Committee for Risk Assessment

RAC

Annex 2

Response to comments document (RCOM)

to the 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

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON 4,4'-ISOPROPYLIDENEDIPHENOL; BISPHENOL A

COMMENTS AND RESPONSE TO COMMENTS ON CLH: PROPOSAL AND JUSTIFICATION

Comments provided during 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 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 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: 4,4'-isopropylidenediphenol; bisphenol A
EC number: 201-245-8
CAS number: 80-05-7
Dossier submitter: Germany

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
30.08.2019	Belgium	PlasticsEurope	Industry or trade association	1
Comment received				
Submission by Plastics Europe Polycarbonate/Bisphenol A Group (PC/BPA Group) on the CLH report for Bisphenol A (April 2019) August 30, 2019 In this box you find the text of our comments; the related tables and figures can be accessed in Annex 0. For ease of reading the complete document including the tables and figures is also attached as: Submission Plastics Europe on CLP report BPA April 2019.pdf. Synopsis The CLH report submitted by the German Competent Authorities proposes a new Harmonised Classification and Labelling for Bisphenol A (BPA) as aquatic acute and aquatic chronic category 1. However, the presented information on acute and chronic aquatic toxicity used to substantiate this proposal is inappropriate. It comprises studies essential for the proposed classification that do not meet the established requirements on scientific quality, validity and reliability – as a consequence of inappropriate study reliability rating of several studies in the CLH report. Further, 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.				

Also, the classification proposed in the CLH report partly builds upon taxonomic groups other than fish, crustacea and algae. However, according to the CLP regulation as well as the respective ECHA guidance document (2017), fish, crustacea and algae should be used for classification.

All in all the proposed classification in the CLH report is not in line with main principles of Regulation (EC) No 1722/2008 on CLP and the respective Guidance document. The classifications for acute and chronic aquatic toxicity as proposed in the CLH report are not justified.

An appropriate application of the CLP criteria and adequate study reliability ratings leads to a classification of Bisphenol A as aquatic chronic category 2 as further explained below.

General considerations

PlasticsEurope is a leading pan-European trade association representing more than 100 plastics manufacturers active in the European plastics industry. The Polycarbonate / Bisphenol A industry group is a product group within PlasticsEurope, comprising the European producers of Bisphenol A and polycarbonate.
The Bisphenol A producing companies are committed to collecting the safety data of their products on the basis of the best available quality, in order to provide scientifically valid, robust and reliable data to assess the potential risks of chemicals to humans and to the environment (i.e. in a classification & labelling context).

Bisphenol A has a very robust and comprehensive database of fully reliable and relevant aquatic toxicity studies. Acute and chronic aquatic toxicity studies include the measurement of apical endpoints related to population relevant effects on survival, growth, development and reproduction. The database contains a diverse set of taxa including several key species of fish, amphibians, pelagic and benthic invertebrates like crustaceans, insects, molluscs, as well as algae and higher plants. The studies employed a diversity of test designs and durations so that data is available for organisms exposed at early life stages, during growth and development, during reproduction, and over the course of multiple generations. All industry contracted studies have been planned and conducted under GLP on the basis of fully validated OECD guidelines or other internationally acknowledged guidelines or standards. In the exceptional cases where no guidelines were available, test protocols were individually developed on the basis of the most advanced technologies according to the state-of-science and technology. All studies contracted by the Bisphenol A producers were performed at fully accredited test institutes of international reputation. The set of acute and chronic toxicity data for Bisphenol A was discussed with the rapporteur of the EU Risk Assessment report on Bisphenol A (2003, 2008, 2010) and studies which were missing in 2003 were conducted in agreement with the rapporteur. The rapporteur and the Technical Committee for New and Existing Substances agreed that the final set of studies for Bisphenol A fulfil the criteria of highest quality and reliability.

Only reliable and relevant studies of high quality should be used for CLP classification of Bisphenol A which is a requirement in the CLP guidance document (v5.0, 2017). Thus, the dataset of studies, fulfilling the Klimisch 1 criterion (reliable without restriction) should be used as the basis of any regulatory decisions including classification & labelling (CLP) of Bisphenol A.

Regarding the use of test data, in general, only reliable information (i.e. with a Klimisch reliability score of 1 (reliable without restrictions) or 2 (reliable with restrictions)) should

be used for classification purposes. However, good quality data may not always be available for all trophic levels. It will be necessary to consider data of lower quality for those trophic levels for which good quality data are not available. Consideration of such data, however, will also need to take into account the difficulties that may have affected the likelihood of achieving a valid result. For larger data sets, preference should be given to information with Klimisch score 1, while information with Klimisch score 2 can be used as supporting information. For more information on the Klimisch reliability scoring system, see IR&CSA, Chapter R.4.2.

The dossier submitter agrees that only reliable and relevant studies should be used for CLP classification. This means according to Klimisch et al. (1997) a reliability of 1 (reliable without restriction, e.g. guideline study) or 2 (reliable with restriction, e.g. comparable to guideline study with acceptable restrictions). This principle is followed also in this CLH report. Despite of this, the evaluation of the study reliability can not only be done according to Klimisch et al. (1997) but also according to other systematic approaches, e.g. CRED (in this case we only refer to Klimisch to be consistent).

The aim of CLP classification and the underlying hazard assessment is to place every substance in a pre-defined hazard category. All substances within a specific category are expected to share a similar (eco)toxicological or physicochemical hazard profile. A 'common' hazard profile within a category, however, is best achieved when substances are evaluated against the same benchmarks, i.e. for the environment this means against a comparable set of standard test species and a standard set of endpoints that represent three-predefined trophic levels (fish, crustacea, 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 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).

Study quality – Relevance and reliability assessments

The Regulation (EC) No 1272/2008 on classification, labelling and packaging of substances and mixtures (CLP-Regulation) and the respective Guidance on the Application of the CLP Criteria, version 5.0, July 2017 (CLP guidance document 2017) repeatedly require that only data of high reliability are to be used for classification purposes.

In section 4.1.3.2.1. of the CLP guidance document, it is stated:
"Regarding the use of test data, in general, only reliable information (i.e. with a Klimisch reliability score of 1 (reliable without restrictions) or 2 (reliable with restrictions)) should be used for classification purposes. … For larger datasets, preference should be given to information with Klimisch score 1, while information with Klimisch score 2 can be used as supporting information."

The CLP guidance document further states in the context of weight of evidence for data rich substances in section 4.1.3.2.4.3.:
"The best quality data should be used as the fundamental basis for classification. … It is essential, that test conditions be clearly and completely articulated."

The reliability scores proposed by Klimisch et al. (1997) are usually taken as a general guidance for how to evaluate toxicity and ecotoxicity data, generated under well-defined laboratory conditions. However, additional criteria, related to specific substance properties are often helpful to underpin the generic assessment according to the Klimisch scores.

This is specifically true for a rapidly biodegradable substance like Bisphenol A, which creates challenges maintaining concentration levels, particularly over longer-term exposures in chronic testing.

A detailed discussion on how the reliability evaluation criteria have been applied and the specific aspects of BPA which have to be taken into account is provided in Annex 1.

General considerations on chronic aquatic toxicity

Regulation (EC) No 1272/2008 of the European Parliament and of the Council (CLP-Regulation) provides the legal basis for the classification of substances and mixtures. Part 4 of Annex I of the CLP-Regulation sets out the criteria with regard to environmental hazards and also sets out additional provisions on how the criteria may be met.

4.1.2.7.2.: "For determining chronic aquatic toxicity for classification purposes data generated according to the standardised test methods referred to in Article 8(3) shall be accepted, as well as results obtained from other validated and internationally accepted test methods. The NOECs or other equivalent ECx (e.g. EC10) shall be used."

Furthermore, section 4.1.2.1 of Annex I, Part 4 of the CLP-Regulation does stipulate that fish, crustacea and algae/aquatic plants shall be used for the chronic classification:

4.1.2.1: "The system for classification recognises that the intrinsic hazard to aquatic organisms is represented by both the acute and chronic toxicity of a substance. For the long-term (chronic) hazard, separate hazard categories are defined representing a gradation in the level of hazard identified. The lowest of the available toxicity values between and within the different trophic levels (fish, crustacean, algae/aquatic plants) shall normally be used to define the appropriate hazard category(ies). There are circumstances, however, when a weight of evidence approach is appropriate."

According to the general definition of 'chronic aquatic toxicity' that is outlined in the CLP-Regulation as introduced by the 2nd ATP to the CLP Regulation (Commission Regulation (EU) No 286/2011), NOEC or other equivalent ECx (e.g. EC10) values should be used for classification purposes.

The ECHA CLP-Guidance (2017) does stipulate that "Valid data for short- and long-term tests on other species at the same trophic level shall also be considered, provided they are equivalent in terms of species relevance, testing conditions and test endpoints."

General remarks on the probabilistic SSD approach for aquatic toxicity data

The relevant REACH Guidance on information requirements and chemical safety assessment (Chapter R.10: Characterisation of dose [concentration]-response for environment; ECHA, 2008) provides details on the application of statistical extrapolation techniques, based on the underlying assumption that chronic NOECs of data-rich substances have a high predictive power for assessing adverse effects on growth, development, reproduction and long-term viability of environmental populations. Acute data as a potential basis for predicting environmental effects, however, are not specifically mentioned (as they are generally assumed to better model acute short-term effects on aquatic populations rather than long-term effects caused by continuous exposure to chemical stressors at low concentrations).

Statistical approaches (i.e. development of Species Sensitivity Distributions (SSD) of

chronic NOECs) make use of the full distribution of ecotoxicity data of key representative species from major taxonomic groups. This approach is confined to data-rich chemical substances with data sets fulfilling specific minimum requirements related to numbers of NOECs and taxonomic groups (REACH Guidance: "… Confidence can be associated with a PNEC derived by statistical extrapolation if the database contains at least 10 NOECs (preferably more than 15) for different species covering at least 8 taxonomic groups…". Based on the huge dataset of reliable chronic studies, this condition is clearly fulfilled for Bisphenol A.

While there is an extensive set of fully validated OECD test guidelines available for assessment of chronic effects to key freshwater and marine test species, there are only few validated test systems for assessment of acute effects, basically confined to three taxonomic groups or trophic levels, respectively: fish (OECD 203), crustaceans (OECD 202), and unicellular algae (OECD 201).

The CLP regulation is very specific in pointing out that "fish, crustacea, and algae", considered as surrogate for all aquatic organisms, should be used for classification, but that valid data for short- and long-term tests with other species at the same trophic level shall also be considered, provided that they are equivalent in terms of species relevance, testing conditions and test endpoints.

The Guidance on the Application of the CLP Criteria (ECHA, 2017) shortly mentions that a weight-of-evidence approach may be used for setting a classification. No specific reference is given, yet, to the use of statistical extrapolation techniques or any other methods how to apply the weight-of-evidence principle in practical terms. There is also no reference that data on other taxonomic groups can be used in this weight-of-evidence methodology.

To our understanding this complex situation precludes the use of statistical extrapolation techniques for derivation of an acute hazard category for Bisphenol A: On one hand, only a small set of validated OECD test guidelines is available, limited to key species of three trophic levels (fish, crustacea, algae). On the other hand, the basic paradigm of using statistical approaches in a regulatory context is to mirror effects to complex aquatic ecosystems by including toxicity data for test species of major taxonomic groups. These opposing positions cannot be solved, especially since the text of the CLP regulation shows a preference for the exclusive consideration of three taxonomic groups.

We conclude that, in the case of Bisphenol A, an acute hazard category should be derived using the conventional deterministic approach, namely to select the lowest, fully valid LC/EC50 value for fish, crustaceans, and algae.

The situation is different with the classification for chronic hazard. While a classification may be set by taking the most sensitive NOEC from chronic testing with fish, crustacea and algae, supportive evidence for a chronic hazard category may be sought by use of statistical extrapolation techniques. A more comprehensive set of validated OECD test guidelines with chronic endpoints is available, and also multiple high quality data for Bisphenol A - within and beyond the above-mentioned taxonomic groups and trophic levels. In line with the approach taken by the authors of the CLP report, we conclude that statistical extrapolation techniques, using valid NOECs from a broad range of aquatic taxa, provide supportive evidence for derivation of a chronic hazard category in a classification & labelling context.

ECHA note – An attachment was submitted with the comment above. Refer to public attachment Submission PlasticsEurope CLH and annexes.zip

Dossier Submitter's Response

Thank you for your comments.

Taxonomic groups considered:
Concerning your comment that "the classification proposed in the CLH report partly builds upon taxonomic groups other than fish, crustacea and algae". This is correct as the Dossier Submitter followed the CLP guidance (version 5.0, July 2017) section 4.1.3.2.3.1 (p.496) where it is stated that normally acute fish, crustacea and algae species is used to determine the toxicity of a substance but „Data on other species (e.g. Lemna spp.) shall also be considered if the test methodology is suitable. […] Valid data for short- and long-term tests on other species at the same trophic level shall also be considered, provided they are equivalent in terms of species relevance, testing conditions and test endpoints."

For the evaluation of the acute toxicity tests with *Acatia tonsa* and *Arcatia clausi* are most sensitive.

As described above, in the CLP guidance no standard test set is required ("…Valid data for short- and long-term tests on other species at the same trophic level shall also be considered…"). Therefore it is possible (and was done in the past already), that for the classification of different substances different data sets are available.

Additionally, the CLP guidance (chapter 4.1.3.2.4.1) states that "The taxa chosen, fish, crustacea and aquatic plants that represent the "base-set" in most hazard profiles, represent a minimum dataset for a fully valid description of hazard. […]Given the wide range of species in the environment, the three taxa tested can only be a poor surrogate and the lowest value is therefore taken for precautionary reasons to define the hazard category".

Study quality:
The dossier submitter agrees that only reliable and relevant studies should be used for CLP classification. This means according to Klimisch et al. (1997) a reliability of 1 (reliable without restriction, e.g. guideline study) or 2 (reliable with restriction, e.g. comparable to guideline study with acceptable restrictions). This principle is followed also in this CLH report. Despite of this, the evaluation of the study reliability can not only be done according to Klimisch et al. (1997) but also according to other systematic approaches, e.g. CRED (in this case we only refer to Klimisch to be consistent).

Consideration of chronic aquatic toxicity data for an SSD:
The quote from CLP guidance from above is also true here. This means that "Valid data for short- and long-term tests on other species at the same trophic level shall also be considered, provided they are equivalent in terms of species relevance, testing conditions and test endpoints" (CLP guidance, version 5.0, p. 496). In CLP Guidance (v.5.0, 2017) 4.1.3.2.4.1 it is also stated that "The taxa chosen, fish, crustacea and aquatic plants that represent the "base-set" in most hazard profiles, represent a minimum dataset for a fully valid description of hazard. The lowest of the available toxicity values will normally be used to define the hazard category. Given the wide range of species in the environment, the three taxa tested can only be a poor surrogate and the lowest value is therefore taken for precautionary reasons to define the hazard category. […] There are some circumstances where it may not be appropriate to use the lowest toxicity value as the basis for classification. 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. […] In case of very large data sets meeting the criteria for applying the Species Sensitivity Distribution (SSD) approach (see IR&CSA, Chapter R.10), statistical techniques (e.g. HC5 derivation) can be considered to estimate the aquatic toxicity reference value for classification (equivalent to using the lowest EC_{50} or NOEC), in a weight of evidence approach." For Bisphenol A we think that it is appropriate to speak of a very large data set (which is also stated by PlasticsEurope in the comment).
The requirements on the composition of the data set for a SSD according to ECHA Guidance R.10 represent a "minimum species requirement". It is also described in the ECHA guidance R.10 that "for some of the taxa mentioned above, no internationally standardized test guidelines for long-term tests are currently available. […] There is need to evaluate additional information in order to assess how relevant and representative this list of taxonomic groups is to the risk assessment scenario being investigated." There it is also described how to deal with multiple data for one species: "The test data applicable to the most sensitive endpoint should be taken as representative for the species…".

Concerning the use of the SSD approach and its "appearance" in the CLP Guidance:
In CLP Guidance (version 5.0, July 2017) on page 502 the use of the Species Sensitivity Distribution approach is described as a possibility for very large data sets. Similar to other parts of the CLP Guidance, it is refered to ECHA Guidance (here: R.10). This referral does not imply a vilification of the SSD approach. This chapter in the CLP guidance (4.1.3.2.4.3) does also not distinguish between short- and long-term data for the applicability use of the SSD approach.

Classification:
For acute aquatic hazards of Bisphenol A the conventional deterministic approach as well as the statistical approach result in the same classification as Aquatic Acute 1, H400 (M=1) (lowest reliable LC_{50}= 0.885 mg/L and HC_5 derived from SSD= 0.60 mg/L).

Similar, for chronic aquatic hazards the deterministic approach, selecting the reliable and most sensitive species as well as the statistical approach result in a classification as Aquatic Chronic 1 (M=10) (lowest reliable value LOEC 0.174 µg/L (new value based on comments) for fish supported by LOEC 0.106 µg/L for snails and a HC5 of 0.543 µg/L (new value based on comments). As described in the CLH dossier, despite the comprehensive set of data available it is important to consider and cover particular sensitive species (below the HC5), which is evident in this case and in particular important for chronic toxicity due to the endocrine mode of action of BPA.

RAC's response

Thank you for your comment.

Study quality: RAC agrees with the DS as this is compatible with the CLP Regulation and Guidance requirements. In addition, RAC also agrees with the Dossier Submitter regarding the use of other evaluating methods (e.g. CRED) for assessment of reliability of ecotoxicity data for use in hazard assessment and for classification of the substances.

Taxonomic groups considered: RAC agrees with Dossier Submitter as this is in line with the CLP regulation and guidance.

Consideration of chronic aquatic toxicity data for an SSD: Noted by RAC.

Concerning the use of the SSD approach and its "appearance" in the CLP Guidance: Noted by RAC.

Classification: RAC agrees with DS that Bisphenol A should be classified as Aquatic Acute 1 with M-factor of 1 and Aquatic Chronic 1 with M-factor of 10.

Use of SSD for derivation of hazard category: Noted by RAC. RAC opinion is presented in the ODD/BD.

OTHER HAZARDS AND ENDPOINTS – Hazardous to the Aquatic Environment

Date	Country	Organisation	Type of Organisation	Comment number
24.08.2019	United Kingdom		MemberState	2

Comment received

Acute classification:
Key endpoints in the proposal:
We note the key acute toxicity endpoint study (Tato et al, 2018) also assessed toxicity from triclosan and 4-nonylphenol. For consistency, please can the DS confirm if the study has been considered in the dossiers or assessment of these chemicals?

We do not consider that the study is Klimish 1 and think Klimish 2 is more appropriate as the study was not conducted to GLP and some study details are missing (e.g. lack of raw data, incomplete DO data, no information on the culture history, incomplete information on final solvent concentrations and full details of reference compound studies).

Overall, we agree that the proposed key study endpoint and acute probabilistic SSD HC5 endpoint are in the range 0.1 to 1mg/L and that Aquatic Acute 1 (M=1) is appropriate.

Chronic classification:
Key endpoints in the proposal:
The chronic classification proposal is based on the 300 day LOEC of 0.000372 mg/L (quoted as mean measured) for Danio rerio based on sex ratio, and larvae effects (Chen et al, 2015).

The CLH report states that this endpoint is supported by a 150 day LOEC of 0.00025 mg/L (nominal) equating to 0.000106 mg/L (median-measured) for Marisa cornuarietis based on egg production at 20oC (Oehlmann et al, 2006).

We do not agree that Chen et al, 2015 endpoint is reliable for hazard classification (see specific points below).

The CLH report does not include a full description of the Chen et al, 2017 study which is relevant for hazard classification as it appears to be in the same classification range as Chen et al, 2015. We have considered this study and feel the quoted 5 month NOEC of 0.000174 mg/L (quoted as mean measured) is also not reliable for hazard classification (see specific points below).

Regarding the M. cornuarietis Oehlmann et al, 2006 data, we are unclear if the study LOEC of 0.00025 mg/L (nominal) or 0.000106 (quoted as median measured) are sufficiently reliable to be considered as the key chronic classification endpoint (Aquatic classification range 0.0001 to 0.001 mg/L) or whether the study endpoint should be considered supporting information (see specific points below). This is relevant as

additional, more reliable, studies with M. cornuarietis did not replicate the same level of effects although we note differences with study design and test species.

SSD and HC5:
The CLH report includes a probabilistic SSD HC5 of 0.00805 mg/L (with lower and upper limits of 0.00017 and 0.00253 mg/L). The dataset for this value includes the Chen et al, 2015 NOEC of 0.000372 mg/L which we do not think is reliable and should therefore be removed.

We are unclear whether the nominal or median-measured LOEC from the Oehlmann et al, 2006 study is included in the dataset as both values are presented in bold formatting in the CLH report (Table 11) indicting both were included. As only one value should be included in the SSD dataset, please can the DS clarify which value has been used?

It may also be useful to calculate a HC5 including the EU, Risk Assessment Report [RAR] (EC, 2010) recalculated EC10 of 0.0021 mg/L for M. cornuarietis (see note below) in the dataset.

As the CLH report does not include a detailed discussion of the Ratte, 2015 EC10 endpoints which are based on a new statistical interpretation, we are unclear if the cited endpoint is appropriate for hazard classification and/or application in a SSD.

If the Oehlmann data are reflected in an updated SSD (noting our above points regarding Chen, et al 2015 and Ratte, 2015), it may be that a HC5 is considered protective of M. cornuarietis, meaning the HC5 could form the basis of the hazard classification.

Can the DS consider if the groups and species represented in the SSD are proportionately represented considering the anticipated mode of action?

As noted in the RAR, it would be useful to consider an SSD without algae/aquatic plants as these species may respond differently than fish and invertebrates.

In most cases the SSD includes the most sensitive species endpoint for a particular genera. However, both the Hydra vulgaris and Hydra oligactis endpoints are included in the chronic SSD in the CLH report. We note the RAR used the H. vulgaris endpoint to represent the Hydra genus and the H. oligactis endpoint was excluded because it was less sensitive and the test employed a lower number of replicates and less chemical analyses. We think that a consistent approach to use the lowest, reliable endpoint for a species or genera should be used in the SSD for the CLH.

Overall, we consider that reasons for inclusion and exclusion of endpoints in the acute and chronic SSDs should be clarified by the DS. The influence of certain omissions on the SSD should be investigated.

In addition, the choice of distribution function to fit the data should be clearly explained.

Oehlmann et al, 2006 data including Ratte, 2015:
We note that this study has been reviewed and described in the EU, Risk Assessment

Report [RAR] (EC, 2010). Several study drawbacks relating to the experimental methodology and study design were noted meaning that interpretation of the results with confidence is difficult.
For example the study was conducted during a period of non-spawning for the test organism and involved a semi-static system (renewal every 1-2 days) with only one analytical measurement of test item stability in test media over one 24 hour renewal period where the substance half-life was estimated to be ~2-3 hours. As effects on egg production were observed at all treatments at 20oC, the LOEC was considered to be 0.00025 mg/L based on nominal concentrations. It is unclear if a median measured calculation of 0.000106 mg/L for this LOEC endpoint is representative of true exposure concentrations which may have been lower. We note 'measured' endpoints have wide 95% C.I.s indicating high variability and limited confidence. Given the available analytical information, we are unclear how a time-weighted average (TWA) has been derived for the quoted 0.000028 mg/L 150-day LOEC endpoint. Please can the DS provide details of additional data/method and consider the uncertainty associated with the concentration.

Overall, the RAR did not consider the Oehlmann et al, 2006 study suitably reliable to calculate the deterministic aquatic PNEC which was based on a chronic fish endpoint of 0.016 mg/L for Fathead minnow.

The Oehlmann et al, 2006 study quoted an EC10 of 0.0000148 mg/L was not reproducible and a recalculated EC10 of 0.0021 mg/L (referenced in the RAR as van der Hoeven, 2005) was used in the chronic ecotoxicity SSD for the RAR although a sensitivity comparison also considered the 0.00025 mg/L LOEC endpoint.

As the CLH report does not include a detailed discussion of the Ratte, 2015 statistical re-evaluation and the EC10 endpoints are based on a new interpretation of the data, we are unclear if the nominal 150-d EC10 0.000038 mg/L for clutch reproduction rate (CRR) is appropriate for hazard classification. Equally, we are unclear how the TWA measurement for this endpoint was calculated. Please can the DS consider if the CRR endpoint and TWA method are valid?

Chen et al, 2015:
The study is considered to be Klimish 2 in the CLH report and was discussed at the Member State Committee (Meeting 57, 11-15 December 2017) during the SVHC identification process (https://echa.europa.eu/documents/10162/23715527/msc-57_minutes_en.pdf/11f11007-1814-48fc-5818-775f9e12e8ec).
We note there are several study deficiencies (listed below) which impact its reliability. This means we do not consider the study endpoint is valid for hazard classification.
Study limitations:
- Study not run to GLP.
- Limit test with one concentration [0.228 µg/L nominal BPA (1 nM) (mean measured based on fresh solutions only: 0.372 µg/L)] and a solvent control (0.01% DMSO) which contained BPA at a mean measured level of 0.032 µg/L.
- 150 day duration study not run to internationally validated test guideline although some exposure parameters reflected OECD TG 234.
- Semi-static system without analytical support for expired solutions – the substance is rapidly biodegradable with anticipated losses over the renewal periods (up to 5 days).
- No measurements of oxygen during the study.
- Lack of information regarding replicate variability.
- Inconsistent results with other studies (e.g. no effects on sex ratio were observed in the two other multi-generation studies (Segner et al., 2003a, Keiter et al., 2012) which were

performed at higher concentrations.

Chen et al, 2017:
The study is considered to be Klimish 2 in the CLH report. However, we note there are several study deficiencies (listed below) which impact its reliability. This means we do not consider the study endpoint is valid for hazard classification.
Study limitations:
- Study not run to GLP.
- 5 month duration study not run to internationally validated test guideline.
- Semi-static test system with inconsistent media renewal periods resulting in periods with anticipated significant losses.
- Inadequate analytical confirmation to support exposure or measured endpoints.
- Single replicates.
- Water quality parameters are not reported.
- Not all endpoints reported – including sex ratio.
- Unclear dose-response relationships for some quoted endpoints.

Lahnsteiner et al, 2005:
The study is considered to be Klimish 2 in the CLH report and used in the SSD. We note that in ECHA (2017b) also includes the following statement 'Some issues (uncertainties about acclimatisation of test animals, appropriateness of statistics, possible influence of environmental factors and lack of tank replication) were raised in the transitional report (ECHA, 2009), so it was not used for PNEC derivation.'. On the basis of these limitations, we do not think the study is robust for use in the SSD dataset.

Dossier Submitter's Response

Thank you for your comments.

Acute classification – key endpoint / Tato et al. 2018:
This study was not used in the dossiers or assessments of 4-nonylphenol or triclosan as the study is newer than these assessments and was not available at the time point of the assessment. The publication describes that the biological quality of the stock of the copepods *Acartia clausi* (obtained from a laboratory stock maintained by ECIMAT, University of Vigo) was checked using 3,5-dichorophenol as reference toxicant and that the test was conducted according to ISO guideline 14669:1999 "Determination of Acute Lethal Toxicity to Marine Copepods (*Copepoda, Crustacea*)".

Chronic classification – more detailed information on studies / (Chen et al., 2015):
It is correct that this study is not run according to GLP and a limit concentration of 0.372 µg BPA/L (mean measured) is used. It is agreed that this is not very favourable for CLP purposes as the result would underestimate the effect with a missing no effect concentration. Many test conditions are similar to the ones recommended in OECD TG 234 (as described in the CLH report). For instance the minimum volume exchanges of test solutions as well as water temperature, photoperiod, age of test organisms was adhered to. Concerning the sex ratio there was information on the replicates and their variability which was provided by the author to the eMS during the SVHC identification process. The sex ratio visually checked (based on the morphological difference of the male and the female zebrafish) by an observer blind to the treatment was in good agreement with the gonad histopathology analised with several samples using the HE staining.

F1 adult sex ratio				T test analysis	
	Male #	Female #	M / F		
Con	14	17	0,82353	Unpaired t test	
con	20	21	0,95238	P value	0,0007

con	14	16	0,875
con	15	18	0,83333
1nM	11	21	0,52381
1nM	12	18	0,66667
1nM	11	19	0,57895
1nM	10	20	0,5

P value summary	***
Significantly different? (P < 0.05)	Yes
One- or two-tailed P value?	Two-tailed
t, df	t=6.434 df=6

F2 adult sex ratio — T test analysis

	Male #	Female #	M / F
Con	14	19	0,73684
con	16	26	0,61538
con	16	17	0,94118
con	13	16	0,8125
1nM	30	59	0,50847
	9	21	0,42857
	11	20	0,55
	10	18	0,55556

Unpaired t test	
P value	0,0117
P value summary	*
Significantly different? (P < 0.05)	Yes
One- or two-tailed P value?	Two-tailed
t, df	t=3.578 df=6

… / (Chen et al., 2017):

The Bisphenol A concentrations were measured by using HPLC analysis (three replicates) on an Agilent 1200s instrument with a C18 solid phase extraction column, a Fisher HPLC grade acetonitrile and water (1:1) mobile phase and a detection by fluorescence with excitation at 229 nm and emission at 315 nm. According to the author (personal communication) at every exposure period three replicates were used. The water was filtered by reverse osmosis (pH 7.0-7.5) and Instant Ocean salt was added for a conductivity of 450 – 1000 µS/cm. Some more details on the study: Zebrafish (*Danio rerio*) (Wildtype AB strain; obtained from spawning adults with sex ratio of 1:1) were exposed to three test concentrations (nominal: 0.001, 0.01, and 0.1 µM BPA/L or mean measured: 0.228, 2.28, and 22.8 µg BPA/L) as well as a solvent control (0.01%DMSO). Semi-static test conditions (at 28°C, 14:10 dark/light photoperiod) were established taking into account the half-life for BPA degradation. Three different exposure periods (developmental stages) were realised (with 50 embryos per replicate): A) embryonic period from 6 hpf to 5 mpf; B) larval period from 6 dpf to 5 mpf, and C) sexually mature period from 3 mpf to 5 mpf. D) Adult zebrafish from the larval stage exposure period (6 dpf to 5 mpf) were paired (6 females with 6 males per replicate) to determine the spawning ability. The produced offspring was assessed for egg production, fertilisation, hatching, larval malformation, and survival rate. From the continuously collected embryos a subsample of 60 embryos per spawn were placed in 6-well plates to assess the hatching rate, malformation, and mortality (2x10 embryos → 3 replicates). Every experiment was conducted with 3 replicates. Feeding was initiated at day five. Results of the experiments were amongst others: For all experiments there was no difference in body weight or length. A) significantly reduced testis weight and sperm volume at 0.228 µg/L bu no difference for higher concentrations; B) here the testis weight was not different but the sperm volume and density was significantly lower at 0.228 µg/L; C) Here the testis weight was also not different but the sperm volume and density was significantly lower at 22.8 µg/L; D) At all concentrations the viable egg production was reduced with significant effects at 2.28 and 22.8 µg/L ($P < 0.05$). Also significantly reduced fertilisation rates were observed at the highest test concentration (22.8 µg/L) but not at lower concentrations ($P < 0.05$). The hatch rate was significantly reduced at the lower test concentrations (0.228 and 2.28 µg/L) but not at the highest one. As three concentrations are tested and a "real" NOEC was derivable, this study is even more suitable for classification and labelling purposes than (Chen et al., 2015).

… / (Lahnsteiner et al., 2005):
The cited limitations in our opinion do not devaluate the study as e.g. no chemical analysis was performed but a flow-through system and DMSO (with concentrations according to OECD recommendations) were used. Additionally, only for the endpoint time point of ovulation for which only 6 fishes were used the test is not robust enough. Therefore, the result for this endpoint was not taken into account. For the endpoints egg production and semen fertility this study is evaluated with Klimisch reliability score 2.

… / (Oehlmann et al., 2006):
The endpoint egg/clutch production (LOEC 0.00025 mg/L nominal, 0.000106 median measured) supports the concentrations from studies with fish and shows that sensitive organism groups are indeed adversely affected in this concentration range. Indeed it is the most sensitive snail species and study. However, the other studies with snails support that adverse effects on snails occur in low µg/L concentrations.

The mentioned available studies for Marisa are very different with respect to study design, test conditions and test species/strain, explaining the higher effect levels of the Warbritton/Forbes study and should be seen as differing not comparable studies.

Despite the discussed deficiencies of the Oehlmann et al. 2006 study with respect to study conditions, analytics and the statistical estimation of effect concentration, we think it is reliable with restrictions, as previously discussed and e.g. results were replicated in several experiments. Furthermore the study provides evidence for a sensitive organism group. Also the RAR at that time acknowledged the high sensitivity of this species and considered the study of Oehlmann 2006 with the lowest estimated EC10 of 0.0000148 mg/L together with an recalculated EC10 of van der Hoeven (0.0021 mg/L nominal, which is approx. 0.001 mg/L measured) and the differing study of Forbes/Warbritton (0.025 mg/l nominal, which is 0.0155 mg/L measured) for PNEC and SSD. The RAR did not recommend to use a geometric mean across the studies, as seasonality was a key factor in snail sensitivity, and the importance of the 'low dose' findings would be diluted.

The estimation of a definite effect concentration was tried by several authors, and is very difficult to determine statistically as effects were already observed at lowest tested concentrations, hence no NOEC, but only a LOEC could be determined.
The estimated EC10 of Oehlmann et al. 2006, also referred to in the RAR, was 0.0000148 mg/L.
Van der Hoeven (2005) estimated an EC10 of 0.021 mg/L (nominal), which was based on a simple linear two-parameter model (significant (p=0.02), fit not good (r2 = 0.718)) as a quadratic model did not result in a better fit. The corresponding mean measured concentrations would result in a value approximately halved. The recalculated EC10 of van der Hoeven (2005) is in our view not appropriate due to the linear regression and nominal concentration used.
A profound statistical analysis was conducted by Ratte et al. 2015 (see below), who estimated an EC10 of 0.000038 nominal (0.0000053 time-weighted average TWA) mg/L using a linear regression only between LOEC and solvent control for the most sensitive endpoint clutch/egg reproduction. Ratte 2015 recalculated concentrations based on TWA to meet the analytical challenges, noting that TWA estimations are also challenging but may be closer to internal concentrations. Details on TWA calculations can be found in the report (page 13). TWA concentrations were about 13% of nominal concentrations. These lowest observed effects occurred at the lowest tested concentration of 0.00025 mg/L nominal (corresponding to 0.000028 mg/L TWA and 0.000106 mg/L median measured).

Ratte et al. 2015 recommended to accept that the BPA concentration eliciting the effects is most probable between the TWA and the nominal concentration.
Due to the difficulties with EC10 determination, we proposed to base the effect concentration on the LOEC as this value is most certain and no extrapolation is needed as this concentration was actually tested (with clear effects observed). We also think that it is more appropriate to use measured concentrations than the nominal concentrations (as used in the RAR for the recalculation of van der Hoeven and the study of Forbes instead of the measured concentrations available). Here TWA or median measured concentrations are possible and reliable. We think that median measured is more straight forward, inbetween the nominal and TWA concentration, most probable and hence a sound estimate. Hence, we decided to use the median measured LOEC for the SSD and for the deterministic approach, being aware that this represents the most conservative and less protective approach. As BPA was rapidly removed from the test systems, actual concentrations most probably were still much lower.

Study Summary of Ratte 2015 (recalculations of Oehlmann 2006):
The study of Ratte (2015) is published and available here:
http://www.umweltbundesamt.de/publikationen/statistical-analysis-of-a-laboratory-study-about
The report of Ratte (2015) provides the results of a statistical analysis of an experiment with *Marisa cornuarietis* (Prosobranchia), published by Oehlmann et al. (2006), including recalculations of effect concentrations and exposure concentrations on the basis of the data provided by the author (test conditions: 2 replicate groups of 30 sexually mature snails, nominal BPA concentrations of 0, 0.25, 0.5, 1, and 5 µg/L and solvent control, 5 months exposure; semistatic renewal system; 8 samples for analytics over 1 day after 1 month exposure; endpoints: survival over time, sex ratio at study end, number of superfemales at study end, cumulative number of eggs, cumulative number of clutches, number of eggs per clutch; mortality and induction of superfemales (NOEC 0.25 µg/L, 0.028 µg/L TWA) caused by BPA, no effect on sex ratio). From the input variables the following endpoints were calculated: cumulative number of eggs per female alive, the cumulative number of clutches per female alive, and the egg and clutch reproduction rates. Among the reproduction parameters the clutch reproduction rate and the egg reproduction rate proved to be the variables of choice to compute time-independent toxicity parameters. As the statistical design does not allow to determine NOECs as effects already occurred at the lowest test concentration of 0.25 µg/L, ECx were computed using a raw estimation of the concentration-response-relationship between the solvent control and the 0.25 µg/L BPA-treatment by linear interpolation. As the BPA concentration was found to decrease rapidly in the experimental vessels, which does not allow basing the risk assessment on nominal concentrations, time-weighted average concentrations (TWA) were calculated in addition to median measured concentrations. Although some uncertainties remain with respect to TWA concentration, these might be closer to the internal effective concentrations.
The clutch reproduction rate with an EC10 of 0,038 nominal (0,0053 TWA) µg/L BPA was the most sensitive variable, followed by the cumulative number of eggs per female with an EC10 of 0.039 (0,0055 TWA) µg/L BPA and the egg reproduction rate with an EC10 of 0,43 (0,0059 TWA) µg/L BPA. Relative to the estimated solvent-control reproduction rates the rates found here under presence of BPA reflect an induction of less than 10%. The nominal effect concentration, where definite effects occurred on clutch/egg reproduction rate and number of eggs per female is 0.25 µg/L and corresponds to a LOEC. For this nominal concentration, the median measured concentration is 0.106 µg/L and the concentration based on TWA is 0.028 µg/L. As this was the lowest tested concentration, a NOEC determination is not possible (NOEC ≤ 0.25 µg/L), and the EC10 estimations are very challenging.

Values used for SSD
In table 11, two values were un-intentionally bolded (indicating the use for SSD) for the endpoint for the species *Marisa cornuarietis* (Oehlmann et al., 2006). Only one value was used for the SSD as also described in chapter 11.6.2: 0.000106 mg/L (median measured concentration).
We agree that the lowest, reliable endpoint for a species or genera should be used in the SSD for the CLH. As the estimation of a EC10 is extremly difficult we find basing the definite concentration on the LOEC for the most sensitive endpoint most reliable in this case. Nominal values should no be used due to the loss in test systems.

Calculations of SSD:
For the SSD we included the most sensitive reliable endpoints and stated the reasons for it. We also checked the influence of inclusion/exclusion of values after the received comments. (see additional document)

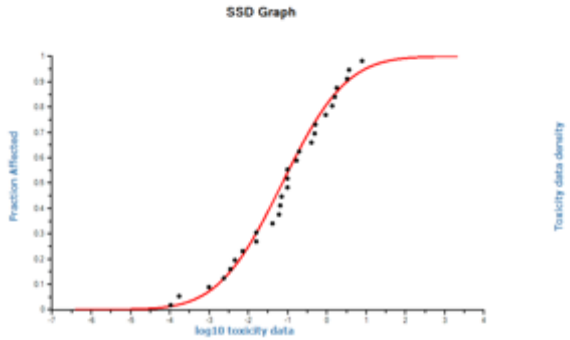
Hydra vulgaris and *Hydra oligactis* endpoints in SSD:
We agree that only the lowest value for one species or genera should be used and therefore the less sensitive value of *H. oligactis* can be excluded (see attached document with different SSD calculations taking the different comments into account).

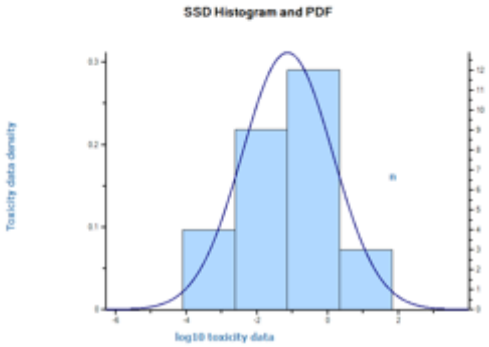
In- or excluding Algae and aquatic plants in the SSD:
We agree that algae and plants may respond differently than fish and invertebrates. Therefore, we included some SSD calculations in the attached document with and without algae and aquatic plants to show the differences.

New SSD:
Taking into account the received comments on the more sensitive endpoints, i.e. not excluding the NOECs from algae and aquatic plant species, including the more sensitive NOEC-value for *Cyprinus carpio* from (Bowmer & Gimeno, 2001) and the NOEC for *Danio rerio* from (Chen et al.,2017) (instead of Chen et al., 2015), excluding the value for the second Hydra species *H. oligactis*, and maintaining the value for Marisa cornurietis, the SSD calculated with ETX 2.1 (RIVM 2014) results in a HC_5 of 0.543 µg/L. We decided not to exclude algae and aquatic plant data as the ECHA Guidance R.10 chapter R.10.3.1.3 describes that the "information on the mode of action of the chemical" is important, in order to "exclude possible over-representation of certain taxonomic groups". With the data (2 algae and 1 aquatic plant) in our opinion this situation is taken into account. In the following the "final" SSD can be found:

Input toxicity data			
Data no	Toxicity data	Label	
1	0,016	Cyprinus (Bowmer&Gimeno, 2001))	
2	0,000174	Danio (Chen et al., 2017)	
3	0,06	Oryzias (Sun et al., 2014)	
4	3,64	Oncorhynchus (Bayer AG, 1999)	
5	0,016	Pimephales (Sumpter et al., 2001)	
6	0,0024	Salmo (Lahnsteiner et al., 2005)	
7	0,5	Poecilia (Kinnberg and Toft, 2003)	
8	0,066	Cyprinodon (Mihaich et al., 2018)	
9	3,23	Daphnia (geomean)	
10	0,94	Ceriodaphnia (Tatarazako et al., 2002)	
11	0,1	Acartia (Andersen et al., 2001)	
12	0,001	Tigriopus (Marcial et al., 2003)	
13	0,49	Hyalella (Mihaich et al., 2009)	
14	0,17	Americamysis (Mihaich et al., 2018)	
15	0,1	Chironomus (Watts et al., 2003)	
16	0,000106	Marisa (Oehlmann et al., 2006)	
17	0,0046	Potamopyrgus (Sieratowicz et al., 2011)	
18	0,2	Planorbis (Benstead, 2010)	
19	0,1	Physa (Sanches-Arguello et al., 2012)	
20	0,0035	Paracentrotus (Özlem and Hatice, 2008)	
21	0,071	Hemicentrotus (Kiyomoto et al., 2005)	
22	1,6	Heteromyenia (Hill et al., 2002)	
23	0,042	Hydra vulgaris (Pascoe et al., 2002)	
24	1,8	Brachiomus (Mihaich et al., 2009)	
25	1,36	Pseudokirchneriella (Alexander et al., 1988)	
26	0,4	Skeletonema (Alexander et al., 1988)	
27	7,8	Lemna (Putt, 2003)	
28	0,0073	Xenopus (geomean Levy Pickford)	

Anderson-Darling test for normality				
Sign. level	Critical	Normal?		
0,1	0,631	Accepted		
0,05	0,752	Accepted	AD Statistic:	0,32629539
0,025	0,873	Accepted	n:	28
0,01	1,035	Accepted		
Kolmogorov-Smirnov test for normality				
Sign. level	Critical	Normal?		
0,1	0,819	Accepted		
0,05	0,895	Accepted	KS Statistic:	0,62870954
0,025	0,995	Accepted	n:	28
0,01	1,035	Accepted		
Cramer von Mises test for normality				
Sign. level	Critical	Normal?		
0,1	0,104	Accepted		
0,05	0,126	Accepted	CM Statistic:	0,04538654
0,025	0,148	Accepted	n:	28
0,01	0,179	Accepted		





RAC's response

Thank you for your comments.

Comments regarding aquatic acute classification – key endpoint

Tato et al., 2018

RAC appreciates the clarification provided by the Dossier Submiter. The view of the commenting MS regarding the appropriate study reliability rating and deficiencies are noted by RAC. Comprehensive analyses of the study by RAC is provided in the ODD. Concerning the Tato et al. 2018 study, the view of the RAC is that despite the shortcomings pointed out by the commenting Member State, RAC considers the 48-h LC_{50} (survival) of 0.885 mg/L (measured) for marine copepod *Acartia clause* as relevant and reliable result therefore is appropriate to use the study as the key study for setting the aquatic acute hazard classification.

Chen et al., 2015

RAC considers the endpoint from the Chen et al., 2015 relevant and reliable and will be used for classification purposes. Please see comprehensive analysis of the study by RAC in the BD. RAC would like to thank the DS for additional data concerning sex ratio.

Chen et al., 2017
RAC support DS for the reliability of the study of Chen et al., 2017. RAC considers the endpoint from Chen et al., 2017 study reliable and relevant and accepted this study for classification. Please see comprehensive analysis of the study by RAC in the BD.

Lahnsteiner et al., 2005

For the reasons explained in the ODD and BD, RAC believes that the study is not realiable and cannot be considered in classification.

Oehlmann et al., 2006
RAC agree with DS that LOEC of 0.000106 mg/L based on median measured concentration is most appropriate value and will be considered in classification.

Values used for SSD
Clarification concerning the value (0.000106 mg/L (median measured concentration)) for the species *Marisa cornuarietis* (Oehlmann et al., 2006) used for derivation of SSD is noted by RAC.

Calculation of SSD
RAC appreciates the clarification by the DS regarding the use of data for calculation of SSD (inclusion/exclusion of endpoints, influence of certain omissions, choice of distribution function to fit the data, etc.).

Hydra vulgaris and *Hydra oligactis* endpoints in SSD
RAC agrees with the Dossier submitter and commenting Member State that only the lowest value for one species or genera should be used. This is also in line with REACH guidance (IR&CSA, Chapter R.10, section R.10.3.1.3). RAC agrees that the *H. vulgaris* endpoint to represent the Hydra genus should be used for SSD. RAC notes that the same endpoint was also selected by commentator in SSD.

In- or excluding Algae and aquatic plants in the SSD
Explanation regarding including/excluding algae data in the SSD is noted by RAC.

New SSD
Noted by RAC.

Date	Country	Organisation	Type of Organisation	Comment number
30.08.2019	Belgium		MemberState	3
Comment received				
BE CA thanks BauA for the submission of the CLH proposal for the substance Bisphenol A. Based on the available information in the CLH report, BE CA supports the proposed classification for the environment: - Aquatic Acute 1, H400 with Macute=1 - Aquatic Chronic 1, H410 with Mchronic=10 but has some remarks/questions : 1. Environmental toxicity: Indeed there are a lot of data available for Bisphenol A. However BE CA regrets that only				

few studies are described more in detail in the CLH report. At least more info could have been provided for the studies used in the SSD (purity, test regime, concentration maintained, …).

Some of the results of the reported studies in the CLH report are nominal values without the performance of analytical monitoring. Thus no information is available on whether the tested concentrations were maintained in these studies, as in Stephenson (1983), Anderson et al (2001),… BPA is considered rapidly degradable and moderately adsorbs to solids, therefore L(E)50/NOEC might have been lower than the reported value, especially under static and semi-static test system.

Furthermore, although this is not recommended in OECD guidelines, in some studies (even recent ones), a vehicle was used while the substance is very soluble in water. Was a vehicle control run in parallel?

Acute toxicity:
For the acute toxicity of Daphnia magna a geometric mean of 9.47 mg/L was used calculated from 8 values, while 9 reliable studies are mentioned in table 10.

Section 11.43. acute toxicity to algae :
- Although both EC50 values of the Alexander et al (1988) study are based upon changes in biomass, one of the values (3.10 mg/l) is reported in table 10 as an ErC50.
- the supporting Stephenson, 1983- study is briefly described. However this study is not listed in table 10, nor in the references list. Was this also published in Alexander et al, 1988?

Chronic toxicity:
In the chronic study of Bowmer and Gimeno (2001) a NOEC of 0.016 mg/L was reported for effects on oviduct formation in male carp. It is not clear why this NOEC was not taken into account for SSD. Instead the NOECgrowth of 0.1 mg/L was used.

Although it does not impact the classification proposal, we wonder why the NOEC of 0.00017mg/L for Danio rerio (Chen et al, 2017 with reliability 2) is not considered the lowest chronic value for fish. Instead it is concluded that the most protective valid long-term toxicity no (in this case: lowest) observed effect concentration is 0.000372 mg/L (Chen et al, 2015).

2. Degradation:
Ready biodegradability studies:
Conclusion that bisphenol A is readily biodegradable can, following the CLP guidance, be based on the positive results (irrespective of negative results) of scientific good quality and well documented studies performed. In this case based on positive results in studies performed according to OECD 301 F. However the 3 studies according to OECD301 B, C and D that showed no ready degradation, are given the same reliability (inherent quality of the test report) as the OECD 301 F studies. However no further explanation/clarification is given for the divergent equally reliable results.

Simulation studies:
In the Klečka et al. study (2001) water was taken upstream and downstream of STPs treating Bisphenol A. In our opinion the inoculum may to a greater or lesser extent be adapted to Bisphenol A leading to an improved biodegradation capacity.

For the other freshwater studies only primary degradation is reported. Although half-lifes

are <16days, no information is given on the classification of the degradation products.

Dossier Submitter's Response

Thank you for your comments.

1. Environmental toxicity:

Unfortunately, most study descriptions unintentionally appeared in a confidential annex. In the attached document the study descriptions can be found:

[Document: 20190924_CLH_BPA_Annex_UBA]

Details on studies:
In the light of the very comprehensive data set and available previous evaluations, e.g. EU Risk Assessment Report (EU, 2010) or SVHC identification, we tried to keep the CLH dossier readable and focused on the main results and arguments, providing detailed data only in the Annex (see above).

For some studies only nominal concentrations were reported and hence represent the most conservative case (as for e.g. Stephenson and Anderson).
Concerning the use of a vehicle/solvent control: yes, for the respective studies a solvent control was used (see attached document with study descriptions).

Acute toxicity - *Daphnia*:
For *Daphnia magna* one result is indeed missing in the calculation of the geometric mean. Taking all 9 values into account the result is a EC_{50} of 9.88 mg/L (instead of 9.47 mg/L).

Acute toxicity – algae study Alexander et al. (1988): We wanted to be consistent with the assessment of e.g. the Risk Assessment Report (European Commission, 2010). The UK MSCA already evaluated this study and considered it as valid. We reviewed the study again and adopted it for the CLH report. You are right that both EC_{50}-values of the Alexander et al. (1988)-study are based upon biomass changes.

Acute toxicity – algae study Stephenson (1983): as described in the CLH report, this study was cited from the Risk Assessment Report (European Commission, 2010). This study is not publically available but supports the results of (Alexander et al., 1988).

Chronic toxicity:
Concering the NOECs from (Bowmer and Gimeno, 2001) for oviduct formation (NOEC= 0.016 mg/L) and (Chen et al., 2017) for reduced egg production (NOEC= 0.000174 mg/L) we agree that these NOECs should be taken into account for the SSD.
We also agree 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) (as this test was a limit test).

New SSD calculation
Including the other values for *Cyprinus carpio* and *Danio* (Bowmer and Gimeno, 2001; Chen et al., 2017) you proposed and removing the second *Hydra spp.*, the resulting HC_5 is 0.000543 mg/L. For the input toxicity data and parameter as well as the goodness-of-fit data please see the answer to comment number 2.

2. Degradation:
The evaluation of the degradation of Bisphenol A is based on a weight of evidence approach.

Ready biodegradability studies
All studies on ready biodegradability have the same reliability (reliable with restriction; deviations are mentioned in the report). Hence, all studies are equivalent based on their reliability. As the studies with positive results are of good scientific quality and the test conditions are well documented, these results were used for the conclusion of the ready biodegradability.

Simulation studies
It is possible that the inoculum in the study of Klečka et al. (2001) was adopted to Bisphenol A due to the sampling location near to a wastewater treatment plant treating Bisphenol A. Nevertheless, the half-life is in the order of magnitude of the half-lives from the studies investigating primary degradation. Unfortunately, no degradation products were given in the studies on primary degradation. Only the study from Ike et al. (2000) identified and mentioned metabolites.

Based on the available results and the weight of evidence approach Bisphenol A should be considered as rapidly degradable for classification purposes.

RAC's response

Thank you for your comments.

RAC notes the support for the proposed acute and chronic environmental hazard classification of Bisphenol A.

Comment on details on studies
Clarifications concerning nominal values and solvent control are noted by RAC.

Acute toxicity - *Daphnia*
RAC agrees thet the geometric mean 9.88 mg/L based on nine toxicity values for *Daphnia magna* (recalculated after public consultation) should be used as a representative toxicity value for this species.

Acute toxicity – algae study Alexander et al. (1988) and Stephenson (1983)
Clarifications provided by Dossier Submiter are noted by RAC.

Chronic toxicity
Clarifications provided by Dossier Submiter are noted by RAC.

New SSD calculation
Noted by RAC.

Comments on degradation
RAC agrees with the Dossier Submitter that Bisphenol A should be considered readily biodegradable following following the three valid OECD TG 301F studies and the 10-day window criteria being fulfilled, including the use of non-adapted inoculum. RAC agrees with the Dossier Submiter that Bisphenol A should be considered as rapidly degradable for classification purposes.

Date	Country	Organisation	Type of Organisation	Comment number
30.08.2019	Belgium	PlasticsEurope	Industry or trade association	4
Comment received				

Submission by Plastics Europe Polycarbonate/Bisphenol A Group (PC/BPA Group) on the CLH report for Bisphenol A (April 2019)

Acute aquatic toxicity

Regulatory provisions

Regulation (EC) No 1272/2008 of the European Parliament and of the Council (CLP-Regulation) provides the legal basis for the classification of substances and mixtures. Part 4 of Annex I of the CLP-Regulation sets out the criteria with regard to environmental hazards and also sets out additional provisions on how the criteria may be met.
Regulation (EC) No 1272/2008, Annex I, Part 4, 4.1.2.7.1.:
"Acute aquatic toxicity is normally determined using a fish 96 hour LC50, a crustacea species 48 hour EC50 and/or an algal species 72- or 96 hour EC50. These species cover a range of trophic levels and taxa and are considered as surrogate for all aquatic organisms. Data on other species (e.g. Lemna spp.) shall also be considered if the test methodology is suitable. The aquatic plant growth inhibition tests are normally considered as chronic tests but the EC50s are treated as acute values for classification purposes (…)."

Dataset on acute aquatic toxicity for Bisphenol A

The dataset in the CLH report on acute aquatic toxicity consists of a selection of studies which is partly based on inappropriate reliability ratings of scientific studies. Specifically, it comprises various studies that do not meet the minimum requirements for scientific reliability, and thus, are not adequate for classification purposes.
The inappropriate reliability rating is of specific relevance for Tato et al. 2018, as this study is determinant for the proposed classification for acute toxicity. Despite its rating in the CLH report as "reliable without restriction" (Klimisch 1), this study can only be rated "reliable with restrictions" (Klimisch 2) due to significant deviations from the respective guideline, detailed further below. For large datasets, as is the case for BPA, preference should be given to fully reliable studies (Klimisch 1), as repeatedly stated in the CLP guidance document (2017).
Furthermore, relevant studies with adequate reliability (Klimisch 1 or 2) are missing in the CLH report. Studies by Reiff and Phil (1979), Bayer AG (1989), Andersen et al. (2001), Kusk and Wollenberger (1999), Hughes et al. (2006) published as Mihaich et al. (2009), and Stephenson (1983) are reliable (Klimisch 1 or 2).

Table 1 provides a list of all studies on acute aquatic toxicity which are regarded as "reliable without restriction" or "reliable with restrictions" (Klimisch 1 and 2) according to the reliability criteria as outlined in Annex 1. The partly deviating reliability ratings as provided in the CLH report are included for comparison.

Table 1. List of reliable and relevant studies (Klimisch 1 and 2) on acute aquatic toxicity, appropriate for use for CLP classification. Studies with inappropriate Klimisch ratings and studies missing in the CLH report are highlighted in red. Concordance of Klimisch ratings is highlighted in green.
See Annex 0 - Tables and Figures

Table 2. Studies on acute aquatic toxicity listed in the CLH report with due to major shortcomings should not be used for CLP classification. Appropriate ratings of these studies are "not reliable", Klimisch 3, or "not assignable", Klimisch 4.
See Annex 0 - Tables and Figures

Acute aquatic toxicity to fish
According to CLP-Regulation, Annex I, Part 4 section 4.1.2.7.1: "Acute aquatic toxicity is normally determined using a fish 96 hour LC50…".
In the CLH report, there are three fully reliable (Klimisch 1) studies on fish reporting 96-h LC50 values relevant for classification:
• Alexander et al. (1985a) conducted a study according to test method ASTM E729-80, which is equivalent/similar to OECD 203, under GLP with Pimephales promelas reporting of a 96-h LC50 of 4.6 mg/L. This study is unanimously rated as "reliable without restriction" (Klimisch 1). (Published in Alexander et al., 1988)
• Sayers (2009) performed a study according to OECD 203 under GLP with Cyprinodon variegatus and determined a 96-h LC50 of 11 mg/L.
• Springborn Bionomics (1985a) performed a study according to OECD 203 under GLP with Menidia menidia and reported a 96-h LC50 of 9.4 mg/L. (Springborn Bionomics (1985a), published in Alexander et al. (1988))
There are several Klimisch 2 studies on acute fish toxicity with several fish species which report of 96-h LC50 values in the range of 3.0 to 9.9 mg/L and which support the results of the Klimisch 1 studies (Table 1).
In conclusion, the 96-h LC50 of 4.6 mg/L reported by Alexander et al. (1985a) for fish is the lowest fully reliable (Klimisch 1) value for aquatic acute toxicity and is thus relevant for aquatic acute classification.

Acute aquatic toxicity to Crustacea

According to CLP-Regulation, Annex I, Part 4, section 4.1.2.7.1: "Acute aquatic toxicity is normally determined using … a crustacea species 48 hour EC50…"
The aquatic acute classification proposal in the CLH report is mainly based on the study by Tato et al. 2018 on Acartia clausi. This study is rated in the CLH report to be fully reliable (Klimisch 1) and relevant for classification. However, the appropriate rating for this study is "reliable with restrictions" (Klimisch 2), as it deviated clearly from the referenced guideline, e.g. using another test species, use of nauplii instead of adults, lack of transparency on test concentrations, and incomplete documentation (see annex 2). Therefore, Tato et al., 2018, may only be considered as reliable with restrictions (Klimisch 2).
There are, however, two fully reliable (Klimisch 1) studies for crustaceans available:
• Springborn Bionomics (1985b) on Americamysis bahia, conducted according to ASTM E 729-80 under GLP, reported a 96-h LC50 of 1.1 mg/L. Even though the test duration of this study was longer than the standard 48 h for Daphnia, it is considered relevant for acute aquatic toxicity classification in a conservative approach (published in Alexander et al. (1988)).
• Alexander et al. (1985c) on Daphnia magna, conducted according to ASTM E 729-80 under GLP, reporting of a 48-h LC50 of 10.2 mg/L (published in Alexander et al. (1988)).

Besides the Tato et al. 2018 study, which reports a 48-h LC50 of 0.89 mg/L, there are several additional Klimisch 2 acute studies with several crustacean test species which report 48-h LC50 in the range of 3.4 to 34.7 mg/L. There is also a 240-h LC50 with the crustacean Gammarus pulex of 1.5 mg/L. These study results support the results of the Klimisch 1 studies (see table 1).

There are some further studies on crustaceans listed in the CLH report which, based on the reported effect levels, could also be of relevance for aquatic acute classification. However, their reliability rating in the CLH report is not appropriate. Due to major

deficiencies, these studies should not be used for classification:
• Whereas considered as Klimisch 2 in the CLH report, the publication of Andersen et al. (1999) on Acartia tonsa does not provide necessary information on concentrations tested, on analytical confirmation of tested concentrations, on number and age of animals used, or on validity criteria. The reliability rating should be (Klimisch 3). The study is not appropriate for CLP classification.
• The publication of Hirano et al. (2004) on Americamysis bahia, rated as Klimisch 2 in the CLH report provides little information on the test design. Hence, Hirano et al. (2004) is rated Klimisch 4 (not assignable). The publication is not appropriate for classification purposes.

Daphnia is the preferred crustacean as stated in the REACH guidance, Chapter R.7b (ECHA 2017) when assessing organisms at the three trophic levels. This is logical given that more studies would be performed with Daphnia for regulatory purposes, allowing comparisons of hazards between substances to be made with the same species. However, as there are two fully reliable (Klimisch 1) studies with crustacea, the conservative approach would be to use the 96-h LC50 of 1.1 mg/L from the study with Americamysis bahia (Springborn Bionomics, 1985b) for CLP purposes.

In conclusion, the lowest effect level for crustaceans relevant for aquatic acute classification based on a fully reliable study is the 96-h LC50 of 1.1 mg/L on Americamysis bahia reported by Springborn Bionomics (1985b), published in Alexander et al. (1988).

Acute aquatic toxicity to Algae

According to CLP-Regulation, Annex I, Part 4. section 4.1.2.7.1: "Acute aquatic toxicity is normally determined using … an algal species 72- or 96-hour EC50…"

There are two studies on algae which are rated fully reliable (Klimisch 1) when the reliability criteria are appropriately applied:
• One study on Pseudokirchneriella subcapitata, conducted according to EPA 600/9-78-018 under GLP, reports of a 96-h EbC50 of 2.7 mg/L (Alexander et al. 1985b, published in Alexander et al., 1988).
• Another fully reliable (Klimisch 1) study is with Skeletonema costatum, conducted according to EPA 560/6-82-002 under GLP, with a 96-h EbC50 of 1.1 mg/L (Springborn Bionomics 1985c, published in Alexander et al. 1988).

In the CLH report, both studies are inappropriately rated as Klimisch 2.

There is also a fully reliable (Klimisch 1) study on aquatic plants, Lemna gibba, conducted according to OECD 221 under GLP, which reports a 7-day EC50 of 20 mg/L (Putt 2003, published in Mihaich et al. 2009).

Additional studies on algae, rated as "reliable with restrictions" (Klimisch 2), reporting 96-h ErC50 of 2.5 and 3.73 mg/L support the effect levels determined in the Klimisch 1 studies (see table 1).

In conclusion, the lowest valid effect level for algae relevant for aquatic acute classification is the 96 h-EbC50 of 1.1 mg/L with Skeletonema costatum (Springborn Bionomics 1985c, published in Alexander 1988).

Acute aquatic toxicity to other taxa

The CLH report includes several studies with taxa other than fish, crustacea, algae/aquatic plants despite the provisions of the CLP-Regulation, Annex I, Part 4, section 4.1.2.7.1: "Acute aquatic toxicity is normally determined using a fish 96 hour LC50, a crustacea species 48 hour EC50 and/or an algal species 72- or 96-hour EC50. These species cover a range of trophic levels and taxa and are considered as surrogate for all aquatic organisms. Data on other species (e.g. Lemna spp.) shall also be considered if the test methodology is suitable. …"

However, to use any data for CLP purposes, including those for other taxa, the prerequisite of an appropriate study reliability applies.

Some of these data included in the CLH report on taxa other than fish, crustacea, and algae might potentially be considered relevant for aquatic acute classification based on the reported effect levels. However, the reliability rating in the CLH report for many of these studies is not appropriate. Due to major deficiencies, many of these studies do not meet the minimum requirements for reliability, as briefly outlined below and further discussed in respective annexes (see annex 2, 5). Hence these data should not be used in any considerations regarding classification of BPA.

For example, in contrast to the assessment by the German authorities, the publication by Arslan and Parlak (2008, erroneously quoted as "Özlem and Hatice 2008" throughout the CLH report) on Paracentrotus lividus is neither fully reliable (Klimisch 1) nor reliable with restrictions (Klimisch 2). Due to methodological and reporting deficiencies, such as no analytical confirmation of test concentrations and lack of key experimental information in the manuscript (e.g., amount of sperm, eggs, number of embryos and animals used, replication), as well as unclear relevance of the reported endpoints, the study by Arslan and Parlak (2008) should be rated "not reliable" (Klimisch 3) (see also annex 2). Thus, the results are not appropriate for use in CLP classification.

Although not included in Table 10 nor in the reference list of the CLH report, the study by Roepke et al. (2005) on Strongylocentrotus purpuratus is discussed in Chapter 11.4.2 (page 17) and Chapter 11.5.2 (page 27). In light of the major deficiencies in the paper by Roepke et al.(2005), especially with regard to lacking information on the actual concentrations, the missing information on controls, no analytical determination of actual BPA concentrations and the equivocal description of developmental changes (e.g., how is this related to ultimate survival, what is the normal variability of these endpoints, and how was they quantitatively assessed?) the study by Roepke et al. (2005) should be rated "not reliable" (Klimisch 3). Hence this study is not appropriate for classification purposes (see also Annex 2).

There are a number of studies on other taxa with appropriate reliability ratings of Klimisch 1 or 2.

- The studies by Warbritton, (2005), and Hughes, (2006), both published in Mihaich et al., (2009), investigated effects on the snail Marisa cornuarietis with 96-h LC50 of 2.24 mg/L 96-h LC50 > 4.03 mg/L (no effect up to highest test concentration)(Klimisch 2).
- The study by Pascoe et al., 2002, which used Hydra vulgaris, reported a 96-h LC50 of 6.9 mg/L, (Klimisch 2).
- Li, 2013, assessed Dugesia japonica according to ISO 6341 and reported a 48-h LC50 of 8.3 mg/L (Klimisch 2)
- Chironomus tentans was the test organism in a study conducted according to EPA-540/9-85-005 which received the score Klimisch 1, reporting a 96-h LC50 of 2.7 mg/L

(Springborn Smithers, 2005, published in Mihaich et al. 2009).
• Finally, the amphibian Rhinella arenarum was the focus of a 168-h study with a reported LC50 of 7.1 mg/L, Klimisch 2 (Hutler Wolkowicz et al., 2014).

Thus, on the other taxa, a range of effect levels (LC/EC50) from 2.24 to 8.3 mg/L was identified. This range is similar to that of the core dataset with fish, invertebrates, and algae. The Klimisch 1 studies identified in the core dataset report lower effect levels and, thus, the other taxa have no impact on the CLP conclusion on acute aquatic toxicity.

Conclusion on acute aquatic toxicity classification

Following the CLP guidance document (2017) general considerations for evaluation of larger data sets (section 4.1.3.2.1), studies with the highest reliability (Klimisch 1) should be considered with preference to derive the appropriate aquatic acute toxicity level. Fully reliable Klimisch 1 studies representing the three trophic levels required for CLP classification and with the lowest effect levels for fish, crustacea, and algae are listed in the table below. It is clearly stated in the CLP guidance document to only consider these taxa for CLP classification when the database is sufficiently robust, which is clearly the case for Bisphenol A.

Table 3. Reliable (Klimisch 1) studies with Bisphenol A for each of three trophic levels relevant for CLP classification for acute aquatic toxicity
See Annex 0 - Tables and Figures

Based on the core data set of fully reliable (Klimisch 1) and relevant results of the three relevant taxonomic groups of fish, crustacea and algae, all LC/EC50 values are > 1 mg/L. A classification as Aquatic Acute Category 1 which was proposed in the CLH report is therefore not justified.

Chronic aquatic toxicity

Dataset on aquatic chronic toxicity for BPA

The dataset in the CLH report on aquatic chronic toxicity consists of a selection of studies of which several were attributed inadequate reliability ratings. Thus, it comprises various studies that do not meet the minimum requirements for reliability, and should not be taken into account for classification purposes. This is particularly true for Chen et al., 2015, and Oehlmann et al., 2006, as in the CLH report both studies are determinant for the proposed chronic toxicity classification. The report rated both studies as "reliable with restrictions" (Klimisch 2). Chen et al., 2015, is referenced to report the lowest LOEC for fish and Oehlmann et al., 2006, the lowest LOEC/EC10 for molluscs. However, both studies reveal serious deficiencies which disqualify them, wherefore they should be rated "not reliable" (Klimisch 3). Both studies are not sufficiently reliable and should be disregarded for CLP classification.

Further studies were used in the CLH report to support the findings of Oehlmann et al., 2006, and Chen et al., 2015,. However, these studies had received inadequate reliability ratings and should not be considered for CLP classification purposes. Study shortcomings are discussed in annex 3 and 4. Diverging Klimisch reliability scores on aquatic chronic toxicity data in the CLH report and the current comments on that report are made transparent in table 4 and 5. It shall be highlighted that for most studies the Klimisch scores were identical, while some studies did not fulfil the minimum requirements for reliability and should be disregarded.

All studies on chronic aquatic toxicity which are regarded as reliable and relevant for CLP classification – "reliable without restriction" (Klimisch 1) or "reliable with restrictions" (Klimisch 2), according to an appropriate reliability rating, are indicated in table 4. All data which are not reliable and relevant for CLP classification purposes are compiled in table 5.

In addition to the shortcomings of several studies, there are some reliable and relevant studies on aquatic chronic toxicity which are missing in the CLH report. These are also listed in table 4 and indicated as "missing in CLH report".

Table 4: List of reliable and relevant studies on aquatic chronic toxicity appropriate for CLP classification. Studies with inappropriate ratings in the CLH report and missing studies are highlighted in red. Data used in the supportive SSD approach are marked in bold.
See Annex 0 - Tables and Figures

Table 5: Studies on aquatic chronic toxicity listed in the CLH report which due to major shortcomings should not be used for CLP classification. These studies were evaluated and received ratings as "not reliable", Klimisch 3, or "not assignable", Klimisch 4.
See Annex 0 - Tables and Figures

Chronic aquatic toxicity to fish

The CLP Regulation stipulates that usually fish should be used to define the appropriate hazard category, besides crustaceans and algae: "For the long-term (chronic) hazard, separate hazard categories are defined representing a gradation in the level of hazard identified. The lowest of the available toxicity values between and within the different trophic levels (fish, crustacean, algae/aquatic plants) shall normally be used to define the appropriate hazard category(ies)."

In the CLH report the chronic fish study of Chen et al., 2015, with Danio rerio was indicated as the study with the lowest NOEC and the study was considered as "reliable with restrictions" (Klimisch 2). However, this study suffers from serious deficiencies in experimental design and the lack of information which is important to conclude on the study reliability. The major shortcomings are:
• There was only one test concentration.
• Insufficient documentation (incomplete or missing at all).
• Lack of a blank control.
• Contaminated test system as BPA was detected in the control and only a factor 10 below the test concentration.
• Endpoint sex ratio shift may only reliably be determined based on histopathology while the authors mention visual inspection at least for the majority of fish.

Further details on the shortcomings of Chen et al., 2015, are provided in annex 3. Based on these major shortcomings and deviations from requirements in validated test methods (e.g. OECD), this study should be rated "not reliable" (Klimisch 3) and not be considered for CLP classification.

There are some more studies on fish listed in the CLH report on chronic aquatic toxicity describing NOECs below the threshold of 0.01 mg/L of CLP category 1 for chronic toxicity, namely Lahnsteiner et al., 2005, Chen et al., 2017, and Keiter et al., 2012. All of them are rated as reliable with restrictions (Klimisch 2) in the CLH report. However, due to

major deficiencies these studies should be rated as "not reliable" (Klimisch 3) and not be used for CLP classification purposes. Major shortcomings were e.g. insufficient number of test animals and replication, lack of histological examination to determine the sex, inconclusiveness of reported effects, incorrect statistical evaluation methods, and basic study validity criteria not met. Details on the deficiencies of these studies are provided in Annex 3.

In addition to the studies with deficiencies which report of NOECs below the threshold for chronic toxicity, category 1, there are also several studies which report of NOECs above the threshold, such as Bhandari et al., 2015, Chen et al., 2017 as well as Shioda and Wakabayashi, 2000. These studies should equally be rated as "not reliable" (Klimisch 3). Shortcomings of these studies are exemplarily detailed in Annex 3.

Contrary to the studies which do not meet the minimum requirements regarding study reliability, there are 12 chronic studies on fish of which 5, based on an appropriate reliability rating, are "reliable without restriction" (Klimisch 1). Three of these 5 studies were also rated Klimisch 1 in the CLH report:

• Rhodes et al., 2008, on Pimephales promelas performed according to EPA OPP 72-5, under GLP conditions, reporting of a 164 d-NOEC of 0.160 mg/L based on adult mortality.
• York, 2010, on Cyprinodon variegatus, conducted according to EPA OPPTS 850.1500, performed under GLP conditions, reporting of a 116 d-NOEC of 0.066 mg/L based on reproduction.
• Bayer AG, 1999, on Oncorhynchus mykiss performed, according to OECD 215, under GLP conditions, reporting on a 28 d-NOEC of 3.64 mg/L based on juvenile growth.

Two further studies with fish are either missing in the CLH report or rated as "reliable with restrictions" (Klimisch 2). For both studies an appropriate rating should be "reliable without restriction" (Klimisch 1) as these were conducted according to validated test methods and used reliable documentation systems (GLP):

• Caunter et al., 1999, on Pimephales promelas, according to OECD 210, performed under GLP, reporting of a 36-d NOEC of 0.64 mg/L on hatchability, survival and growth.
• Sumpter et al., 2001, on Pimephales promelas, according to EPA OPP 72-5 (431 day multi-generational study), performed under GLP, reporting of a NOEC of 0.016 mg/L on F2 egg hatchability.

The reliable and relevant NOECs of all fully reliable Klimisch 1 studies range from 0.016 to 3.64 mg/L.

Additionally, there are 7 further studies which are "reliable with restrictions" (Klimisch 2) that support the fully reliable data. These data cover three fish species, were conducted equivalent or similar to validated test methods, and report of NOEC (and one LOEC) in the range of 0.05 to 0.84 mg/L based on mortality, growth, development, and reproduction (more details are provided in table 4).

In accordance with the CLP guidance document, the reliable (Klimisch 1) studies with fish should be used with preference for the CLP classification based on the deterministic approach. Following this approach, the lowest valid NOEC on fish relevant for aquatic chronic classification is 0.016 mg/L, based on Sumpter et al., 2001, on Pimephales promelas.

Chronic toxicity to crustaceans

The CLP Regulation stipulates that usually crustaceans should be used to define the appropriate hazard category, besides fish and algae: "For the long-term (chronic) hazard, separate hazard categories are defined representing a gradation in the level of hazard identified. The lowest of the available toxicity values between and within the different trophic levels (fish, crustacean, algae/aquatic plants) shall normally be used to define the appropriate hazard category(ies)."

There is only one study on crustaceans mentioned in the CLH report which presents a NOEC below the threshold of 0.01 mg/L for a chronic toxicity, category 1, namely Marcial et al., 2003, with a NOEC of 0.001 mg/L. However, based on major deficiencies such as e.g. lack of analytical confirmation of exposure concentrations and questionable statistical significance of observed effects, an appropriate reliability rating is "not reliable" (Klimisch 3), contrary to its rating in the CLH report as Klimisch 2. Hence, this study should not be used for CLP classification purposes.

For crustaceans, there are three studies, which are "reliable without restriction" (Klimisch 1), which is also the rating in the CLH report:

• Lee, 2010, on Americamysis bahia, according to EPA OPPTS 850.1350, conducted under GLP conditions, reporting a 28 d-NOEC of 0.17 mg/L.
• Caspers, 1998, on Daphnia magna, according to OECD 211, performed under GLP conditions, reporting of a 21-d NOED ≥ 3.146 mg/L.
• Cafarella, 2006, on Hyalella azteca, according to EPA 100.4, applying GLP, reporting of a 42 d-NOEC of 0.49 mg/L.

Moreover, there are four studies with an appropriate reliability rating of Klimisch 2 (reliable with restrictions).

While the Klimisch 1 data report of NOECs in the range of 0.17 - ≥ 3.15 mg/L, the Klimisch 2 studies report of NOECs in the range of 1 to 3 mg/L and thus support these findings (see also table 4).

The lowest fully reliable NOEC on crustaceans relevant for aquatic chronic toxicity classification is 0.17 mg/L, based on Lee, 2010, with a mysid shrimp (Americamysis bahia).

Aquatic chronic toxicity to algae/aquatic plants

The CLP Regulation stipulates that usually algae should be used to define the appropriate hazard category, besides fish and crustaceans: "For the long-term (chronic) hazard, separate hazard categories are defined representing a gradation in the level of hazard identified. The lowest of the available toxicity values between and within the different trophic levels (fish, crustacean, algae/aquatic plants) shall normally be used to define the appropriate hazard category(ies)."

There are two studies on algae, which are rated as "reliable with restrictions" (Klimisch 2) in the CLH report, whereas an appropriate rating should be "reliable without restriction" (Klimisch 1):

• Alexander et al., 1988, on Pseudokircheriella subcapitata (= Selenastrum capricornutum), according to EPA-600/9-78-018, conducted under GLP, reporting a 96 h-EC10 of 1.36 mg/L based on growth rate.

• Suprenant, 1985, on the marine algae Skeletonema costatum, according to EPA-560/6-82-002, using GLP documentation, reports of a 96 h-EbC10 of 0.40 mg/L based on biomass.

There is one further study with a duckweed species (= aquatic macrophyte), unanimously rated as "reliable without restriction" (Klimisch 1) here as well as in the CLH report.

• Putt, 2003, on Lemna gibba, according to OECD 221, conducted under GLP conditions, reporting of a 7d-NOEC of 7.8 mg/L.

Thus, the lowest fully reliable NOEC on algae/other plants relevant for aquatic chronic classification is 0.40 mg/L, based on Suprenant, 1985, and Skeletonema costatum.

Chronic toxicity to invertebrates other than crustacea
a) Snails:
The CLH report bases its proposed chronic classification not on crustaceans, as required by the CLP regulation, but on molluscs, namely snails. In particular the study of Oehlmann et al., 2006, on Marisa cornuarietis and the LOEC of 0.00025 mg/L (nominal) has been used as the basis in the CLH report to derive aquatic chronic toxicity category 1. This study is rated "reliable with restrictions" (Klimisch 2) in the CLH report. However, there are several major deficiencies so that an appropriate rating should be "not reliable" (Klimisch 3), such as e.g. use of inappropriate test design, insufficient replication, inadequate analytical BPA confirmation, and erroneous statistical evaluation. Hence, regardless the question of suitability of data on snails for CLP classification in general, for lack of reliability, Oehlmann et al., 2006, should not be used for classification purposes (for more details see Annex 4).

Contrary, for snails, there is a reliable and relevant study with conclusive design (Forbes et al., 2007a, 2007b, 2008), which has been performed with the same species, Marisa cornuarietis, under the auspices of the EU Technical Committee for New and Existing Chemicals in the context of the former EU Risk Assessment process. In the absence of a validated test method on snail reproduction this study followed state of science and technology and should be unanimously considered "reliable without restriction" (Klimisch 1). It was conducted using GLP and reported a NOEC of 0.025 mg/L based on impaired female growth.

There are some further studies on snails listed in the CLH report. Most of these studies suffer from serious deficiencies in study design, documentation of important parameters and relevance, so that they should be rated "not reliable", (Klimisch 3). The only study on snails which should partly be rated "reliable with restrictions" (Klimisch 2) is Sieratowicz et al., (2011). This study on the prosobranch snail Potamopyrgus antipodarum includes three experiments at different temperatures (7, 16, and 25 °C) of which only one is acceptable. The published OECD test method 242 (Potamopyrgus antipodarum Reproduction Test) clearly requests to conduct the study at 16 °C as only this temperature is within the optimum temperature range of this species in the natural habitat. Thus, only the results achieved at 16 °C by Sieratowicz et al., 2011, are reliable (for further details see Annex 4).

While snail data is not part of the focus dataset for CLP classification, a weight of evidence approach may still consider snail data. However, only reliable data should be considered while all invalid data such as Oehlmann et al., 2006, but also the study parts of Sieratowicz et al., 2011, conducted at other temperatures than 16 °C should not be considered for CLP classification.

In contrast, the NOEC of 0.025 mg/L determined in a fully reliable study (Forbes et al. 2007a, 2007b and 2008) should be taken into account in a weight of evidence approach.

b) Insects:
There is only one study on insects in the CLH report which presents results for various endpoints related to larval growth and development of the epibenthic midge species Chironomus riparius (Watts et al., 2003). This study was rated as "reliable with restrictions" (Klimisch 2), which is appropriate. While the endpoint "mouthpart deformities" is of doubtful ecological significance and therefore was disregarded in EU risk assessment report, 2008, only the NOEC of 0.1 mg/L (based on time to first moult and first instar larval weight) appears to be relevant and reliable although there was only limited analytical verification of the test concentration in the study.

c) Echinoderms
In the CLH report there are 2 studies on echinoderms (Arslan and Parlak, 2008 (Misquoted in the CLH report as Özlem and Hatice, 2008.), and Kiyomoto et al., 2006). Both studies suffer from serious deficiencies and the appropriate reliability rating should be "not reliable" (Klimisch 3). For details see Annex 4.

Chronic toxicity to other taxa
Amphibia:
There are few data on chronic toxicity to amphibians (all with Xenopus laevis). Amphibians are not among the taxa which are requested under CLP. This data does not report a lower NOEC and, thus, is not further considered for the CLP classification in the deterministic approach.

The studies of Baba et al., 2009, and Heimeier et al., 2009, are not reliable (Klimisch 3) due to methodological shortcomings. The same is true for Levy et al., 2004. For details on the shortcomings see Annex 5. These studies which were considered Klimisch 2 in the CLH report should be disregarded for CLP classification.

In contrast, the data reported by Pickford et al., 2000, are considered as fully reliable. The NOEC was determined to be ≥ 500 µg/L (based on survival, sex ratio, length and weight).

In a weight of evidence approach the NOEC reported by Pickford et al., 2000/2003, should be used for amphibians.

Probabilistic SSD approach on CLP classification for aquatic chronic toxicity to support the deterministic approach.

Specific remarks on the SSD approach for chronic toxicity data

In a first approach the aim was to comprehend and re-calculate the SSD approach for chronic data presented in the CLH report. The calculations were conducted with the ETx software v2.1 (Van Vlaardingen, 2014). The same software was used by the authors of the CLH proposal. It was not possible to re-calculate the HC5 values reported in the CLH report, based on the data indicated to be used in the SSD calculation.

The second step was to conduct an SSD calculation based on all reliable and relevant chronic toxicity data identified according to our reliability assessment, which included a total of 19 chronic toxicity studies (see Annex 0 – Tables and Figures, table 6).

The CLH report stated in the SSD chapter that there is indication of two particular sensitive groups of organisms. This is not comprehensible based on the data presented there and there is no indication of such a sensitivity among the reliable chronic toxicity studies.

The CLH report stated that the chronic toxicity data is not normally distributed. However, if only the reliable data are taken into consideration than normal distribution is given, as the 'goodness-of fit' was confirmed by the ETx software by all three statistical tests on normal distribution: Anderson-Darling test, Kolmogorov Smirnov test, and Cramer van Mises test. For details on the SSD calculation see further below.

Additional information on the SSD calculation see Annex 0 - Tables and Figures

The HC 5 based on all reliable and relevant chronic toxicity data calculates as 13.6 µg/L. This HC 5 supports CLP classification of BPA for aquatic chronic toxicity in category 2.

Conclusion on chronic aquatic toxicity classification

Table 7. Reliable (Klimisch 1) studies with Bisphenol A for each of three trophic levels relevant for classification for chronic aquatic toxicity

See Annex 0 - Tables and Figures

Additionally, and as the CLH report pointed to chronic toxicity on snails, the reliable and relevant study which reports of the lowest NOEC and which could be considered in a weight of evidence approach is Forbes et al. 2007a, 2007b, 2008, with Marisa cornuarietis, reporting a NOEC of 0.025 mg/L.

As an overall conclusion, based on the set of fully reliable (Klimisch 1) and relevant data of the three relevant taxonomic groups (fish, crustacea, and algae), the lowest NOEC was reported by Sumpter et al., 2001, with fish: 0.016 mg/L.

This is supported by the HC5-value of 0.0136 mg/L determined via probabilistic SSD calculation.

Based on this data the adequate CLP classification of BPA for aquatic chronic toxicity is category 2. This conclusion equally applies if the reliable data of all other taxa is taken into account. Moreover, all studies with an appropriate Klimisch 2 rating support this result as all of them determined chronic toxicity values above the lower limit of the chronic CLP category 2. Thus, in a weight of evidence approach and based on the chronic toxicity study which reports of the lowest chronic toxicity (deterministic approach) the adequate classification is aquatic chronic category 2.

The overall conclusion is that based on the reliable aquatic chronic toxicity data BPA should be classified in category 2 of the CLP regulation, which is also the classification chosen in the Joint REACH registration dossier.

Overall conclusion on aquatic classification of BPA

Based on the reliable and relevant aquatic acute and chronic toxicity data and in accordance with the criteria of the CLP regulation BPA should be classified as:
a) Aquatic acute toxicity: no classification

b) Aquatic chronic toxicity: category 2

References

ECHA note – An attachment was submitted with the comment above. Refer to public attachment Submission PlasticsEurope CLH and annexes.zip

Dossier Submitter's Response

Thank you for your comments.

Please take also the responses to comment 1 and 2 into account.

Acute aquatic toxicity – dataset

The dossier submitter agrees that only reliable and relevant studies should be used for CLP classification. This means - as mentioned in comment 1 - according to Klimisch et al. (1997) a reliability of 1 (reliable without restriction) or 2 (reliable with restriction, e.g. comparable to guideline study with acceptable restrictions). The most sensitive reliable result was included for each species as recommended in the Guidance for Classification and Labelling and the respective ECHA Guidance.

As already described above, previous assessments as the one from European Commission (2010) or for the SVHC identification were taken into account. Already there, some of the above mentioned studies, e.g. Reiff (1979), Stephenson (1983) were included. They were also taken into account for classification purposes as well as Hughes et al. (2006) published as Mihaich et al. (2009) (see Table 10 and also the study descriptions). Unfortunately, for the citation Bayer AG (1989) the title is missing in your reference list above. - As we can see from the submitted annex 0 you refer to the acute toxicity to *Danio rerio (*Report 114A/89F) in this case. This study was also included in the EU Risk Assessment Report (European Commission, 2010). But as there was a more sensitive reliable value for acute toxicity on *Danio rerio* from another study this one affected not the assessment.

As many studies were published not all unpublished reports are cited but taken into account.

Acute aquatic toxicity – fish

All mentioned studies were used for the classification and labelling report (see Table 10). For *Cyprinodon variegatus* a more sensitive and reliable test result is available (and also known from the EU Risk Assessment Report) (Dow Company, 1978 cited also as Emmitte 1978). Therefore, this result was also included in the table and analysis for classification purpose.

Acute aquatic toxicity – Crustacea

As we agree with PlasticsEurope that appropriate ratings for classification are Klimisch 1 and 2 ("studies on acute aquatic toxicity […] with due to shortcomings should not be used for CLP classification. Appropriate ratings of these studies are not reliable, Klimisch 3, or "not assignable", Klimisch 4.")[1], all studies should be taken into account and the most sensitive reliable one should be used for classification purpose as described by CLP guidance. Using the SSD approach, for each species the most sensitive reliable E/LC50 has to be used.

In our assessment the reliability rating for (Andersen et al., 1999) should be Klimisch 2 as only the analytical confirmation of the exposure concentration was missing. The study was conducted according to ISO/DIS 14669 (similar to the other available study with *Acartia spp.*).

[1] For studies which were provided for regulatory purpose and evaluated as reliable (Klimisch 1 or 2) by a member state in the past but "not assignable" for the dossier submitter were accepted for classification purpose.

The study reported by (Hirano et al., 2004) did also not include an analytical confirmation of the test concentrations but was conducted according EPA-600/4-90-027F. The LC50 was considered suitable for the derivation of a saltwater PNEC in the EU Risk Assessment (European Commission, 2010). The dossier submitter also considered the study suitable for classification purpose.

Acute aquatic toxicity – algae

Both mentioned studies on algae (Alexander et al., 1985c and Springborn Bionomics, 1985c) only report EC50 based upon biomass. According to ECHA Guidance R.7b chapter R.7.8.4.1 "Often both acute growth rate EC50 and biomass endpoints are reported however the latter should not be used. […] Where other supporting data exist as part of a Weight-of-Evidence approach it may be possible to consider an EbC50 value if only this value is reported." Therefore, the studies were assessed as "reliable with restriction".

Acute aquatic toxicity – other taxa

The study reported by Özlem and Hatice (2008): The name of the authors in the publication is: Çakal Arslan Özlem and Parlak Hatice. Normally, the Christian name is given first and the family name is given last. This is the way Pubmed cites the publication (Özlem CA, Hatice P). Experimental information, e.g. use of DMSO for the stock solution DMSO was provided. Answers to some other reporting or methological points of critizism from comment 4: Additionally to the untreated negative control also a positive control was used as well as a solvent control. It is correct that no analytical confirmation of the test concentrations were carried out. 6 replicates were used for the experiment. 100 embryos were observed for the 72h-embryotoxicity test. The test startet at 10 min after fertilisation and after 72h the pluteus larval stage was reached. For classification purpose embryotoxic effect was taken into account for which the relevance of the reported endpoints (larval malformation) should be obvious.

As correctly described in the comment, (Roepke et al., 2005) was not used for classification purpose.

As correctly described in the comment, the cited reliable studies for other taxa, e.g. (Li, 2013), Springborn Smithers, 2005) and (Wolkowitcz et al., 2011) were – amongst others - included in the classification derivation.

Acute aquatic classification

The studies cited in the comment were all included in the derivation of the acute classification for BPA. As described by CLP guidance the most sensitive reliable E/LC50 was used as basis for the classification. As agreed in the comment, studies with Klimisch reliability score 1 and 2 were used. Therefore, BPA has to be classified with Aquatic Acute Category 1 (M=1).

Chronic aquatic toxicity – dataset

The dossier submitter agrees that only reliable and relevant studies should be used for CLP classification. This means - as mentioned in comment 1- according to Klimisch et al. (1997) a reliability of 1 (reliable without restriction) or 2 (reliable with restriction, e.g. comparable to guideline study with acceptable restrictions). The most sensitive reliable result was included for each species as recommended in the Guidance for Classification and Labelling and the respective ECHA Guidance.

Chronic aquatic toxicity – fish

Please, refer also to the answer to comment 2.

According to our assessment (Chen et al., 2015), as well as (Chen et al., 2017) should be evaluated with Klimisch 2.

Chen et al., 2015):
It is correct that this study is not run to GLP and a limit concentration of 0.372 µg BPA/L (mean measured) is used. It is agreed that this is not very favourable for CLP purposes as the result would underestimate the effect with a missing no effect concentration. Many test conditions are similar to the ones recommended in OECD TG 234 (as described in the CLH report). For instance the minimum volume exchanges of test solutions as well as water temperature, photoperiod, age of test organisms was adhered to. Concerning the sex ratio, there was information on the replicates and their variability which was provided by the author to the eMS during the SVHC identification process. The sex ratio visually checked (based on the morphological difference of the male and the female zebrafish) by an observer blind to the treatment was in good agreement with the gonad histopathology analised with several samples using the HE staining.
(Chen et al., 2017):
The Bisphenol A concentrations were measured by using HPLC analysis (three replicates) on an Agilent 1200s instrument with a C18 solid phase extraction column, a Fisher HPLC grade acetonitrile and water (1:1) mobile phase and a detection by fluorescence with excitation at 229 nm and emission at 315 nm. According to the author (personal communication) at every exposure period three replicates were used. The water was filtered by reverse osmosis (pH 7.0-7.5) and Instant Ocean salt was added for a conductivity of 450 – 1000 µS/cm. Some more details on the study: Zebrafish (*Danio rerio*) (Wildtype AB strain; obtained from spawning adults with sex ratio of 1:1) were exposed to three test concentrations (nominal: 0.001, 0.01, and 0.1 µM BPA/L or mean measured: 0.228, 2.28, and 22.8 µg BPA/L) as well as a solvent control (0.01%DMSO). Semi-static test conditions (at 28°C, 14:10 dark/light photoperiod) were established taking into account the half-life for BPA degradation. Three different exposure periods (developmental stages) were realised (with 50 embryos per replicate): A) embryonic period from 6 hpf to 5 mpf; B) larval period from 6 dpf to 5 mpf, and C) sexually mature period from 3 mpf to 5 mpf. D) Adult zebrafish from the larval stage exposure period (6 dpf to 5 mpf) were paired (6 females with 6 males per replicate) to determine the spawning ability. The produced offspring was assessed for egg production, fertilisation, hatching, larval malformation, and survival rate. From the continuously collected embryos a subsample of 60 embryos per spawn were placed in 6-well plates to assess the hatching rate, malformation, and mortality (2x10 embryos → 3 replicates). Every experiment was conducted with 3 replicates. Feeding was initiated at day five. Results of the experiments were amongst others: For all experiments there was no difference in body weight or length. A) significantly reduced testis weight and sperm volume at 0.228 µg/L bu no difference for higher concentrations; B) here the testis weight was not different but the sperm volume and density was significantly lower at 0.228 µg/L; C) Here the testis weight was also not different but the sperm volume and densitiy was significantly lower at 22.8 µg/L; D) At all concentrations the viable egg production was reduced with significant effects at 2.28 and 22.8 µg/L ($P < 0.05$). Also significantly reduced fertilisation rates were observed at the highest test concentration (22.8 µg/L) but not at lower concentrations ($P < 0.05$). The hatch rate was significantly reduced at the lower test concentrations (0.228 and 2.28 µg/L) but not at the highest one. As three concentrations are tested and a "real" NOEC was derivable, this study is even more suitable for classification and labelling purposes than (Chen et al., 2015).

(Lahnsteiner et al., 2005):
The cited limitations in our opinion do not devaluate the study as e.g. no chemical analysis was performed but a flow-through system and DMSO (with concentrations according to OECD recommendations) were used. Additionally, only for the endpoint time point of ovulation for which only 6 fishes were used the test is not robust enough. Therefore, the result for this endpoint was not taken into account. For the endpoints egg production and semen fertility this study is evaluated with Klimisch reliability score 2.

Chronic aquatic toxicity – crustaceans
As stated above, also other taxa than crustaceans may be used for classification purposes. Crustaceans did not represent the most sensitive taxa in this case. The mentioned studies have been considered for evaluation (see Annex).

Chronic aquatic toxicity – algae/plants
Here, all responses are valid and already provided for the comments on acute aquatic toxicity as the same studies are affected.

Chronic aquatic toxicity – other invertebrates
Snails
Please refer also to the answer to comment 2. The studies with snails were also intensively discussed during the SVHC identification process and layed down in the respective dossier (ECHA 2017. https://echa.europa.eu/documents/10162/769b2777-19cd-9fff-33c4-54fe6d8290d5).
As stated above, also other taxa than crustaceans may be used for classification purposes. Yes, the Oehlmann et al. 2006 study has been intensively discussed and indeed had some deficiencies as we also stated. We evaluated it carefully and rated it reliable with restrictions and are in the opinion that this is appropriate. It was also used in the RAR as the high sensitivity of this species and the low concentrations could not be disregarded. We also considered the uncertainties of the difficult estimation of extremely low test concentrations and relied on the more conservative LOEC. We also considered and evaluated the studies of Forbes et al. (2007a+b and 2008). Here, different test conditions and another strain was used and seasonality was not considered, which came out is important as explained. Hence it is not comparable to the Oehlmann study. For classification purposes based on the deterministic and SSD approach we selected the most sensitive reliable study and endpoint. Hence, also the other reliable studies with snails listed were considered.

Insects
We agree with your comments – this is how we used it.

Echinoderms
Please refer to our answers above below acute aquatic toxicity – other taxa. We think that the mentioned studies are reliable with restriction.

Chronic aquatic toxicity – other taxa – amphibia
Please refer also to response to comment 1. There is no "standard data set" for classification purpose. Despite of data on fish, crustacea and algae, also "valid data for short- and long-term tests on other species at the same trophic level shall also be considered…" (CLP guidance chapter 4.1.3.2.4.1). "Given the wide range of species in the environment, the three taxa tested can only be a poor surrogate …".
The studies from (Baba et al., 2009) and (Heimeier et al., 2009) were not used in the SSD approach and also not in the deterministic approach. Similar to the EU Risk Assessment (European Commission, 2010) a geometric mean of the results of (Levy et al., 2004) and (Pickford et al., 2003+2010) was used for the SSD approach.

SSD approach (to support deterministic approach)
We recalculated the "original" SSD of the submitted CLH dossier again and came to the same values as already reported in the dossier. We also reach normal distribution in all cases considered. Please refer also to the other calculations in response of the comments received.

RAC's response

Thank you for your comment.

Aquatic acute and chronic toxicity – dataset

RAC agrees with Dossier Submitter regarding the use of reliable and relevant studies which are according to Klimisch et al. (1997) rated as Klimisch 1 (reliable without restriction) or Klimisch 2 (reliable with restriction) for classification purposes. The studies showing the highest toxicity (*e.g.* the one with the lowest $L(E)C_{50}$ or $NOEC/EC_x$) should be chosen as key studies for aquatic hazard classification.

RAC takes note on studies (Reiff and Phil (1979), Bayer AG (1989), Andersen et al. (2001), Kusk and Wollenberger (1999), Hughes et al. (2006) published as Mihaich et al. (2009), and Stephenson (1983)) pointed out by the commentator and what the DS stated about these studies.

Acute aquatic toxicity – fish

RAC agrees with the DS and the commentator that the fathead minnow *Pimephales promelas* was the most sensitive fish species tested in the acute studies, with a nominal 96-h LC_{50} of 4.6 mg/L (Alexander et al. (1985a)) thus relevant for aquatic acute classification.

Acute aquatic toxicity to Crustacea

RAC considers the Tato et al., 2018 relevant and reliable result therefore as appropriate to use as the key study for setting the aquatic acute hazard classification. Comprehensive analyses of the study by RAC is provided in the ODD.

RAC considers the Andersen et. al., 1999 study reliable and suitable for classification. Comprehensive analaysis of Andersen et. al., 1999 study by RAC is provided in BD.

Acute aquatic toxicity to algae

According to the current CLP Guidance (Version 5.0, July 2017), the endpoint based on growth rate reduction is preferred for algae because it is not dependent on the test design, whereas the endpoint biomass (growth) inhibition (EbC_{50}) depends on both, growth rate of the test species, as well as test duration and other elements of test design. Thus in circumstances where the basis of the EC_{50} is not specified and no ErC50 is recorded, classification shall be based on the lowest EC_{50} available. Therefore RAC agree with the DS that the marine diatoma *Naviculla incerta* was the most sensitive algae species tested in acute studies, with measured 96-h E_rC_{50} of 3.73 mg/L (Liu et al., 2010). This value is in the same range as other values for other algae species.

Acute aquatic toxicity to other taxa

Explanation concerning authors' names by DS and commentator is noted. RAC notices that both versions of the names appeared as different citations in the open literature, even in the same paper, e.g. Sanchez-Arguello et. al., 2012.

RAC considers the endpoint immobilization in the study Özlem and Hatice (2008) reliable for acute classification, but it is only used as supporting information for acute toxicity classification. Please see comprehensive assessment of the study by RAC in BD.

RAC takes note that the study Roepke et al., 2005 was not considered to be suitable for classification purpose by the DS and industry association.

RAC takes note on the studies of Li (2013), Springborn Smithers (2005) and Wolkowitcz et al. (2011) pointed out by the industry association. RAC notes that these studies were taken into account for classification purposes by DS and the industry association.

Chronic toxicity to fish
For studies Chen et al. 2015, Chen et al., 2017 and Lahnsteiner et al., 2005, please see respond to Comment 2.

Chronic toxicity to Crustacea
RAC agrees with the DS that other taxa beside crustaceae could be considered for determination of environment hazard. RAC considers Marcial et al., 2003 relevant and reliable and will be used for classification purposes. Please see comprehensive analysis of the study by RAC in the BD.

Chronic toxicity to algae
RAC agrees with the DS and industry association that the marine diatoma *Skeletonema costatum* was the most sensitive algae species tested in chronic studies, with 96-h EC_{10} of 0.40 mg/L (Alexander et al., 1988).

Aquatic chronic toxicity to invertebrates other than crustacea
Please see detailed respond to Comment No. 2.

Insects
RAC agrees with DS.

Chronic toxicity to other taxa
Taxonomic group used: Please see detailed respond to Comment No. 1. RAC agrees with the DS that other taxa beside fish, crustacea and algae could be considered for determination of environment hazard. Consequently, the data on amphibians should also be considered for setting the hazard classification.

The explanation of DS regarding the use/not use studes in deterministic approach and Species Sensitivity Distribution (SSD) approach is noted by RAC.

RAC considers the endpoint sex ratio from Levy et al., 2004; Pickford et al., 2003+2010 not reliable. RAC considers the endpoint as supporing information. Please see comprehensive analysis of the study by RAC in the ODD.

SSD approach: Noted. See RAC analysis in ODD.

Date	Country	Organisation	Type of Organisation	Comment number
21.08.2019	France		MemberState	5
Comment received				
France support the proposed classification as aquatic acute 1 H400 (M-factor 1) and Aquatic Chronic 1 H410 (M-factor 10) and thanks German competent authority for this work.				
Dossier Submitter's Response				
Thank you for your support.				
RAC's response				
Thank you for your comment. RAC notes the support for the proposed environmental classification.				

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON 4,4'-ISOPROPYLIDENEDIPHENOL; BISPHENOL A

PUBLIC ATTACHMENTS
1. Submission PlasticsEurope CLH and annexes.zip [Please refer to comment No. 1, 4]