Committee for Risk Assessment

RAC

Opinion

proposing harmonised classification and labelling
at EU level of

4,4’-isopropylidenediphenol; bisphenol A

EC Number: 201-245-8
CAS Number: 80-05-7

CLH-O-0000006910-75-01/F

Adopted

8 October 2020

8 October 2020

CLH-O-0000006910-75-01/F

OPINION OF THE COMMITTEE FOR RISK ASSESSMENT ON A DOSSIER PROPOSING HARMONISED CLASSIFICATION AND LABELLING AT EU LEVEL

In accordance with Article 37 (4) of Regulation (EC) No 1272/2008, the Classification, Labelling and Packaging (CLP) Regulation, the Committee for Risk Assessment (RAC) has adopted an opinion on the proposal for harmonised classification and labelling (CLH) of:

Chemical name: **4,4'-isopropylidenediphenol; bisphenol A**

EC Number: **201-245-8**

CAS Number: **80-05-7**

The proposal was submitted by **Germany** and received by RAC on **18 April 2019.**

In this opinion, all classification and labelling elements are given in accordance with the CLP Regulation.

PROCESS FOR ADOPTION OF THE OPINION

Germany has submitted a CLH dossier containing a proposal together with the justification and background information documented in a CLH report. The CLH report was made publicly available in accordance with the requirements of the CLP Regulation at ***http://echa.europa.eu/harmonised-classification-and-labelling-consultation/*** on **1 July 2019**. Concerned parties and Member State Competent Authorities (MSCA) were invited to submit comments and contributions by **30 August 2019**.

ADOPTION OF THE OPINION OF RAC

Rapporteur, appointed by RAC: **Anja Menard Srpčič**

Co-Rapporteur, appointed by RAC: **Irina Karadjova**

The opinion takes into account the comments provided by MSCAs and concerned parties in accordance with Article 37(4) of the CLP Regulation and the comments received are compiled in Annex 2.

The RAC opinion on the proposed harmonised classification and labelling was adopted on **8 October 2020** by **consensus**.

Classification and labelling in accordance with the CLP Regulation (Regulation (EC) 1272/2008)

	Index No	Chemical name	EC No	CAS No	Classification		Labelling			Specific Conc. Limits, M-factors and ATE	Notes
					Hazard Class and Category Code(s)	Hazard statement Code(s)	Pictogram, Signal Word Code(s)	Hazard statement Code(s)	Suppl. Hazard statement Code(s)		
Current Annex VI entry	604-030-00-0	4,4′-isopropylidenediphenol; bisphenol A	201-245-8	80-05-7	Repr. 1B STOT SE 3 Eye Dam. 1 Skin Sens. 1	H360F H335 H318 H317	GHS08 GHS05 GHS07 Dgr	H360F H335 H318 H317			
Dossier submitters proposal	604-030-00-0	4,4′-isopropylidenediphenol; bisphenol A	201-245-8	80-05-7	**Retain** Repr. 1B STOT SE 3 Eye Dam. 1 Skin Sens. 1 **Add** Aquatic Acute 1 Aquatic Chronic 1	**Retain** H360F H335 H318 H317 **Add** H400 H410	**Retain** GHS08 GHS05 GHS07 Dgr **Add** GHS09	**Retain** H360F H335 H318 H317 **Add** H410		**Add** M=1 M=10	
RAC opinion	604-030-00-0	4,4′-isopropylidenediphenol; bisphenol A	201-245-8	80-05-7	**Retain** Repr. 1B STOT SE 3 Eye Dam. 1 Skin Sens. 1 **Add** Aquatic Acute 1 Aquatic Chronic 1	**Retain** H360F H335 H318 H317 **Add** H400 H410	**Retain** GHS08 GHS05 GHS07 Dgr **Add** GHS09	**Retain** H360F H335 H318 H317 **Add** H410		**Add** M=1 M=10	
Resulting Annex VI entry if agreed by COM	604-030-00-0	4,4′-isopropylidenediphenol; bisphenol A	201-245-8	80-05-7	Repr. 1B STOT SE 3 Eye Dam. 1 Skin Sens. 1 Aquatic Acute 1 Aquatic Chronic 1	H360F H335 H318 H317 H400 H410	GHS08 GHS05 GHS07 GHS09 Dgr	H360F H335 H318 H317 H410		M=1 M=10	

GROUNDS FOR ADOPTION OF THE OPINION

ENVIRONMENTAL HAZARD EVALUATION

RAC evaluation of aquatic hazards (acute and chronic)

Summary of the Dossier Submitter's proposal

Bisphenol A was classified under the Dangerous Substance Directive (DSD, Directive 67/548/EEC) for environmental effects with R52 ('Harmful to aquatic organisms', 30th ATP to DSD; Commission Directive 2008/58/EC). Currently there is no harmonised classification under the CLP Regulation for environmental hazards.

The Dossier Submitter (DS) proposed to classify the substance as Aquatic Acute 1 - H400 (M=1) based on a 48-h mean measured EC_{50} value of 0.885 mg/L for the marine crustacean *Acartia clausi,* and as Aquatic Chronic 1 – H410 (M=10) based on rapid degradation and a 300-d mean measured LOEC value of 0.000372 mg/L for the fish *Danio rerio* supported by a 150-d LOEC value of 0.000106 mg/L (median-measured)/0.00025 mg/L (nominal) for the snail *Marisa cornuarietis*. The determination of No Observed Effect Concentrations (NOEC) in the snail study was not feasible, therefore the Lowest Observed Effect Concentrations (LOEC) were used as an alternative. There are also other studies in the CLP report available which provide toxicities within the same range.

Bisphenol A has gone also through an EU risk assessment (European Commission, 2010). It has also has been identified as a substance of very high concern based on its potential endocrine disrupting properties for both human health and environment (ECHA, 2017b). The proposed endocrine mode of action of the Bisphenol A requires additional consideration where the interpretation of the results obtained from the experimental studies in the CLH report is concerned.

Degradation

The physical and chemical properties of Bisphenol A suggest that hydrolysis under environmental relevant conditions is negligible.

Three OECD TG 301F tests (Manometric respirometry test) are available. In the first test using non-adapted inoculum from activated sludge from a municipal wastewater treatment plant, 78.2 to 81.0 % degradation based on O_2 consumption and 76.3 to 81.2 % degradation based on CO_2 production was indicated at day 28. In the second test using non-adapted inoculum derived from activated sludge from a municipal wastewater treatment plant, the O_2 consumption was found to be 85 to 93% after 28 days. A third test in which the activated sludge from a municipal wastewater treatment plant was used (adaptation not specified), reported 87.8±6.9 % O_2 consumption after 28 days. In all these tests, the 10-day window was fulfilled.

No degradation was observed in OECD TG 301D (Closed Bottle Test; 0 % O_2 consumption after 28 days), OECD TG 301B (Modified Sturm Test; 1-2 % CO_2 evolution after 28 days) and OECD TG 301C (0 % degradation after 14 days) tests. Bisphenol A was not inhibitory to micro-organisms under the test conditions in OECD TG 301D and OECD TG 301B tests.

All six studies are equivalent based on their reliability scoring (reliable with restriction; the deviations are mentioned in the CLH report). The DS also referred to additional studies on ECHA's dissemination page by the REACH Registrants but these studies were not used for classification

of the substance by DS due to a lack of information on experimental details. Based on the available results, the DS concluded that Bisphenol A is readily biodegradable.

The degradation of Bisphenol A was examined in surface water by Klečka *et al*. (2001). The water samples from seven different rivers across the United States and Europe were collected upstream and downstream from wastewater treatment plants known to treat wastewater containing Bisphenol A. Two different methods were conducted: River-die-away studies for ^{14}C- Bisphenol A (initial Bisphenol A concentrations 50-5500 µg/L) and respirometry studies (initial Bisphenol A concentration 5000 µg/L). Bisphenol A was not detected in the river samples prior to the addition of the test compound. Negligible losses of Bisphenol A were observed in autoclaved controls, indicating no abiotic degradation. There was no significant difference between the tests conducted with different river waters or river waters upstream or downstream from wastewater treatment plants. The results indicated rapid biodegradation of Bisphenol A after an initial lag phase.

In the ^{14}C river die-away studies lag periods of 2-8 days were observed and half-lives between 0.5 and 1.4 days were estimated. Degradation of ^{14}C- Bisphenol A resulted in mineralization with an average yield of 65-80 % $^{14}CO_2$ at the end of the test period (18 days). In the respirometry studies, after a lag period of 2.3-4.4 days, 59 - 96 % $ThCO_2$ was formed after 18 days. The estimated half-lives ranged from 0.5 to 2.6 days. In addition, the authors conducted studies with lower Bisphenol A concentrations (0.05 and 0.5 µg/L). Due to analytical limitations, only primary biodegradation was measured. After 28 days the Bisphenol A concentration was below 0.005 µg/L and the estimated half-lives ranged from 3 to 6 days.

Two studies on primary degradation of Bisphenol A are available. In the first study, the primary degradation of Bisphenol A in river water was studied (Kang and Kondo, 2002). Under aerobic conditions Bisphenol A was rapidly primarily degraded with half-lives of 2-3 days. After 10 days the concentration was below the LOD. In the second study performed by same authors (Kang and Kondo, 2005), the primary degradation in seawater and in river water at different temperatures (25 °C, and 35 °C and additional 4 °C for seawater) was investigated. In river water, half-lives were 4 and 3 days at 25 °C and 35 °C, respectively. In seawater, lag periods of 30 days (25 °C and 35 °C) and 40 days (4 °C), respectively, were observed. At the end of the experiment (60 days), the initial concentration decreased to ~200 µg/L at 25 °C/35 °C (80 % primary degradation) and ~700 µg/L at 4 °C (30 % primary degradation). In autoclaved seawater, no degradation was observed over 60 days, indicating no abiotic removal process.

Ike *et al*. (2000) studied the degradation of Bisphenol A in 44 water microcosms. The river water microcosms were prepared from water samples from seven rivers, at 15 sites, with conditions ranging from clean to heavily polluted. Degradation was noted in forty of the river water systems. Six of the river water systems were able to mineralise the substance completely, and 34 others showed TOC removal of 40-90 %. Degradation tended to be greater in microcosms from more polluted waters. Two metabolites were identified: 2,3-bis(4-hydroxyphenyl)1,2-propanediol and p-hydroxyphenacyl alcohol. According to the DS, these metabolites cannot be removed by Bisphenol A-degrading bacteria.

The DS refers to the presence of additional studies on the degradation of Bisphenol A in surface water on ECHA's dissemination page (REACH Registration dossier). All studies showed rapid (primary) degradation of Bisphenol A in surface water.

Based on the available results and a weight of evidence approach, the DS concluded that Bisphenol A should be considered as **rapidly degradable** for classification purposes.

Bioaccumulation

The experimentally derived Log K_{ow} of Bisphenol A is 3.4 at 21.5°C and pH 6.4 (OECD TG 107).

Three bioaccumulation studies are available for Bisphenol A performed with fish and freshwater clams. In the first study performed according to the MITI guideline, carp (*Cyprinus carpio*) were exposed to Bisphenol A concentrations of 150 µg/L and 15 µg/L in a flow-through system for 6 weeks. The bioconcentration factors of <20 to 67.7 for low exposure and 5.1 to 13.3 for high exposure were measured.

In the second study performed with freshwater clams (*Pisidium amnicum*), the uptake and depuration rates were measured using ^{14}C radiolabelled Bisphenol A at temperatures between 2 and 12 °C. Both uptake and depuration rates increased with temperature, although the uptake rate decreased slightly at the highest temperature. The bioconcentration factor was calculated from the concentration ratios at steady state and from the two rates. The maximum value was obtained at 8 °C by both methods as 144, based on concentrations and 134, based on rates.

In the third study, killfish (*Oryzias latipes*) were exposed to Bisphenol A concentration of 17 µg/L in a flow-through system for 6 days. Fish were analysed at intervals, and the results at 5 and 6 days showed that steady state had been reached. The mean BCF from these two times was 73.4 L/kg.

The DS concluded that Bisphenol A has a low potential to bioconcentrate and is therefore **not considered to be a bioaccumulative substance** for classification purposes.

Aquatic toxicity

The available database for Bisphenol A is large. The CLH report presents data from aquatic toxicity tests with 24 (acute) and 32 (chronic) species. For Bisphenol A, there are reliable aquatic acute and chronic toxicity data for fish, invertebrates, algae, aquatic plants and amphibians. All studies used for evaluation are rated with reliability index (R.I., Klimisch) score of 1 or 2 by the DS. All studies included were considered valid by the DS.

For determination of environmental hazard (aquatic toxicity reference value) the DS used two approaches, deterministic (using effect values from relevant and reliable experimental studies) and probabilistic (Species Sensitivity Distribution - SSD) approach. The probabilistic approach was used by the DS as supportive evidence for both acute and chronic hazard classifications.

Acute toxicity

The summary of the relevant information on acute toxicity is provided in Table 10 of the CLH report.

Deterministic approach

For fish, eight studies with five different fish species were available in the CLH dossier. Fathead minnow *Pimephales promelas* was the most sensitive fish species tested in the acute studies performed according to ASTME E-729-80, with a nominal 96 h LC_{50} of 4.6 mg/L.

Twenty-one studies with different taxonomic groups were provided for aquatic invertebrates. The geometric mean of 9.88 mg/L based on nine toxicity values for *Daphnia magna* (re-calculated after the consultation) was used as a representative toxicity value for this species. The lowest study value, according to ISO 14669:1999, resulted in a 48 h LC_{50} (survival) of 0.885 mg/L (mean measured) for marine copepod *Acartia clausi* (Tato *et. al*., 2018). Two other toxicity studies performed with aquatic invertebrates were reported by the DS, with toxicity values below 1 mg/L. In the first study (Andersen *et al*., 1999), the 72 h EC_{50} based on immobilization was

0.96 mg/L, while in the second study (Özlem and Hatice, 2008) a 72 h EC_{50} value of 0.71 mg/L based on embryotoxicity was reported.

Five acute toxicity studies were available for algae and aquatic plants. The marine diatom *Naviculla incerta* was the most sensitive species tested in the acute studies performed according to similar to OECD TG 201, with a measured 96 h E_rC_{50} of 3.73 mg/L.

For other aquatic organisms (amphibians), there were non-guideline studies on African clawed frog (*Xenopus laevis*) and Argentine Toad (*Rhinella arenarum*) available with nominal 168 h LC_{50} of 7.1 mg/L and 72 h LC_{50} of 4.8 mg/L, respectively.

Species Sensitivity Distribution (SSD) approach (probabilistic approach)

In the CLH report, the DS pointed out that according to the CLP and REACH Guidance on information requirements and chemical safety assessment (Chapter R.10), in case of very large data sets, statistical techniques (e.g. HC_5 derivation via a SSD) can be used to estimate the aquatic toxicity reference value for classification (equivalent to using the lowest EC_{50}), when the criteria for applying the SSD approach are met. In the opinion of the DS, sufficient species (>10) and taxonomic groups (>8) are available to meet the criteria for applying the SSD approach. The lowest, reliable endpoints for a species or genera were used in the SSD. The acute freshwater and marine ecotoxicity values displayed in bold in the Table 10 of the CLH report were used for the SSD analysis. For *Daphnia magna*, a geometric mean of 9.88 mg/L calculated from 9 studies was used for the 48 h EC_{50} (re-calculated after the consultation).
The SSD model assumes normal distribution of species sensitivities. In the view of the DS, this may be assumed for acute toxicity as the endocrine mode of action of Bisphenol A rather exerts effects over longer periods of time (e.g. in long-term toxicity tests). The data followed a normal distribution according to three goodness-of-fit tests (Kolmogorov-Smirnov, Anderson-Darling and Cramer-von Mises). An HC_5 of 0.60 mg/L was obtained with lower and upper limits of 0.29 and 1.01 mg/L, respectively.

DS conclusion on acute aquatic classification

The acute aquatic classification proposed by the DS (based on the deterministic approach) was based on the Tato *et al*., 2018 toxicity study with the marine copepod *Acartia clausi*. The DS proposed Aquatic Acute 1, with an M-factor of 1 based on a 48 h LC_{50} = 0.885 mg/L (mean measured). A very similar HC_5 value of 0.60 mg/L was obtained with the SSD approach. Both values are below 1 mg/L and support a classification of Bisphenol A as Aquatic Acute 1 with an M-factor of 1, in the proposal of the DS.

Chronic toxicity

The summary of the relevant information on chronic toxicity is provided in Table 11 of CLP report.

Deterministic approach

For fish, nineteen studies with nine different fish species are available in the CLP report. Zebrafish *Danio rerio* was the most sensitive fish species tested in the chronic studies with a mean measured 300 d LOEC of 0.000372 mg/L and mean measured 300 d NOEC of < 0.000372 mg/L based on effects on sex ratio, larval malformations and larval mortality (Chen *et al*., 2015). There were two other studies with very low effect concentrations conducted with *Dania rerio*, a 5 m NOEC for reduced egg production of 0.000174 mg/L (mean measured) (Chen *et al*., 2017) and NOEC for growth of < 0.01 mg/L (nominal) (Keiter *et al*., 2012).

Twenty-six studies with different taxonomic groups were provided for aquatic invertebrates. The geometric mean 3.23 mg/L based on four toxicity values for *Daphnia magna* was used as a

representative toxicity value for this species. Marcial *et al*. (2003) determined a 21 d NOEC for developmental delay for marine copepod *Tigriopus japonicus* of 0.001 mg/L (nominal).

The gastropod *Marisa cornuarietis* was the most sensitive species tested. The study resulted in 150 d LOEC (effects on egg, clutch production) of 0.00025 mg/L (nominal) and 0.000106 (median-measured) (Oehlmann *et al*., 2006). In this study, the NOEC could not be established because the lowest test concentration already exhibited significant effects. There is one another gastropod study with *Potamopyrgus antipodarum* by Sieratowicz *et al*. (2011) which resulted in a NOEC (increased embryo production) of 0.0046 mg/L (mean measured).

Three chronic toxicity studies were available for algae and aquatic plants. The marine algae *Skeletonema costatum* was the most sensitive species tested in the chronic studies performed according to EPA-560/6-82-002, with a measured 96 h E_bC_{10} of 0.40 mg/L.

For other aquatic organisms (amphibian) there were four non-guideline studies on African clawed frog (*Xenopus laevis*) available with nominal NOEC values in range from 0.0073 mg/L to 0.5 mg/L, depending on test design and endpoint.

Species Sensitivity Distribution (SSD) approach (probabilistic approach)

In the CLH report, the DS pointed out that according to the REACH Guidance on information requirements and chemical safety assessment (Chapter R.10), in order for a reliable SSD approached to be used, the comparability of test conditions and different endpoints for long-term toxicity, as well as the specific modes of action and the differences between taxa need to be considered. The SSD model assumes a normal distribution of species sensitivities. The chronic ecotoxicity values displayed in bold in Table 11 of the CLP report were used for the SSD analysis. The DS indicated that for some species there were studies where no definite NOEC could be determined as there were effects even at the lowest concentration tested. In the view of the DS, it would not be appropriate to take into account only the studies in which these definite NOEC were able to be derived as this would not correctly represent the properties of Bisphenol A and, therefore, underestimate the effects. Therefore, when the use of the other NOECs available for the species would not adequately represent the properties of Bisphenol A, the LOEC was used. The HC_5 of 0.00805 mg/L was obtained with lower and upper limits of 0.00017 and 0.00253 mg/L, respectively.

DS conclusion on chronic aquatic classification

The DS proposed a chronic classification as Aquatic Chronic 1, with an M-factor of 10 based on the Chen *et al*. (2015) toxicity study using zebrafish (*Danio rerio*) that derived a 300 d LOEC of 0.000372 mg/L, based on mean-measured concentrations. The substance was considered to be rapidly degradable. After the consultation in the ECHA website, the view of the DS was that a 5m NOEC of 0.000174 mg/L (mean measured) from Chen *et al*. (2017) should be considered as the lowest chronic value for fish. These results are supported by a 150 d LOEC of 0.000106 mg/L for the gastropod *Marisa cornuarities*, based on median measured concentrations. In this study, as determination of NOECs was not feasible, the LOECs represented, according to the DS, a "best case".

Comments received during consultation

Three Member States (MS) and one industry association submitted comments on the DS's proposal during the consultation. All commenting MSs agreed with the proposed aquatic acute classification as Aquatic Acute 1, with an M-factor of 1. Two commenting MSs supported aquatic chronic classification of the substance as Aquatic Chronic 1, with an M-factor of 10.

The industry association disagreed with the DS proposal to classify the substance as Aquatic Acute 1, M-factor = 1 and Aquatic Chronic 1, M-factor = 10 due, in their opinion, to inappropriate application of the CLP criteria and inadequate study reliability rating by the DS. In their opinion, a more appropriate application of the CLP criteria and more adequate study reliability ratings would lead to a classification of Bisphenol A as no classification for aquatic acute toxicity and Aquatic Chronic 2. The industry association also performed their own statistical analyses that derived an HC_5 value of 0.0136 mg/L that would also support the classification of the substance in category Aquatic Chronic 2 (SSD argumentation are presented in this RCOM below). The following sections present a summary of the key issues raised by the industry association and MS, with the full comments, as well as the analytical DS and RAC responses, found in the RCOM document and later on in the current opinion document:

Taxonomic groups considered

The industry association pointed out that the classification proposed in the CLH report partly builds upon taxonomic groups other than fish, crustacea and algae/higher plants. Using test species that represent other trophic levels or are not typically required in a regulatory framework (e.g., snails, insects, amphibians) in the CLP process would be, in their opinion, contrary to the basic principle that the hazard of different substances should be compared on the same basis (i.e. same trophic levels/species when available). Therefore, the classifications for acute and chronic aquatic toxicity as proposed in the CLH report are not justified, in the commenter's opinion.

The DS responded that they followed the CLP guidance (version 5.0, July 2017, section 4.1.3.2.3.1, p.496) where it is stated that normally fish, crustacea and algae species is used to determine the toxicity of a substance **but** data on other species can also be considered under given conditions. Additionally, the CLP guidance (section 4.1.3.2.4.1) states that the three mentioned taxa are only a base/ minimum dataset that may be, in cases, a poor surrogate for the wide range of species in the environment and that a weight-of-evidence approach may be used for setting a classification (section 4.1.2.1.). RAC agrees with the DS as this is in line with the CLP regulation and guidance.

Reliability

The industry association mentioned that the CLP Regulation requires that only data of high reliability are to be used for classification purposes. Such reliability should normally be assessed using the criteria proposed by Klimisch et al. (1997) but additional criteria, related to specific substance properties, can often be helpful to underpin the generic assessment. Furthermore, the association noted that the proposed classifications are not based on fully reliable studies (Klimisch 1), but on studies which are rated reliable with restrictions (Klimisch 2) or should even be rated not reliable (Klimisch 3) – contrary to respective CLP guidance, which gives preference to fully reliable (Klimisch 1) studies for data rich substances, as is Bisphenol A. Several Annexes have been provided were the reliability of each experimental study in the CLH report has been re-assessed.

The DS agreed that only reliable and relevant studies should be used for CLP classification. Thus, studies fulfilling the Klimisch 1 **and 2** criteria according to Klimisch *et al*. (1997) should be used and highlighted that this principle was followed in the CLH report. In addition, section 4.1.3.2.4.3. of the CLP guidance further states that the best quality data should be used and test conditions be clearly and completely articulated. The DS also agreed with the comment in that the evaluation of study reliability can **also** be done according to other systematic approaches, e.g. CRED. RAC agrees with the DS as this is compatible with the CLP Regulation and Guidance requirements, for example section 4.1.3.2.1.

Use of Species Sensitivity Distributions (SSD) techniques

The industry association highlighted that no reference is given for the use of statistical extrapolation techniques and use of data on other taxonomic groups in weight-of-evidence methodology. This complex situation precludes the use of statistical extrapolation techniques for derivation of an acute hazard category for Bisphenol A because only a small set of validated OECD TGs is available, limited to key species of three trophic levels (fish, crustacea, algae) and that the basic paradigm of using statistical approaches in a regulatory context is to mirror effects on complex aquatic ecosystems by including toxicity data for test species of major taxonomic groups. Consequently, an acute hazard category should be derived using the conventional deterministic approach, i.e. selecting the lowest, fully valid LC/EC_{50} value for fish, crustaceans, and algae. In case of chronic classification, the view of the industry association was in line with the approach taken by DS. The statistical extrapolation techniques, using valid NOECs from a broad range of aquatic taxa, should be used as supportive evidence for derivation of a chronic hazard category.

Concerning the use of the SSD approach, the DS pointed out that in the CLP Guidance (p. 502), referring to the REACH Guidance on information requirements and chemical safety assessment (Chapter R.10), the use of the Species Sensitivity Distribution approach is described as a possibility for very large data sets, meeting certain criteria for applying it. The CLP guidance (section 4.1.3.2.4.3) does not distinguish between short- and long-term data for the applicability of the SSD approach. In the view of the DS, for data-rich Bisphenol A the REACH guidance considerations are fulfilled and are presented in the CLH report. Based on the comments received during the consultation in the ECHA website, the DS revised the data used for the derivation of HC_5 that resulted in a value of 0.000543 mg/L.

Based on the considerations presented in Supplemental information - In depth analyses by RAC/ background document (BD), RAC is of the opinion that the SSD approach for acute and chronic classification should be used as additional information. The acute and chronic toxicity dataset used for the SSD approach and calculation by RAC are also presented therein.

Individual acute and chronic toxicity study reliability

In the view of the industry association, the dataset in the CLH report on acute and chronic aquatic toxicity consists of a selection of studies which is partly based on inappropriate reliability ratings of scientific studies by the DS. Specifically, in their view it comprises various studies that do not meet the minimum requirements for scientific reliability and are, therefore, not adequate for classification purposes. In brief, the industry association claimed major deficiencies in study design, methodologies and weak documentation as reasons for a downgrade in the Reliability scoring. The DS generally disagreed with the industry commentator's evaluation repeating that the evaluation took place following the Klimisch and CRED principles. Based on the comments received, the DS did not change the opinion regarding reliability of the studies. More information on the study quality is provided in the BD.

Specific comments from individual MSs

One MS commented on the following issues:

Acute classification: The MS asked whether the key aquatic acute toxicity study performed with the marine crustacean *Acartia clausi* (Tato *et al.*, 2018) was considered in the dossier or assessment of triclosan and 4-nonylphenol. The DS responded that the study was not used in the assessment of the above-mentioned substances. The same MS was of the opinion that the key aquatic acute toxicity study (Tato *et al.*, 2018) should be considered as Klimisch 2 and not Klimisch 1 because the study was not conducted to GLP and some study details were missing (lack of raw data, incomplete dissolved oxygen data, no information on the culture history, incomplete information on final solvent concentrations and full details of reference compound

studies). The DS provided additional data on the biological quality of the stock and that the study was run according to ISO guideline 14669:1999. In the view of RAC, the study by Tato *et al*. (2018) is reliable and should be used as a key study for setting the hazard classification.

Chronic classification: In view of the MS the aquatic chronic toxicity studies performed with fish *Danio rerio* (Chen *et al*., 2015; Chen *et al*., 2017) were not valid for hazard classification due to several deficiencies.

For the Chen *et al*. (2015) study, different deficiencies were indicated by the MS. The DS agreed that study was not run according to GLP and that the study result would underestimate the effect with a missing no effect concentration. However, the DS pointed out that many of the test conditions in the study were similar to the ones recommended in OECD TG 234, it provided information on replicates and their variability for endpoint sex ratio and considered the study valid and reliable. RAC agrees with the DS.

Similarly, the MS mentioned several deficiencies regarding the Chen *et al*. (2017) study. The DS responded by providing more study details and still argued that the study is valid and reliable. RAC agrees with the DS.

The MS also questioned if the LOEC value from the aquatic chronic toxicity study with gastropod *Marisa cornuarietis* (Oehlmann *et al*., 2006) was sufficiently reliable to be considered as the key chronic classification endpoint or whether the study endpoint should be considered supporting information (detailed assessment of the study was provided in the RCOM). The commenting MS pointed out that other, more reliable, studies with gastropod *Marisa cornuarietis* did not replicate the same level of effects although there were differences with study design and test species. The DS responded that the effects endpoint egg/clutch production supported the results from studies with fish and showed that sensitive organism groups are indeed adversely affected in this concentration range. Regarding the other studies with the gastropod l *Marisa cornuarietis*, the DS pointed out that these studies were very different with respect to study design, test conditions and test species/strain, explaining in that way the higher effects levels of Warbritton/Forbes study that should be seen as different and not comparable studies.

Regarding the aquatic chronic toxicity study performed with *Salmo trutta* (Lahnsteiner *et al.*, 2005), the same commenting MS was of the opinion that due to limitations and uncertainties this study is not robust enough to be used in the SSD dataset. In the view of the DS, the cited limitations do not devalue the study and only for the endpoint 'time point of ovulation', for which only 6 fishes were used, is the test not robust enough and the related results were not taken into account. For the endpoints egg production and semen fertility, the study was evaluated as Klimisch 2. In the view of RAC, as explained later on in the opinion, the study is not reliable and should not be used for hazard classification.

Regarding the SSD approach, the MS asked for clarification regarding the use of values for different species, endpoints and inclusion or exclusion of algae and aquatic plants in SSDs. The DS clarified that the most sensitive reliable endpoints for a species or genera have been used and that the influence of inclusion/exclusion of values has been checked (details provided in RCOM document). The DS also provided the SSD calculations with and without algae and aquatic plants to show any differences.

The second commenting MS provided comments regarding the lack of a detailed description of the studies in the CLH report that were used in the SSD (e.g. purity, test regime, concentrations maintained, etc.). In addition, the MS requested clarification on the use of some study results in the SSD. The MS highlighted that nine reliable aquatic acute toxicity studies with *Daphnia magna* were available in the CLH report and all of them should be used for the calculation of a geometric mean. The DS agreed and recalculated the geometric mean which resulted in an EC_{50} of 9.88 mg/L (instead of 9.47 mg/L).

A third MS also asked for an explanation as to why the NOEC of 0.00017 mg/L for *Danio rerio* (Chen *et al*., 2017) was not considered the lowest chronic value for fish by the DS instead of the LOEC of 0.000372 mg/L (Chen *et al*., 2015). The DS agreed that the NOEC from Chen *et al*. (2017) should be considered as the lowest chronic value for fish as this is a "real" NOEC which was not derivable from Chen *et al*. (2015).

Regarding ready biodegradability of Bisphenol A, the same MS pointed out that no explanation was given for the divergence of equally reliable results. The DS explained that the evaluation of degradation of Bisphenol A was based on a weight of evidence approach including studies of an equivalent reliability. In this context, the studies with positive results (OECD TG 301F) were of good scientific quality and the test conditions were well documented.

In the view of this MS, the inoculum used in the simulation study (Klečka *et al*., 2001) may be adapted to Bisphenol A due to the sampling location near to a wastewater treatment plant treating Bisphenol A, which could lead to an improved biodegradation capacity. The DS agreed and explained that the half-life in this study is in the same order of magnitude of the half-lives from the studies investigating primary degradation.

The MS pointed out that in other freshwater studies only primary degradation was reported. Although half-lives are <16 days, no information is given on the classification of the degradation products. The DS responded that no degradation products were identified in the studies on primary degradation. Only the study from Ike *et al*. (2000) identified any metabolites.

Assessment and comparison with the classification criteria

Degradation

Bisphenol A is hydrolytically stable under environmentally relevant conditions. There are six valid and equally reliable ready biodegradation studies available, three of which showing that the substance is readily biodegradable (OECD TG 301F) and three not (OECD TG 301D, OECD TG 301B and OECD TG 301C). In line with the current CLP Guidance (version 5.0, July 2017, section II.3.5, p. 569), RAC is of the opinion that Bisphenol A should be considered readily biodegradable following the three valid OECD TG 301F studies and the 10-day window criteria being fulfilled, including the use of non-adapted inoculum.

In an aerobic water simulation study, whole system half-life for Bisphenol A was between 0.5 and 2.6 days at 20°C. Rapid primarily degradation with half-lives between 2 and 4 days in water were reported in two other water/sediment simulation studies. However, information on transformation products is lacking (amount, identity, classification). Another water/sediment simulation study in which 40 – 100 % degradation (TOC removal) was observed identified degradation products (2,3-bis(4-hydroxyphenyl)1,2-propanediol and p-hydroxyphenacyl alcohol). Classification information for identified degradation products is lacking. Following the CLP guidance (version 5, July 2017, section II.3.4, p. 569) data on primary degradation may be used for demonstrating rapid degradability only when it can be satisfactorily demonstrated that the degradation products formed do not fulfil the criteria for classification as hazardous to the aquatic environment.

Bisphenol A is considered readily biodegradable following a valid OECD TG 301F study and the 10-day window criteria are fulfilled and, as the OECD TG 301F test is considered to be performed in stringent conditions, RAC is of the opinion that Bisphenol A should be considered as **rapidly degradable** for the purpose of aquatic hazard classification.

Bioaccumulation

RAC agrees with the DS that Bisphenol A has a **low potential to bioaccumulate** in aquatic organisms. The basis for this is that measured BCF values in aquatic organisms were below the decisive CLP Regulation criterion of 500 (BCF = 144). This is supported by the Log K_{ow} value being below the CLP Regulation criterion of 4 (Log K_{ow} = 3.4).

Aquatic acute toxicity

As reported before, the Species Sensitivity Distribution (SSD) approach (HC_5 value of 0.60 mg/L) for aquatic acute classification of Bisphenol A was considered as additional evidence by the DS. As elaborated in the BD, RAC acknowledges the merits of using the SSD approach for a data-rich substance such as Bisphenol A and has tried to replicate the related computations, resulting in a HC_5 value of 0.83 mg/L, which is in alignment with the DS calculations. However, RAC is of the opinion that in the presence of good quality experimental information for Bisphenol A, classification of the substance for acute aquatic hazard should primarily be based on a deterministic approach (most sensitive species) and that the SSD approach for acute classification should be used as additional information due to some of the uncertainties described in the BD.

According to the toxicity data presented in Table 10 of the CLP report, invertebrates are the most sensitive trophic level. Apart from the entire acute aquatic dataset, three studies deriving an EC_{50}/LC_{50} below or equal to 1 mg/L have been comprehensively assessed by the RAC, with the detailed assessment presented in the BD. Based on this comprehensive analysis, all three studies (Tato *et al*., 2018; Andersen *et al*., 1999; Özlem and Hatice, 2008) were deemed reliable, albeit some drawbacks that in RAC's opinion do not have a serious impact on the study outcomes. Thus, RAC believes that data from these studies have been generated according to internationally accepted guidelines, appropriate both standard and "non standard" species were used, with *Acartia tonsa* being taxonomically the closest equivalent species to *Acartia clausi* (same genera).

RAC proposes to base the aquatic acute classification on the study performed with the marine copepod *Acartia clausi* with a 48 h mean measured EC_{50} value of 0.885 mg/L. This result is supported by the two other studies that also provide toxicities within the same range (72 h EC_{50} = 0.96 mg/L, Andersen *et al*., 1999 and 72h-EC_{50} =0.71 mg/L, Özlem and Hatice, 2008). Based on these values Bisphenol A warrants classification as **Aquatic Acute 1**, **M-factor of 1**, as the acute toxicity is in the range $0.1 < L(E)C_{50} \leq 1$.

Aquatic chronic toxicity

RAC is of the opinion that in the presence of good quality experimental information for Bisphenol A, classification of the substance for chronic aquatic hazard should be based on a deterministic approach (numerical results from experimental studies and use of the most sensitive species) and that the SSD approach for chronic classification should be used as additional information due to some of the uncertainties presented in the BD. As reported before, the SSD approach (HC_5 value of 0.000543 mg/L) for aquatic chronic classification of Bisphenol A was considered as additional evidence by the DS. As elaborated in the BD, RAC acknowledges the merits of using the SSD approach for a data-rich substance such as Bisphenol A and has tried to replicate the related calculations, resulting in a HC_5 value of 0.0012 mg/L

According to the toxicity data presented in Table 11 of the CLP report, four studies with fish, one study with crustacea, three studies fwith mollusc and one study with amphibians showed NOEC/LOECs below 0.01 mg/L. All of these studies, as the most conservative ones, apart from the entire chronic aquatic dataset, have been assessed in depth by the RAC, as presented in the

BD. Based on that comprehensive analysis, two studies for fish (Chen *et al*., 2015; Chen *et al*., 2017), one for crustacea (Marcial *et al*., 2003) and one for mollusc (Oehlmann *et al*., 2006) have been found reliable and appropriate to use for classification purposes.

One toxicity test with fish (Lahnsteiner *et al*., 2005) and one with amphibians (Levy *et al*., 2004; Pickford *et al*., 2003 & 2010) have been found not to be reliable by RAC. RAC considers the study by Lahnsteiner *et al*. (2005) not reliable due to the fact that fish derived from a wild population (caught by electroshocking) were used, no information on the health of the fish and possible influence of environmental factors was available, issues with the acclimatisation of the test animals, small numbers of fish were used, no replicates, low statistical power based on low number of individuals at each endpoint and no analytical confirmation.

In the view of RAC the amphibians study as cited by Levy *et al*. (2004) should not be considered for classification due to the absence of a concentration-response relationship, insufficient replication, statistical methodology introducing statistical bias and the absence of significant incidences of gonadal abnormalities at the histological level.

RAC is also of the opinion that the NOEC of 0.0046 mg/L (mean measured) at 7 and 25 °C from the Sieratowicz *et al*. (2011) study is not reliable because the study was not carried out at the required temperature (16°C) in OECD TG 242. Consequently, the NOEC (0.0194 mg/L (mean measured)) at 16°C should be used for classification.

RAC considers the toxicity study with fish by Keiter *et al*. (2012) as additional information due to the presence of PFOS in the test water and miscounting of numbers of fish per aquaria.
From the four studies found reliable based on RAC's assessment, the Committee proposes to base the chronic classification on the study performed with fish *Danio rerio* with 5 m NOEC value of 0.000174 mg/L (mean measured) (Chen *et al*., 2017). This result is supported by one fish (Chen *et al*., 2015), one crustacea (Marcial *et al*., 2003) and one mollusc (Oehlmann *et al*., 2006) studies, which provide toxicities within the same range. Based on these toxicity studies and the substance considered as rapidly degradable, RAC agrees that Bisphenol A warrants classification as **Aquatic Chronic 1** with an **M-factor** of **10** ($0.0001 < NOEC \leq 0.001$).

ANNEXES:

Annex 1 The Background Document (BD) gives the detailed scientific grounds for the opinion. The BD is based on the CLH report prepared by the Dossier Submitter; the evaluation performed by RAC is contained in 'RAC boxes'.

Annex 2 Comments received on the CLH report, response to comments provided by the Dossier Submitter and RAC (excluding confidential information).