solutions 'had a slight purple tint'. Is there additional information considering the paleness observation in relation to test organism immobility and/or length and any potential dose-response?

We are aware Daphnia growth endpoints were considered relevant in the hazard assessment of HBCDD but note the NOEC(length) and NOEC(reproduction) were similar at 3.1 and 5.6 ug/L respectively supporting population relevant effects within the same hazard classification range.

We note that OECD TG211 considers growth (length and weight) endpoints as additional information. It states that 'growth measurements are highly desirable since they provide information on possible sublethal effects which may be useful in addition to reproduction measures alone'. In addition, ECHA (2017) notes that 'Reproduction and lethality are the most sensitive endpoints' and that 'Typically the 21 day study may report ECx/NOEC values for survival or reproductive endpoints. The lowest value should be used for establishing ECx/NOEC for reproduction although in practice the two endpoints results tend to be close to each other'.

In this instance, where there is a large magnitude difference between the growth (length) endpoint and the clear population-relevant reproductive endpoint, we are therefore unclear if the conservative approach to apply the lowest NOEC is justified. Further information (noted above) on the above uncertainties would be useful to support application of the NOEC(length).

We note that the substance is poorly water soluble, not rapidly degradable and meets

hazard classification bioaccumulation criteria. On this basis, the hazard classification criteria for Aquatic Chronic 4 may be relevant if there is uncertainty regarding long-term effects.

ECHA (2017) Guidance on the application of the CLP criteria. Guidance to Regulation (EC) No 1272/2008 on classification, labelling and packaging (CLP) of substances and mixtures, version 5.0, ref: ECHA-17-G-21-EN. Available at https://www.echa.europa.eu/