CLH report

Proposal for Harmonised Classification and Labelling

Based on Regulation (EC) No 1272/2008 (CLP Regulation),
Annex VI, Part 2

International Chemical Identification:

4,4'-isopropylidenediphenol; Bisphenol A

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

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

Index Number: **604-030-00-0**

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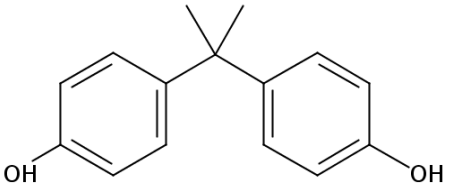
CONTENTS

1 IDENTITY OF THE SUBSTANCE

1.1 Name and other identifiers of the substance

Table 1: Substance identity and information related to molecular and structural formula of the substance

Name(s) in the IUPAC nomenclature or other international chemical name(s)	4,4'-propane-2,2-diyldiphenol
Other names (usual name, trade name, abbreviation)	Bisphenol A
EC number (if available and appropriate)	201-245-8
EC name (if available and appropriate)	4,4'-Isopropylidenediphenol
CAS number (if available)	80-05-7
Molecular formula	C_{15} H_{16} O_2
Structural formula	
SMILES notation (if available)	CC(C)(C1=CC=C(C=C1)O)C2=CC=C(C=C2)O
Molecular weight or molecular weight range	228.28 g/mol
Degree of purity (%) (if relevant for the entry in Annex VI)	100 %

1.2 Composition of the substance

Table 2: Constituents (non-confidential information)

Constituent (Name and numerical identifier)	**Concentration range (% w/w minimum and maximum in multi-constituent substances)**	**Current CLH in Annex VI Table 3 (CLP)**	**Current self-classification and labelling (CLP)**
4,4'-Isopropylidenediphenol *EC No: 201-245-8* *CAS No: 80-05-7*		see table 5	

Table 3: Impurities (non-confidential information) if relevant for the classification of the substance

Impurity (Name and numerical identifier)	**Concentration range (% w/w minimum and maximum)**	**Current CLH in Annex VI Table 3 (CLP)**	**Current self-classification and labelling (CLP)**	**The impurity contributes to the classification and labelling**
-				

Table 4: Additives (non-confidential information) if relevant for the classification of the substance

Additive (Name and numerical identifier)	Function	Concentration range (% w/w minimum and maximum)	Current CLH in Annex VI Table 3 (CLP)	Current self-classification and labelling (CLP)	The additive contributes to the classification and labelling
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2 PROPOSED HARMONISED CLASSIFICATION AND LABELLING

2.1 Proposed harmonised classification and labelling according to the CLP criteria

Table 5: Proposed harmonised classification and labelling according to the CLP criteria

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

Table 6: Reason for not proposing harmonised classification and status under public consultation

Hazard class	Reason for no classification	Within the scope of public consultation
Explosives	not assessed in this dossier	No
Flammable gases (including chemically unstable gases)		
Oxidising gases		
Gases under pressure		
Flammable liquids		
Flammable solids		
Self-reactive substances		
Pyrophoric liquids		
Pyrophoric solids		
Self-heating substances		
Substances which in contact with water emit flammable gases		
Oxidising liquids		
Oxidising solids		
Organic peroxides		
Corrosive to metals		
Acute toxicity via oral route		
Acute toxicity via dermal route		
Acute toxicity via inhalation route		
Skin corrosion/irritation		
Serious eye damage/eye irritation		
Respiratory sensitisation		
Skin sensitisation		
Germ cell mutagenicity		
Carcinogenicity		
Reproductive toxicity		
Specific target organ toxicity-single exposure		
Specific target organ toxicity-repeated exposure		
Aspiration hazard		
Hazardous to the aquatic environment	Aquatic Acute 1 Aquatic Chronic 1	Yes
Hazardous to the ozone layer	not assessed in this dossier	No

3 HISTORY OF THE PREVIOUS CLASSIFICATION AND LABELLING

Bisphenol A has been classified under Dangerous Substance Directive (DSD, Directive 67/548/EEC) for environmental effects with R52 (30th ATP to DSD; Commission Directive 2008/58/EC). This classification was included in Annex VI Table 3.2 of CLP Regulation by 1st ATP (Commission Regulation (EC) No 790/2009). Nevertheless, no comparable criteria for R52 is available under CLP Regulation, therefore the classification was not included in Annex VI Table 3.1.

4 JUSTIFICATION THAT ACTION IS NEEDED AT COMMUNITY LEVEL

Reason for a need for action at Community level:

Change in existing entry due to new data
Change in existing entry due to changes in the criteria
Differences in self-classification
Disagreement by DS with current self-classification

5 IDENTIFIED USES

Not relevant.

6 DATA SOURCES

Registration dossiers

Data from open literature

SVHC dossier (ECHA, 2017b)

Risk Assessment Report (European Commission, 2003; European Commission, 2010)

7 PHYSICOCHEMICAL PROPERTIES

Table 7: Summary of physicochemical properties

Property	Value	Reference	Comment (e.g. measured or estimated)
Physical state at 20 °C and 101,3 kPa	Bisphenol A is a white solid at environmentally relevant temperatures	REACH lead registration dossier 2018	
Melting/freezing point	155 °C		
Boiling point	Boiling Point at 17 hPa: 250 - 252 °C (with potential decomposition), Boiling Point at 1013 hPa: 360 °C (with decomposition)		
Relative density	1.2 g/cm3 at 25 °C		
Vapour pressure	4.12E-09 hPa at 25 °C		
Surface tension	Waiver		In accordance with column 2 of REACH Annex VII a study does not need to be conducted as, based on structure, surface activity is neither expected or predicted nor a desired property of the substance.
Water solubility	300 mg/L at 25 °C		
Partition coefficient n-octanol/water	3.4 at 21.5 °C and pH 6.4		
Granulometry	Waiver		In accordance with column 2 of REACH Annex VII, a study does not need to be conducted as the substance is marketed or used in a non granular form.
Stability in organic solvents and identity of relevant degradation products	Waiver		In accordance with column 1 of REACH Annex IX, a study does not need to be conducted as the stability of the substance is not considered to be critical.
Dissociation constant	11.3 at 20 °C		
Viscosity	Waiver		In accordance with section 1 of REACH Annex XI, a study does not need to be conducted as the substance is a solid at ambient temperatures.

8 EVALUATION OF PHYSICAL HAZARDS

Not assessed in this dossier.

9 TOXICOKINETICS (ABSORPTION, METABOLISM, DISTRIBUTION AND ELIMINATION)

Not assessed in this dossier.

10 EVALUATION OF HEALTH HAZARDS

Not assessed in this dossier.

11 EVALUATION OF ENVIRONMENTAL HAZARDS

The reliability of all studies used was evaluated according to (Klimisch et al., 1997). The reliability of the studies not used in the Support Document for SVHC Identification of Bisphenol A (ECHA, 2017b) has been (re-)assessed by the dossier submitter as there is not reliability score metioned in the Risk Assessment Report of Bisphenol A (European Commission, 2010).

11.1 Rapid degradability of organic substances

Table 8: Summary of relevant information on rapid degradability

Method	Results	Remarks	Reference
OECD 301 F	78.2 – 81.0 % O_2 consumption after 28 days 76.3 – 81.2 % CO_2 production after 28 days 10 day window fulfilled Reference substance: 98.3 % O_2 consumption after 28 days 77.0 % CO_2 production after 28 days (no data after 14 days mentioned)	Rel. 2	(West et al., 2001)
OECD 301 F	85 – 93 % O_2 consumption after 28 days 10 day window fulfilled Reference substance: > 60 % biodegradation by day 14	Rel. 2	(Karagiri, 2004)
OECD 301 F	87.8 ± 6.9 % O_2 consumption after 28 days 10 day window fulfilled Reference substance: > 60 % biodegradation by day 14 Toxicity control: > 25 % biodegradation by day 14	Rel. 2	(Stasinakis et al., 2008)
OECD 301 D	0 % O_2 consumption after 28 days	Rel. 2	(European Commission, 2010) (Stone and Watkinson, 1983)
OECD 301 B	1-2 % CO_2 evolution after 28 days	Rel. 2	(European Commission, 2010) (Stone and Watkinson, 1983)
OECD 301 C	0 % biodegradation after 14 days	Rel. 2	(MITI, 1992)
EPA OPPTS 835.3170 (shake flask die-away) Freshwater	20 °C ^{14}C-die away studies DT_{50} = 0.5-1.4 days 65-80 % $^{14}CO_2$ after 18 days	Rel. 1	(Klečka et al., 2001)

Method	Results	Remarks	Reference
	Respirometer studies: DT_{50} = 0.5-2.6 days 59-96 % $ThCO_2$ after 18 days		
River die-away test	30 °C DT_{50} = 2-3 days (primary degradation)	Rel. 2	(Kang and Kondo, 2002)
Shake flask die- away test Freshwater and seawater	Freshwater: 25 °C DT_{50} = 4 days (primary degradation) 35 °C DT_{50} = 3 days (primary degradation) Seawater: 25 °C and 35 °C: 80 % primary degradation after 60 days 4 °C: 30 % primary degradation after 60 days	Rel. 2	(Kang and Kondo, 2005)
Shake flask die-away test Freshwater	34 of 44 river water microcosms: 40-90 % removal after 14 days 6 of 44 river water microcosms: 100 % removal after 14 days 4 of 44 river water microcosms: 0 % removal after 14 days Metabolites: 2,3-bis(4-hydroxyphenyl)-1,2-propanediol and p-hydroxyphenacyl alcohol.	Rel. 2	(Ike et al., 2000)

11.1.1 Ready biodegradability

The ready biodegradability of Bisphenol A was evaluated in a manometric respirometry test (OECD 301F) at 22 °C (West et al., 2001). The initial concentrations of Bisphenol A used in this study were 7 and 25 mg/L (test material). The 7 mg/L concentration was used to evaluate biodegradation of Bisphenol A at the lowest concentration at which the respirometer could distinguish biodegradation of the test substance from background respirometer. As inoculum (30 mg/L suspended solid), activated sludge from a municipal wastewater treatment plant was used which was rated to be not adapted to the test substance. After a lag-phase of 4.7 days (7 mg/L Bisphenol A) and 5.2 days (25 mg/L Bisphenol A) the extent of biodegradation reached 78.2 to 81.0 % based on O_2 consumption and 76.3 to 81.2 % based on CO_2 production at day 28. 10 day window was met.

In a second OECD 301F test, Bisphenol A with an initial concentration of 100 mg/L and activated sludge (non-adapted, unknown concentration) from a municipal wastewater treatment plant was used (Karagiri, 2004). The lag phase ended in the time between day 7 and day 14. Bisphenol A was mineralised with 85-93 % (O_2 consumption) at day 28. 10 day window was met.

In a further OECD 301F test, Bisphenol A with an initial concentration of 35 mg/L (88.4 mg/L as ThOD) and 30 mg/L activated sludge from a municipal wastewater treatment plant was used (Stasinakis et al., 2008). In addition 10 mg/L allythiourea was added for preventing nitrification. After a lag phase of 4.3±0.3 days, Bisphenol A was mineralised with 87.8±6.9 % at day 28. Degradation reached 10 % by day 4.5 and exceeded 60 % by day 6.2.

The study of Stone and Watkinson (1983) was discussed in the Risk Assessment Report of Bisphenol A, which has been copied here in italic letters (European Commission, 2010):

Stone and Watkinson (1983) studied the biodegradation of Bisphenol-A in the OECD 301D Closed Bottle Test and the OECD 301B Modified Sturm Test. They also conducted an inhibition test on the growth of

Pseudomonas fluorescens. The theoretical oxygen demand (ThOD) was calculated as 2.53 mg O_2/mg and the theoretical carbon dioxide evolution ($ThCO_2$) as 2.90 mg CO_2/mg.

In the Closed Bottle Test the initial test concentration used was 3 mg/L (test substance). The oxygen concentration in the bottles was measured at 5, 15, and 28 days. At the end of the test no degradation was observed. Inhibition of microbial activity was negligible under the test conditions.

In the Modified Sturm Test the initial concentration of bisphenol-A used was 20 mg/L (test substance). The test medium was dispensed into the Sturm vessels, inoculated and aerated with CO_2 free air. The extent of biodegradation was measured at 3, 7, 11, 18, 25, 27, and 28 days by titrating the total carbon dioxide released from the incubation. On day 27 the medium was acidified to release the total carbon dioxide by day 28. At the end of the test no degradation was observed.

In the microbial inhibition test the IC50 for the inhibition of growth of Pseudomonas fluorescens by Bisphenol-A was 54.5 mg/L.

An OECD 301C test confirmed the results of Stone and Watkinson (1983). No biodegradation was observed after 14 days (MITI, 1992).

In the registration dossier further studies on ready biodegradability are available. Due to lack of information on experimental details these studies are not used for classification and labelling.

Conclusion on ready biodegradability:

If positive as well as negative results in ready biodegradability tests are available, then the data of the highest quality and the best documentation should be used for determining the ready biodegradability (ECHA, 2017a). Positive results could be considered valid (irrespective of negative results), when the scientific quality is good and the test conditions are well documented (e.g. guideline criteria fulfilled, non-adapted inoculum). Hence, based on above mentioned data Bisphenol A is readily biodegradable. Therefore, the substance is considered to be rapidly degradable for classification purposes.

11.1.2 BOD_5/COD

No data available.

11.1.3 Hydrolysis

The physical and chemical properties of Bisphenol A suggest that hydrolysis under environmental relevant conditions is negligible (European Commission, 2010).

11.1.4 Other convincing scientific evidence

No data available.

11.1.4.1 Field investigations and monitoring data (if relevant for C&L)

Not relevant

11.1.4.2 Inherent and enhanced ready biodegradability tests

No study with sufficient information on experimental design available.

11.1.4.3 Water, water-sediment and soil degradation data (including simulation studies)

The degradation of Bisphenol A was examined in surface water by Klečka et al. (Klečka et al., 2001). The water samples from seven different rivers across the United States and Europe were collected upstream and downstream from wastewater treatment plants known to treat wastewater containing Bisphenol A. Two different methods were conducted: River-die-away studies for ^{14}C- Bisphenol A (initial Bisphenol A concentrations 50-5500 µg/L) and respirometry studies (initial Bisphenol A concentration 5000 µg/L). The

test vessels were incubated at 20 ± 2 °C in the dark and were continuously stirred with 100 rpm. Bisphenol A was not detected in the river samples prior to the addition of the test compound. Negligible losses of Bisphenol A were observed in autoclaved controls, indicating no abiotic degradation. There was no significant difference between the tests conducted with different river waters or river waters upstream or downstream from wastewater treatment plants. The results indicated rapid biodegradation of Bisphenol A after an initial lag phase. In the ^{14}C river die-away studies lag periods of 2 - 8 days were observed and half-lives between 0.5 and 1.4 days were estimated. Degradation of ^{14}C- Bisphenol A resulted in mineralization with an average yield of 65-80 % $^{14}CO_2$ at the end of the test period (18 days). In the respirometry studies, after a lag period of 2.3-4.4 days, 59 - 96 % CO_2 was formed after 18 days. The estimated half-lives ranged from 0.5 to 2.6 days. In addition, the authors conducted studies with lower Bisphenol A concentrations (0.05 and 0.5 µg/L). Because of analytical limitations, only primary biodegradation was measured. After 28 days the Bisphenol A concentration was below 0.005 µg/L and the estimated half-lives ranged from 3 to 6 days.

Kang and Kondo studied the primary degradation of Bisphenol A in river water (Kang and Kondo, 2002). Three river water samples were spiked with 1 mg/L Bisphenol A and incubated at 30 °C. In the river water samples no Bisphenol A was detected (LOD = 0.005 mg/L using HPLC analysis). Under aerobic conditions Bisphenol A was rapidly primarily degraded with half-lives of 2 - 3 days. After 10 days the concentration was below the LOD.

The same authors investigated primary degradation in seawater and in river water at different temperatures (25 °C, and 35 °C and additional 4 °C for seawater) (Kang and Kondo, 2005). The seawater samples were taken from five sites over one kilometer away from a junction of river and sea. The river water samples were collected from three rivers. All water samples were spiked with 1 mg/L Bisphenol A. In river water, half-lives were 4 and 3 days at 25 °C and 35 °C, respectively. In seawater lag periods of 30 days (25 °C and 35 °C) and 40 days (4 °C), respectively, were observed. At the end of the experiment (60 days) the initial concentration decreased to ~200 µg/L at 25 °C/35 °C (80 % primary degradation) and ~700 µg/L at 4 °C (30 % primary degradation). In autoclaved seawater, no degradation was observed over 60 days, indicating no abiotic removal process.

The biodegradation potential of Bisphenol A in 44 river water microcosms were investigated (Ike et al., 2000). The river water samples were collected from 15 sites of seven rivers with water quality ranging from clean to heavily polluted. A Bisphenol A solution was added to the systems to give a final TOC concentration of 20 mg/L. The systems were incubated at 28 °C with rotary shaking and dark conditions. 34 of the 44 river water systems showed TOC removal of 40 to 90 % after 14 days. Six microcosms could completely remove TOC and four microcosms showed no TOC removal within the test period. The removal of Bisphenol A in microcosms with unpolluted and less polluted river water is lower than in microcosms spiked with heavily polluted river water. Two metabolites were identified: 2,3-bis(4-hydroxyphenyl)1,2-propanediol and p-hydroxyphenacyl alcohol. These metabolites cannot be removed by Bisphenol A degrading bacteria.

Further studies on degradation of Bisphenol A in surface water are available in the registration dossier. All studies show rapid (primary) degradation of Bisphenol A in surface water.

Degradation data of Bisphenol A in water-sediment and soil do not need to be considered for the decision on rapid degradation, as Bisphenol A is demonstrated to be readiliy biodegradable based on available information from ready biodegradability tests ((ECHA, 2017a) Annex II.4 decision scheme).

Conclusion on surface water degradation data:

The available data demonstrate a rapid degradation of Bisphenol A in surface water once the system had become acclimated (lag-period).

11.1.4.4 Photochemical degradation

An atmospheric half-life of 0.2 days was calculated (AOPWIN) for the reaction of Bisphenol A with OH-radicals (European Commission, 2010).

11.2 Environmental fate and other relevant information

The adsorption coefficients for environmental media were estimated using technical guidance document methods and a log Kow value of 3.40. The organic carbon-water partition coefficient (Koc) was estimated with a value of 715 L/kg. Several experimental studies observed a Koc value in the range of 251 to 1750 L/kg (outlier: 11,220 – 17,000). Bisphenol A is likely to be moderately adsorbed to solids (European Commission, 2010).

Volatilisation is not considered to be a significant removal mechanism for Bisphenol A from water systems (Henry's Law constant = $4.03 \cdot 10^{-6}$ Pa·m³·mol^{-1}) (European Commission, 2010).

11.3 Bioaccumulation

Table 9: Summary of relevant information on bioaccumulation

Method /Species	Results	Remarks	Reference
OECD 107	Log Kow 3.4	Rel. 2	(European Commission, 2010)
MITI guideline Carp *(Cyprinus carpio)*	BCF < 20 – 67.7 (15 µg/L) BCF = 5.1 – 13.3 (150 µg/L)	Rel. 1	(European Commission, 2003; European Commission, 2010)
Freshwater clams *(Pisidium amnicum)*	BCF = 144	Rel. 2	(European Commission, 2003; European Commission, 2010)
Killfish (*Oryzias latipes)*	BCF = 73.4	Rel. 2	(European Commission, 2010)

11.3.1 Estimated bioaccumulation

Not data available.

11.3.2 Measured partition coefficient and bioaccumulation test data

A log Kow of 3.4 was determined at 21.5 °C and pH 6.4 according to OECD Guideline 107.

Bioaccumulation was evaluated in the Risk Assessment Report of Bisphenol A, which has been copied here in italic letters (European Commission, 2010).

The available measured data suggested that bisphenol-A has a low potential for bioaccumulation in fish, in contrast to the moderate potential indicated by the log Kow value. A slightly higher potential was indicated by the measured bioconcentration in freshwater clams (up to 144). Measured data are preferred over calculated values when the studies are valid. A BCF of 67 for fish was therefore used in the published risk assessment, and the accumulation in clams was considered in the risk characterisation (EC, 2003).

The studies are specified in the Risk Assessment Report from 2003 and have been copied here in italic letters (European Commission, 2003).

Bioconcentration factors for bisphenol-A have been measured by MITI (1977). Bioconcentration factors were determined for carp (Cyprinus carpio) exposed to bisphenol-A concentrations of 150 µg/L and 15 µg/L in a flow through system. The carp were exposed to bisphenol-A for six weeks. At the 150 µg/L exposure concentration bioconcentration factors of 5.1 to 13.3 were measured over the 6-week exposure period. At the 15 µg/L exposure concentration bioconcentration factors of <20 to 67.7 were measured over the 6-week exposure period. Bisphenol-A was judged to have a low bioaccumulation potential.

The accumulation of bisphenol-A in freshwater clams (Pisidium amnicum) has been studied at ecologically relevant low temperatures (Heinonen et al., 2002). Uptake and depuration rates were measured using ^{14}C-labelled substance at temperatures between 2 and 12 °C. Both uptake and depuration rates increased with

temperature, although the uptake rate decreased slightly at the highest temperature. The bioconcentration factor was calculated from the concentration ratios at steady state and from the two rates. The maximum value was obtained at 8 °C by both methods, as 144 based on concentrations and 134 based on rates.

Information from 2003 to 2010 was also evaluated in (European Commission, 2010), but *the new BCF values for fish are generally similar to that used in the published risk assessment and so no change is necessary.* Two representative studies are described below.

Lindholst et al. (2003) studied the metabolism of bisphenol-A in zebrafish (Danio rerio) and rainbow trout (Oncorhynchus mykiss). Adult zebrafish were exposed to 100 µg/L bisphenol-A in a flow through system for 168 hours. Exposures took place in a 100 l aquarium, with a flow rate of 8 replacement volumes per day, and 150 fish. The bisphenol-A concentration was measured every two days; the actual concentration found was 97.5±5.2 µg/L. Fish were sampled to a system to which bisphenol-A was not added and kept for the same length of time, with sampling at the same intervals. Zebrafish tissue samples were analysed for Bisphenol A, Bisphenol A glucuronic acid (BPAGA) and Bisphenol A sulphate (BPAS).
Rainbow trout were exposed under similar conditions for eight days to 100 µg/L bisphenol-A (actual concentration from 2-day samples 107.3±6.3 µg/L). After eight days, gall bladder and blood samples were taken, and the bile fluid and blood plasma analysed for the same three substances (Bisphenol A, BPAGA and BPAS). Uptake and excretion rates for fish were calculated by fitting data to exponential uptake and decay models (much of the data for rainbow trout came from earlier publications). Uptake was fitted to a first order model, excretion to a first or second order model depending on the goodness of fit. Bisphenol A was detected in zebrafish after two hours' exposure, and steady sate was reached by 24 hours. Steady state concentrations were 569 ng/g for Bisphenol A, 12.6 µg/g for BPAGA and 39.3 ng/g for BPAS. The whole body uptake rate for zebrafish was calculated as 0.23; tissue specific values from rainbow trout plasma, liver and muscle were 0.73, 0.11 and 0.16, so the rates were similar between the two species despite the different matrices. Elimination from zebrafish was fitted to a second order model; the first compartment had a half life of <1.1 hours, the second compartment half life was 139 hours. The three trout tissues had elimination half-lives of 3.7, 1.8 and 5.8 hours for plasma, liver and muscle respectively, as first order elimination. The authors suggest that in zebrafish Bisphenol A is rapidly removed from tissues, metabolised by the liver and excreted primarily as BPAGA into the gall bladder (compartment 2). Elimination from the tissues in zebrafish is much more rapid than from trout tissues. Zebrafish have a lower sensitivity to Bisphenol A than trout when considering vitellogenin synthesis. It is suggested that this may be due to the more rapid metabolism resulting in lower Bisphenol A concentrations and a reduced response. Data on specific tissue concentrations in the liver for Bisphenol A and metabolites was needed to confirm this.

Killifish (Oryzias latipes) were exposed to bisphenol-A at 17 µg/L in a flow-through system for six days (Takino et al, 1999). Fish were analysed at intervals, and the results at five and six days showed that steady state had been reached. The mean BCF from these two times was 73.4 l/kg.

Conclusion on bioaccumulation:

Bisphenol A has a low potential to bioconcentrate and is therefore not considered a bioaccumulative substance for classification purposes.

11.4 Acute aquatic hazard

There is much data available for short-term toxicity of BPA. Data was already evaluated in the Risk Assessment Report of Bisphenol A (European Commission, 2010) and briefly summarized in the Support Document for SVHC Identification of Bisphenol A (ECHA, 2017b). Further studies retrieved from literature dated beyond the last literature search for the Risk Assessment Report of Bisphenol A (European Commission, 2010) were also assessed. Most of them were evaluated and used in the Environmental Quality Standars (EQS) Dossier and also in the REACH registration dossiers.

In the following table, the reliable studies relevant for classification purposes are listed with their respective observed effect concentrations (e.g. EC/LC_{50}). More detailed descriptions of the lowest relevant and reliable effect concentrations are provided in the following sections for fish, aquatic invertebrates as well as algae and aquatic plants.

Table 10: Summary of relevant information on acute aquatic toxicity*

Taxonomic group	Method	Species	Results [mg/L]	Remarks	Rel.	Reference
Fish	OECD 236	*Danio rerio*	96h-EC50= 5.25 96h-LC50= 8.04	Nominal	2	(Chan and Chan, 2012)
Fish	OECD 236	*Danio rerio*	72h-EC50= 13.8	Measured (analytical verification: HPLC)	2	(Duan et al., 2008)
Fish	No guideline	*Danio rerio*	**120h-LC50= 5**	Nominal (analytical verification: GC-MS); Embryos 3hpf; 25 replicates;experiment 3 times repeated	2	(McCormick et al., 2011)
Fish	OECD 203	*Orycias latipes*	**72h-LC50= 6.8 (adults)**	Nominal (0.1 mL DMSO/L; no analytical verification); Flow-through test	2	(Kashiwada et al., 2002)
Fish	ASTM E-729-80	*Pimephales promelas*	**96h-LC50= 4.6**	Nominal (analytical verification: RPC)	1	(Alexander et al., 1988)
Fish	OECD 203/ GLP	*Cyprinodon variegatus*	96h-LC50= 11	.Measured	1	(Springborn Smithers Lab., 2009)
Fish	No guideline	*Cyprinodon variegatus*	**96h-LC50= 7.5**	Measured	2	(Dow Company, 1978) = (Emmitte 1978)
Fish	ASTM E729-80	*Menidia menidia*	**96h-LC50= 9.4**	Measured	1	(Alexander et al. 1988)
Crustacean	ASTM E729-80	*Daphnia magna*	48h-EC50= 10.2	Measured	1	(Alexander et al., 1988)
Crustacean	OECD 202	*Daphnia magna*	48h-EC50= 10.4	Nominal	2	(Jeong et al., 2013)
Crustacean	ISO 6341	*Daphnia magna*	24h-EC50= 13.8	Nominal, but measured	2	(Jemec et al., 2012)
Crustacean	OECD 202	*Daphnia magna*	48h-EC50= 9.9	Nominal (analytical verification: GC-MS)	1	(Mansilha et al., 2013)
Crustacean	No guideline	*Daphnia magna*	48h-EC50= 3.9	Nominal (no analytical verification); vehicle used	2	(Stephenson 1983)
Crustacean	OECD 202 (Daphtoxkit F magna)	*Daphnia magna*	48h-EC50= 10	Nominal	2	(Chen et al., 2002)
Crustacean	OECD 202 (Daphtoxkit F magna)	*Daphnia magna*	48h-EC50= 12.8	Nominal	2	(Hirano et al., 2004)
Crustacean	EPA-660/3-75-009	*Daphnia magna*	48h-EC50= 16	Nominal (no analytical verification); static	2	(Mu et al., 2005)
Crustacean	ISO 6341 15	*Daphnia magna*	48h-EC50= 7.75	Nominal (no analytical verification); static	2	(Brennan et al., 2006)

Crustacean	No guideline	*Gammarus pulex*	**120h-LC50= 1.5**	Measured (GC-MS/MS); vehicle: > 0.5 % ethanol	2	(Watts et al., 2001)
Crustacean	ASTM E729-80	*Americamysis bahia*	96h-LC50= 1.1	Measured; Flow-through test	1	(Alexander et al., 1988)
Crustacean	EPA-600/4-90-027F	*Americamysis bahia*	**96h-LC50= 1.03**	n.a.	2	(Hirano et al., 2004)
Crustacean	Standard method developed at Artemia Reference Center (ARC-Test)	*Artemia franciscana*	**48h-LC50= 34.7**	Nominal	2	(Castritsi-Catharios et al., 2013)
Crustacean	No guideline.	*Tigriopus japonicus*	**48h-LC50= 4.32**	Nominal; vehicle used; semi-static	2	(Marcial et al., 2003)
Crustacean	ISO/DIS 14669	*Acartia tonsa*	72h-EC50= 0.96 (immobilization)	Nominal	2	(Andersen et al., 1999)
Crustacean	ISO 14669:1999	*Acartia clausi*	**48h-LC50= 0.885**	measured	1	(Tato et al., 2018)
Insect	EPA-540/9-85-005	*Chironomus tentans*	**96h-LC50= 2.7**	Measured	2	(Springborn Smithers Lab., 2005)
Mollusc	no guideline ("generally following OECD 203")	*Marisa cornuarietis*	**96h-LC50= 2.24**	Measured; semi-static; test at 25.3 to 25.5 °C	1	(Mihaich et al., 2009)
Echinoderm	No guideline	*Paracentrotus lividus*	**72h-EC50= 0.71 (embryotoxicity)**	Nominal; vehicle: DMSO; positive control: $CdCl_2$	2	(Ozlem and Hatice, 2008)
Cnideria	No guideline	*Hydra vulgaris*	**96h-LC50 = 6.9**	Measured; reference substance used	1	(Pascoe et al., 2002)
Platyhelminthes	ISO 6341	*Dugesia japonica*	**48h-LC50= 8.3**	Nominal; vehicle. 0.1 % DMSO	2	(Li, 2013)
Algae	EPA-600/9-78-010/ EPA-560/6-82-002	*Pseudokirchneriella subcapitata*	96h-EbC50= 2.73 **96h-ErC50= 3.10**	n.a.	2	(Alexander et al., 1988)
Algae	EPA-600/9-78-010/ EPA-560/6-82-002	*Skeletonema costatum*	96h-EbC50= 1.1	n.a.	2	(Alexander et al., 1988)
Algae	Similar to OECD 201	*Cyclotella caspia*	96h-ErC50= 7.96	Nominal (no analytical verification), vehicle: 0.50 % methanol	2	(Li et al., 2008)
Algae	Similar to OECD 201	*Navicula incerta*	**96h-ErC50= 3.73**	Measured (GC-MS)	2	(Liu et al., 2010)
Aquatic plants other than algae	OECD 221	*Lemna gibba*	**7d-EC50= 20 mg/L (fond density)**	Measured	1	(Putt 2003); (Mihaich et al., 2009)
Amphibian	No guideline	*Rhinella arenarum*	**168h-LC50= 7.1**	Nominal	2	(Hutler et al., 2014) (is the same as Wolkowitcz et al., 2011)
Amphibian	No guideline	*Xenopus laevis*	**72h-LC50= 4.8 (embryos)**	Nominal	2	(Iwamuro et al., 2003)

* values in bold were also used for SSD

11.4.1 Acute (short-term) toxicity to fish

Short-term toxicity to fish was evaluated in the Risk Assessment Report of Bisphenol A (European Commission, 2010). There are additional studies available dating beyond the last literature search for the EU RAR. This data was evaluated for the CLH report. As these studies do not provide results lower than the one of 4.6 mg/L, they are listed in the table but not below in the text. The conclusions from the EU RAR have been copied here in italic letters (European Commission, 2010) as they are still relevant:

For freshwater species the lowest acute toxicity value is a 96-hour LC50 of 4.6 mg/L (nominal concentration) for the fathead minnow (Pimephales promelas). The test conditions and methods are fully described in the test report, and this test is considered valid.

For saltwater species the lowest acute toxicity value is a 96-hour LC50 of 7.5 mg/L (measured concentration) for the sheepshead minnow (Cyprinodon variegatus). The test method used appears to be acceptable, although no information is given as to temperature, pH or dissolved oxygen during the test.

In summary, for fish the 96h-LC_{50}-value of 4.6 mg/L for *Pimephales promelas* is the lowest value for this trophic level.

11.4.2 Acute (short-term) toxicity to aquatic invertebrates

Short-term toxicity to aquatic invertebrates was evaluated in the Risk Assessment Report of Bisphenol A (European Commission, 2010) for PNEC derivation. Some new data was added and is also listed in Table 10.

For custaceans much data is available. According to the Guidance on the application of the CLP criteria (ECHA, 2017a) chapter 4.1.3.2.4.3 "where more than one acceptable test is available for the same taxonomic group, the most sensitive is generally used for classification. […] When larger data sets (four or more values) are available for the same species, the geometric mean of toxicity values may be used as the representative toxicity value for that species. […] This implies that for substances, where four or more ecotoxicity data on the same species and endpoint are available, the data should be grouped, and the geometric mean used as a representative toxicity value for that species." The results for *Daphnia magna* (EC_{50}; 8 studies) range from 3.9 to 16 mg/L (geometric mean 9.47 mg/L calculated from 8 values). There is one study with *Artemia franciscana* and one with *Gammarus pulex* resulting in LC_{50}s of 34.7 and 1.5 mg/L, respectively. Two studies with *Americamysis bahia* provide similar results (LC_{50}s of 1.05 and 1.1 mg/L). One study with *Tigriopus japonicus* results in a LC_{50} of 4.32 mg/L.

There are two studies with *Acartia sp.* with low effect concentrations. The one with *Acartia tonsa* results in a EC_{50} of 0.96 mg/L. The other study was conducted with *Acartia clausii*, resulted in a LC_{50} of 0.885 mg/L (measured concentrations) and is described in more detail below.

Tato et al. (2018) assessed the effects of the three phenolic compounds bisphenol A, triclosan and 4-nonylphenol to the marine organisms *Isochrysis galbana*, *Mytilus galloprovincialis*, *Paracentrotus lividus*, and *Acartia clausi*. The experiments used 0.22µm-filtered sea water (34 ± 2 psu salinity, 8.2 ± 0.1 pH, 8.0 ± 0.1 mg/L dissolved oxygen). The acute lethal toxicity test with copepods followed standard methods (Water Quality. Determination of Acute Lethal Toxicity to Marine Copepods. ISO 14669:1999) using nauplius larvae. As reference substance for the biological quality of the stock 3,5-dichlorophenol was used. In total 40 vials per treatment were used. The vials were placed in an isothermal room at a temperature of 20 ± 1 °C and kept under an 18h light/6h dark photoperiod. The surivial of the copepod was recorded after 48 hours of exposure. Stock solutions were prepared with dimethyl sulfoxide (DMSO) (0.01 %). The concentrations of Bisphenol A were analysed (DLLME-LC-MS/MS) with a limit of quantification (LOQ) of 20 ng/L. The measured concentrations ranged from 96.2 to 106.7 % (concentrations used: 150 – 300 – 600 – 1200 – 4800 µg/L). The exposure of *Acartia clausii* for 48h resulted in a NOEC of 300, a LOEC of 600 (44 % effect), an EC_{10} of 186 and an EC_{50} of 885 µg/L.

For the insect *Chironomus tentans* there is an LC_{50} of 2.7 mg/L. For the mollusc *Marisa cornuarietis* the LC_{50} is 2.24 mg/L. For echinoderms, the lowest acute toxicity value is an 96h-EC50 of 0.227 mg/L for *Strongylocentrotus purpuraus*. For cnidarians there is only one relevant study with *Hydra vulgaris* resulting in a LC_{50} of 3.9 mg/L. And for the plathelminth *Dugesia japonica* a LC_{50} of 8.3 mg/L is reported.

In summary, the 48h-LC_{50}-value of 0.885 mg/L for the crustacean *Acartia clausi* is considered valid and relevant for classification.

11.4.3 Acute (short-term) toxicity to algae or other aquatic plants

Short-term toxicity to algae and other aquatic plants was evaluated in the Risk Assessment Report of Bisphenol A (European Commission, 2010), which has been copied here in italic letters.

Alexander et al. (1985b; 1988) report 96-hour EC50 values, based upon cell count and total cell volume, of 2.73 mg/L and 3.10 mg/L for the green alga Selenastrum capricornutum, respectively. Both of the test results are based upon changes in biomass. The test report describes the test methods and test concentrations, and this test was considered valid for use in the PNEC derivation. In addition to the EC50 values reported, the percentage inhibition of cell count and cell volume is reported for the concentrations tested. From these data it is possible to derive an EC10 using probit analysis. The calculated 96 hour EC10 values are 1.36 mg/L based upon cell count and 1.68 mg/L based upon cell volume.

Springborn Bionomics Inc. (1985c) (also published in Alexander et al. (1988)) report 96-hour EC_{50} values, based upon cell count and chlorophyll content, of 1.0 mg/L and 1.8 mg/L, respectively for the marine alga Skeletonema costatum. The test report describes the test methods and test concentrations were measured. The method used to estimate the effect concentrations was non-linear interpolation. The percentage inhibition of cell count and chlorophyll content is reported for the concentrations tested. These original data have been analysed by the rapporteur [of the risk assessment report (European Commission, 2010)] *using probit analysis in accordance with the OECD Guideline. The resulting EC_{50} for cell count is 1.1 mg/L, and that for chlorophyll content is 1.4 mg/L. It is also possible to derive EC_{10} values using the probit analysis. The calculated 96-hour EC_{10} values are 0.69 mg/L based on chlorophyll content and 0.40 mg/L based upon cell count.*

Stephenson (1983) reports a 96-hour EC_{50} of 2.5 mg/L, based upon cell count, for the green alga Selenastrum capricornutum. The test report describes the test method used, however it does not give details of the test conditions. The test concentration is based upon nominal concentrations. This result should be used to support the data presented by Alexander et al. (1985).

Springborn Bionomics Inc. (1985c) (also published in Alexander et al. (1988)) report 96-hour EC_{50} values, based upon cell count and chlorophyll content, of 1.0 mg/L and 1.8 mg/L, respectively for the marine alga Skeletonema costatum. The test report describes the test methods and test concentrations, and is considered valid for use in the PNEC derivation. However the method used to estimate the effect concentrations was non-linear interpolation. The percentage inhibition of cell count and chlorophyll content is reported for the concentrations tested. These original data have been analysed by (European Commission, 2010) *using probit analysis in accordance with the OECD Guideline. The resulting EC_{50} for cell count is 1.1 mg/L, and that for chlorophyll content is 1.4 mg/L. It is also possible to derive EC_{10} values using the probit analysis. The calculated 96-hour EC_{10} values are 0.69 mg/L based on chlorophyll content and 0.40 mg/L based upon cell count.*

Stephenson (1983) reports a 96-hour EC50 of 2.5 mg/L (nominal), based upon cell count, for *P. subcapitata*. This result supports the data reported by Alexander et al. (1985b).

Liu et al. (2010) investigated the toxicity of BPA to the marine diatom *Navicula incerta* in a semi-static 96-h-test and estimated a EC50 value for growth inhibition of 3.73 mg/L (analytically confirmed).

According to CLP guidance (ECHA, 2017a) the EC_{50} value based on growth rate reduction is preferred. Therefore, in summary, the 96h-E_rC_{50} of 3.73 mg/L for *Navicula incerta* is considered valid and relevant for classification.

11.4.4 Acute (short-term) toxicity to other aquatic organisms

There is an acute toxicity test for amphibians available, which was evaluated in the SVHC Support Document of Bisphenol A (ECHA, 2017b).

The EC_{50} for survival for *Rhinella arenarum* is 7.1 mg/L (Wolkowicz et al. 2014). This value is considered valid and relevant for classification.

Iwamuro et al. (2003) determined a 72h-LC_{50} for survival for *Xenopus laevis* of 4.8 mg/L (nominal). About 60 to 100 mebryos at stage 7 were exposed for 72 h to six different BPA concentrations, two E2 concentrations, or vehicle alone and then transferred to dechlorinated water. The number of surviving embryos was counted at 48, 96, and 120 h after the treatment.

11.5 Long-term aquatic hazard

There is much data available for the long-term toxicity of BPA. Data was already evaluated in the Risk Assessment Report of Bisphenol A (European Commission, 2010) and in the Support Document for SVHC Identification of Bisphenol A (ECHA, 2017b).

In the following table, the reliable studies relevant for classification purposes are listed with their respective observed effect concentrations (e.g. EC_{10}/NOEC/LOEC). More detailed descriptions of the lowest relevant and reliable effect concentrations are provided in the following sections for fish, aquatic invertebrates as well as algae and aquatic plants.

Table 11: Summary of relevant information on chronic aquatic toxicity*

Taxonomic group	Method	Species	Results[1] [mg/L]	Endpoint	Reliability	Reference
Fish	Partial ELS test; No guideline; GLP	*Cyrpinus carpio*	**49d-NOEC= 0.1 (n)**	Growth	2 (extended abstract, but already evaluated in EU RAR + considered suitable for PNEC derivation)	(Bowmer & Gimeno 2001)
Fish	FFLC EPA OPP 72-5 method developing study	*Danio rerio*	Full life-cycle 75dpf-NOEC= 0.75 (n)	Multiple end points growth, time to spawning, mating behaviour, eggs per female and fertilisation success	2	(Segner et al., 2003)
Fish	2-Generation-study; no guideline; conditions acc. to OECD 234	*Danio rerio*	300d-LOEC= 0.000372 (mean meas.) **NOEC< 0.000372 (mean meas.)**	Female biased sex ratio; malformation + mortality of larvae	2	(Chen et al., 2015)
Fish	No guideline; conditions similar OECD 234	*Danio rerio*	5 m-NOEC= 0.000174 (mean measured)	Reduced egg production	2	(Chen et al., 2017)
Fish	2-Gen.-study; no guideline;conditions acc. to OECD 234	*Danio rerio*	F2 180dpf NOEC= 0.2 (n) F0 90dpf-LOEC= 0.01 (= lowest conc. used)(n)	Growth	2	(Keiter et al., 2012)
Fish	No guideline	*Oryzias latipes*	14d-NOEC= 0.68	Reproduction	2	(Shioda and Wakabayashi, 2000)
Fish	OECD 210 (equivalent)	*Oryzias latipes*	60dph-NOEC= 0.355 (meas.)	Growth	2	(Yokota et al., 2000)

Fish	Partial life-cycle test	*Oryzias latipes*	NOEC= 2.12 (mean meas.)	Growth	2	(Japanese Ministry of the Environment 2006)
Fish	Full life-cycle test	*Oryzias latipes*	NOEC= 0.247 (mean meas.)	F0 survival	2	(Japanese Ministry of the Environment 2006)
Fish	3-Gen.-study; No guideline	*Oryzias latipes*	Multi-generation LOEC= 0.084 (meas.)	Reduced embryo survival F3 generation	1	(Bhandari et al., 2015)
Fish	Similar to OECD 234	*Oryzias latipes*	**44d- NOEC= 0.060 (n; analytically verified)**	Reduced hatchability	2	(Sun et al., 2014)
Fish	Similar to OECD 230 (extended)	*Oryzias latipes*	21d-LOEC= 0.837 (meas.)	Gonadal histology	2	(Kang et al., 2002)
Fish	OECD 215 (proposal); GLP	*Oncorhynchus mykiss*	**28d-NOEC= 3.64 (mean meas.)**	Mortality	1	(Bayer AG 1999b)
Fish	FFLC EPA OPP 72-5 method developing study; GLP	*Pimephales promelas*	164d-NOEC= 0.16 (n, analytically verified)	Male survival	1	(ABC Laboratories, 2008); (Mihaich et al., 2012) = (Rhodes et al., 2007)
Fish	Similar to EPA OPP 72-5	*Pimephales promelas*	**Full life-cycle 444d NOEC=0.016 (n, analytically verified)**	Reduced egg hatchability F2 generation	2	(Brixham Environmental Labs, 2000a); (Brunel University, 2001); (Sohoni et al., 2001) = (Sumpter et al., 2001)
Fish	No guideline	*Salmo trutta*	**5w-NOEC= 0.0024 (n)**	Reproduction (no eggs)	2	(Lahnsteiner et al., 2005)
Fish	No guideline	*Salmo salar*	42d-NOEC= 0.1 (n)	Fry: lethargic, darker color, some with yolk sac oedemas	2	(Honkanen et al., 2004)
Fish	No guideline	*Poecilia reticulata*	**30d-NOEC= 0.5 (n)**	Survival	2	(Kinnberg and Toft, 2003)
Fish	OPPTS 850.1500	*Cyprinodon variegatus*	**116d- NOEC= 0.066 (meas.)**	F0 reproductive success	1	(Springborn Smithers, 2010)(Mihaich et al., 2018)
Crustacean	OECD 211	*Daphnia magna*	21d-NOEC≥ 3.146 (n.a.)	Reproduction	1	(Bayer AG, 1996); (Caspers, 1998)
Crustacean	ISO 10706	*Daphnia magna*	21 d NOEC 1.73 (n, analytically verified)	Reproduction	1	(Jemec et al., 2012)
Crustacean	OECD 211	*Daphnia magna*	21d NOEC 6.67 (n)	Reproduction	2	(Jeong et al., 2013)
Crustacean	OECD 211	*Daphnia magna*	21d NOEC 3 (n)	Reproduction	2	(Mansilha et al., 2013)
Crustacean	EPA-600/4-91/003	*Ceriodaphnia dubia*	**7d-NOEC= 0.94 (n)**	Reproduction	2	(Tatarazako et al., 2002)
Crustacean	ISO/DIS 14669	*Acartia tonsae*	**5d-EC10=0.1 (n)**	Development inhibition	2, No analytics	(Andersen et al., 2001)
Crustacean	No guideline	*Tigriopus japonicus*	**21d-NOEC=0.001 (n)**	Developmental delay (maturity) parental generation	2, no analytics	(Marcial et al., 2003)

Crustacean	EPA 100.4	*Hyalella azteca*	**42d-NOEC= 0.49**	Reproduction	1	(Springborn Smithers 2006a); (Mihaich et al., 2009)
Crustacean		*Gammarus pulex*	14d-NOEC= 0.1 (n)	Survival (NOEC reproduction >1 mg/L)	2, conc. measured at start	(Johnson et al., 2005)
Crustacean	OPPTS draft 850.1350; GLP	*Americamysis bahia*	**28d-NOEC= 0.17**	Reproduction	1	(Lee 2010); (Mihaich et al., 2018)
Insect	No guideline	*Chironomus riparius*	Life-cycle **NOEC= 0.1** (n, analytics: measured 83 % of nominal)	Time to larval moult + wet weight of 1st instar larvae	2	(Watts et al., 2003)
Mollusc	No guideline; 25 °C	*Marisa cornuarietis*	181d/90d-NOEC= 0.0155 (meas., nom: 0.025 mg/L)	Adult fecundity/ Juvenile female growth,	1, GLP	(Forbes et al., 2007; Forbes et al., 2008); (Warbritton etal. 2007a+b)
Mollusc	No guideline; 20 °C	*Marisa cornuarietis*	150d-LOEC= **0.00025 (n), 0.000106 (med-meas.,** 0.000028 (twa) 150d-EC_{10}= 0.000038 (0.000053 twa, clutch)	Effects on egg / clutch production	2	Oehlmann et al. 2006, EC10 recalculation by (Ratte, 2015)
Mollusc	No guideline	*Potamopyrgus antipodarum*	90d-NOEC= 0.001 (n) 90d-NOEC= 0.025 (n)	Increased embryo prod. Decreased embryo p.	2, no analytics	(Jobling et al., 2004)
Mollusc	OECD detailed review paper on Molluscs life-cycle tox. testing	*Potamopyrgus antipodarum*	NOEC= 0.02 (n, 16 °C) 0.0194 meas NOEC=0.005 (n, 7 and 25 °C) **0.0046 meas**)	Increased embryo prod.	2	(Sieratowicz et al., 2011)
Mollusc	No guideline	*Potamopyrgus antipodarum*	28d LOEC=0.0002 (n) 0.000168 (meas)	Increased embryo prod.	2, contaminated controls	(Benstead, 2010)
Mollusc	No guideline	*Planorbis corneus*	**56d-NOEC= 0.2 (n)**	Reproduction	2	(Benstead, 2010)
Mollusc	Conditions acc. OECD 202	*Physa acuta*	**21d-NOEC= 0.1**	Reproduction	2	(Sanchez-Arguello et al., 2012)
Mollusc	No guideline	*Haliotis diversicolor*	8h NOEC=0.05 (n)	Embryo larval development	2	(Zhou et al., 2011)
Mollusc	No guideline	*Haliotis diversicolor*	EC10= 0.016 (n, but m)	Embryo development	2	(Liu et al., 2011)
Echinoderm ata	No guideline	*Paracentrotus lividus*	**72h-NOEC= 0.0035 (n)**	Larval malformations	2	(Özlem and Hatice 2008)
Echinoderm ata	No guideline	*Hemicentrotus pulcherrimus*	**80d-LOEC=0.071 (n)**	Suppressed juvenile growth	2	(Kiyomoto et al., 2005)
Porifera	No guideline	*Heteromyenia sp*	**9d-NOEC= 1.6 (n, analytical verification of highest test conc.)**	growth	2 used in RAR	(Hill et al., 2002)
Cnidaria	No guideline	*Hydra vulgaris*	**6w-NOEC= 0.042 (n, analytically verified)**	Growth, polyp structure	2 used in RAR	(Pascoe et al., 2002)
Cnidaria	No guideline	*Hydra oligactis*	**50d-NOEC= 0.17 (n, analytically verified)**	Reproduction	2 used in RAR	(Fukuhori et al., 2005)
Rotifer	No guideline	*Brachionus calyciflorus*	**2d-NOEC= 1.8 (n.a.)**	Rate of population increase	1	(Springborn Smithers 2006b); (Mihaich et al., 2009)

Algae	EPA-560/6-82-002	*Pseudokirchneriella subcapitata*	**4d-EC_{10}= 1.36 (n.a.)**	Biomass	2	(Alexander et al. 1988)
Algae	EPA-560/6-82-002	*Skeletonema costatum*	**4d-EC_{10}= 0.4**	Biomass	2	(Alexander et al. 1988)
Macrophyte	OECD 221	*Lemna gibba*	**7d-NOEC= 7.8**	Growth	1	(Putt, 2003); (Mihaich et al., 2009)
Amphibian	No guideline	*Xenopus laevis*	**120d-NOEC= 0.0073**	Sex ratio (geomean of 1st and 2nd experiment)		(Levy, 2004; Pickford, 2010; Pickford et al., 2003)
Amphibian	No guideline	*Xenopus laevis*	90d-NOEC= 0.5 (n)	Mortality, growth, sexual differentiation	1	(Pickford, 2010; Pickford et al., 2003)
Amphibian	No guideline	*Xenopus laevis*	NOEC= 0.228 (n)	Abnormal development	2	(Baba et al., 2009)
Amphibian	No guideline	*Xenopus laevis*	21d-NOEC= 0.0228 (n)	T3-induced metamorphosis inhibition	2	(Heimeier et al., 2009)

[1] Results are based on the measured (no letter) concentration or nominal (n) or it is not applicable (n.a.); durations of the exposure phases are often given in the following way: days post-fertilisation (dpf); days post-hatch (dph); hours post-fertilisation (hpf); weeks (w); days (d)

* values in bold were also used for SSD (for *Daphnia*: geomean used = **3.23 mg/L**)

11.5.1 Chronic toxicity to fish

Chronic toxicity to fish was evaluated in the Risk Assessment Report (European Commission, 2010) and the SVHC Support Document of Bisphenol A (ECHA, 2017b). Citations from these reports are written in italic letters. Only the most sensitive reliable studies relevant for classification are described below in detail and are otherwise summarized for each species.

Carp *(Cyprinus carpio)*

For *Cyprinus carpio* Bowmer and Gimeno (2001) observed a 49d-NOEC for growth of 0.1 mg/L. Also effects on oviduct formation were observed in male carp in the same study (NOEC= 0.016 mg/L).

Zebrafish *(Danio rerio)*

Depending on the endpoint and study design the results (NOECs) for *Danio rerio* range from 0.000372 to 0.75 mg/L. The test design of these four studies differed, e.g. with test durations from 75 to 300 days. The lowest reliable effect concentration (LOEC) was observed by Chen et al. (2015) for the endpoints sex ratio, larval malformations and larval mortality and was already considered during SVHC identification with a female-biased sex ratio as clear endocrine mediated and adverse endpoint. This study is described in detail below (cited in italics from ECHA, 2017b):

Chen et al. (2015) investigated the effects of BPA exposure on Danio rerio (wild type AB strain) in a non-GLP two-generation study. It was a limit-test with a test concentration of 0.228 µg/L BPA (1 nM) (mean measured: 0.372 µg/L) and a solvent control (0.01 % DMSO) (mean measured BPA: 0.032 µg/L) (reliability 2). The exposure concentration was analytically confirmed by HPLC analysis in fresh but not in expired solutions (personal communication with the author Jiangfei Chen, November 2017: equal to (Chen et al., 2017)). The test was conducted semi-static at 28 °C (in the publication; personal communication of the registrant with the author: 22-25 °C) with 14 hours light per day as recommended in OECD Test guideline 234. The oxygen supply was obtained by using an air pump system. The precise oxygen saturation was not measured. Zebrafish embryos were obtained from spawning adults in tanks overnight with a sex ratio of 1:1. Embryos were collected within 0.5 h of spawning and rinsed in an embryo medium. They were used to start the first generation (F1) for the solvent control and BPA-exposure. Adult F1 fish (150 d) within the same treatment group were mated (4 females x 4 males/replicate; 3 replicates) to produce F2 embryos. Mating was conducted in clean water. The F2 embryos obtained from the F1 fish exposed to BPA were exposed at 8 hpf to BPA again (B2 – exposed for two generations), or not exposed (solvent only – exposed for one

generation) (B1). There was also a group without exposure to BPA at all (B0). According to (Chen et al., 2015) the whole experiment was repeated three times each starting with a new batch of embryos (with a minimum of 90 embryos per replicate). The sex ratio was checked visiually based on the morphological difference of the male and female zebrafish by an observer blind to the treatment. This was confirmed histologically on some fishes. Most were checked visually. There were no significant differences between the visually and histologically checked sex of fish (personal communication December 2017). The embryos were exposed from 8 hpf in a petri dish. After 8-72 hpf the water once was changed. 5 dpf the fish was moved to a 2 L tank. From 5 to 150 dpf the water was changed every 5 days. At day 21 post fertilisation the fish was moved to 9 L tanks. 90 eggs were used from each replicate to evaluate the embryo development. Chen et al. (2015) used 30 eggs per replicate. Four replicates were used for the first generation and three for the second generation. The sex ratio of control fishes was 57 % females (OECD 234: 30 to 70 % males or females). The statistical analysis was performed using an ANOVA followed by Tukey's multiple comparison test. For gene expression test, an unpaired t-test with 5 % FDR was performed. The control mortality was 2 to 16 %, the control fish body weight was 280 mg (mean) and the control length was 18 mm (mean). This is well in line with OECD 234 (<25 %). Chronic exposure to 1 nM BPA for only F1 generation or both F1 and F2 generation had no effect on adult fish survival nor were there any obvious malformations in parental F1 and F2 fish. The exposure resulted in a significantly altered sex ratio of the F1 and F2 population with more female in both F1 and F2 adults. BPA exposure also significantly reduced sperm counts and quality of F1 and F2 males (reduced sperm density, sperm motility, sperm ATP production, and significant increase in sperm lipid peroxidation). Despite the observation that BPA exposure reduced sperm density and quality, they found no evidence of histological lesions in testes of exposed fish. There were no significant differences in egg production and fertilisation of F1 and F2 females or adverse effects of embryo hatching or survival in offspring from F1 parents. The results fit well to the fact that sperm cells that successfully fertilized eggs are more likely to be normal in motility because only one sperm is required to fertilize one egg. Also with less motile sperm there is still enough to fertilise a typical spawn of eggs from the females. Paternal BPA exposure had a significant adverse effect on malformation (e.g., uninflated swim bladder, pericardial oedema and bent body) and mortality at 8 dpf. For example, % malformation in larvae derived from females paired with males from B0 was in a range of 7 ~ 17 %, which was increased to ~30 % in those paired with males from B1 and ~46 % in those paired with males from B2. Similarly, mortality increased from 2 % to 18 % in larvae derived from females paired with males from B0 to ~24 % and ~44 % in those paired with males from B1 and B2, respectively. It is possible that that this malformation and higher mortality results from an effect of BPA on sperm DNA. Chen et al. (2015) found reduced expression of dnmt1, dnmt3, dnmt5 and sp3 in 5 d old larvae which may contribute to the paternal-specific reproduction failure. This is similar to the result from a study with rats (Doshi et al., 2012). Chen et al. (2015) state that further studies are needed. In Chen et al. (2017) further effects of BPA exposure (nominal: 0.228, 2.28, and 22.8 µg/L) during different developmental stages (embryonic, larval, sexual mature) were examined. Exposure to 0.228 µg/L BPA during embryonic development increased malformations and mortality of offspring while egg production and fertilisation were reduced in higher concentrations (22.8 µg/L). Additionally, sperm quality (density, velocity, motility) and testis weight were decreased in F0 after embryonic exposure to 0.228 µg/L BPA.

Japanese medaka *(Oryzias latipes)*

For *Oryzias latipes* the No Observed (adverse) Effect Concentrations (NOECs) range from 0.060 to 2.12 mg/L, depending on the endpoint and test design.

Rainbow trout *(Oncorhynchus mykiss)*

For *Oncorhynchus mykiss* there is a 28-day juvenile growth test resulting in a NOEC for growth rate of 3.64 mg/L.

Fathead minnow *(Pimephales promelas)*

For *Pimephales promelas* there are studies with a range of NOECs from 0.016 to 0.16 mg/L, depending on the endpoint and test design.

Brown trout *(Salmo trutta)*

For Salmo trutta f. fario *Lahnsteiner et al. (2005) described a 103 d-study starting with male and female fish during late pre-spawning and spawning period. The approximately three years old wild caught brown trout were exposed via a flow-through test system to 1.75, 2.40 and 5.00 µg BPA/L (one tank per test concentration). DMSO was used with concentrations following OECD recommendations. There is no indication for a chemical analysis but due to the flow-through system and DMSO use, no loss of BPA is expected. Lahnsteiner et al. (2005) observed effects on egg production and semen fertility (LOEC= 5 µg/L; NOEC= 2.4 µg/L). At the highest exposure concentration (5.00 µg/L) no females gave eggs and the semen fertility was 28 %. They observed also a delay in the time point of ovulation (LOEC = 1.75 or 2.4 µg/L) but with only 6 fishes for this endpoint no significance can be proven and therefor is not used in the assessment* (ECHA, 2017b).

Guppy *(Poecilia reticulata)*

For *Poecilia reticulata* there is a study observing effects of BPA after 30 days on survival above 0.5 mg/L (NOEC).

Sheepshead minnow (*Cyprinodon variegatus)*

There is 1.5-generation test available for *Cyprinodon variegatus* examining effects of 6 different BPA concentrations (control, 9.4, 19, 38, 75, 150, and 300 µg/L) in flow-through aquaria at 28 ± 1 °C. 50 embryos (< 30 hph) were placed into 28 incubation cups, with one cup in each of 4 replicate aquaria. On test day 4, 25 newly hatched fry in each incubation cup were placed in their respective growth chambers. At approximately 55 dph, spawning groups (2 males and 5 females) from each test aquarium were placed in one section of the corresponding spawning chamber in all test vessels, where they were held for 22 days. Exposure of F0 fish was terminated at 111 dph. Exposure of F1 fish was initiated by incubating groups of 50 embryos on the day they were spawned by placing them in the third section of the replicate tanks. Following hatching of the embryos, F1 exposure was continued by impartially placing a group of 25 newly hatched larvae (per replicate aquarium) into a corresponding larval growth chamber. The BPA concentrations were analytically confirmed (HPLC), resulting in measured concentrations of 76 to 88 % of the nominal ones (7.1, 17, 31, 66, 130, and 250 µg/L). Dissolved oxygen concentration and pH ranged from 5.1 to 8.3 mg/L (≥75 % saturation) and 6.7 to 8.2, respectively. Salinity ranged from 19 to 22‰, and exposure solution temperatures ranged from 26 to 29 °C. No effects were observed for larval surivial or growth. The number of eggs per female per day was reduced, resulting in a NOEC of 0.066 mg/L.

Summary for fish

In summary, for classification the most sensitive fish species is *Danio rerio* with effects on sex ratio, larval malformations and larval mortality at 0.000372 mg/L (LOEC; measured concentration). The resulting NOEC is < 0.000372 mg/L (measured concentration). This test was assessed, discussed and taken into account for the Annex XV dossier for the identification of Bisphenol A as an substance of very high concern because of its endocrine disrupting properties (Article 57f) causing probable serious effects to the environment which give rise to an equivalent level of concern to those of CMR and PBT/vPvB properties, which was adopted on 14.12.2017 (ECHA, 2017b). The endpoint sex ratio is considered adverse. As this study used only one concentration (Limit-test), on which the described effects occurred, no definite NOEC could be derived. There are two other studies with very low effect concentrations conducted with *Dania rerio* (Chen et al., 2017;Keiter et al., 2012) – with a NOEC for egg production of 0.000174 mg/L and a NOEC for growth of < 0.01 mg/L, respectively – supporting this result.

11.5.2 Chronic toxicity to aquatic invertebrates

Chronic toxicity to aquatic invertebrates was already evaluated in the Risk Assessment Report of Bisphenol A (European Commission, 2010) as well as in the context of the identification of BPA as SVHC (ECHA 2017).

Crustacea

Daphnids were shown to be quite insensitive towards BPA with regard to chronic effect. This is shown in several studies with NOEC values between 1.7 and 6.6 mg/L for *Daphnia magna*. According to the Guidance on the application of the CLP criteria (ECHA, 2017a) chapter 4.1.3.2.4.3 “where more than one acceptable

test is available for the same taxonomic group, the most sensitive is generally used for classification. […] When larger data sets (four or more values) are available for the same species, the geometric mean of toxicity values may be used as the representative toxicity value for that species. […] This implies that for substances, where four or more ecotoxicity data on the same species and endpoint are available, the data should be grouped, and the geometric mean used as a representative toxicity value for that species." For *Daphnia magna* there are four toxicity values available and therefore the geometric mean was used, which is 3.23 mg/L. For *Ceriodaphnia dubia* there is a NOEC value of 0.94 mg/L available (see table). Copepods are more sensitive, but no studies with verified exposure concentrations are available although well-documented: an EC_{10} of 100 µg/L for *Acartia tonsae* for larval developmental inhibition (Andersen et al. 2001) and 21d-NOECs of 0.1 (maturity parental) and **0.01 µg/L** (delay nauplii stage parental and maturity F1 generation). For the amphipod *Hyalella azteca* a NOEC for cumulative number of offspring per female was estimated as 490 µg/L by Mihaich et al. (2009) in a GLP-study using US EPA guidelines. For *Gammarus pulex* no effects on molting and reproduction could be discerned in concentrations up to 1000 µg/L (Johnson et al., 2005) without reporting results from analytics.

Insects

(Watts et al., 2003) observed a delay in time to the first molt and mean wet weights of first instar larvae at the highest test concentration (1000 µg/L). The actual concentration of the 1 mg/L test solution was measured to be 83 % of nominal concentrations and within 20 %. A NOEC of 0.1 mg/L was determined valid and was used in the RAR. Mouthpart deformities occurred at 0.01-100 µg/L (LOEC 0.01 µg/L), but the ecological significance is unclear.

Molluscs

Molluscs are a sensitive taxon with several valid results for the sexually reproducing *Marisa cornuarietis* and parthenogenetically reproducing *Potamopyrgus antipodarum*:

For ***Marisa cornuarietis*** (Oehlmann et al., 2006) reported results from two exposure series. While the first exposure series I (Oehlmann et al., 2000) and Schulte-Oehlmann et al. 2001) is not fully valid due to incomplete experimentation and only may be used as support, the second series II is valid. Both experiments used a strain originating from Aquazoo Düsseldorf with regular indbreeding and were conducted under a semi-static exposure regime, with medium renewal every day (every second day for weekends), a light:dark cycle of 12:12, acceptable water parameters and included a solvent control (12.5 µg/L Ethanol).

In exposure series II, 2 replicate groups of 30 sexually mature snails each were exposed to 0 - 0.25 - 0.5 - 1 and 5 µg/L BPA (additionally 5 µg/L bisphenol-A with either 3 µg/L of the anti-estrogen ICI 182 780 or 10 µg/L of the anti-estrogen tamoxifen) at 20 +/- 1 °C and 27+/- 1 °C in parallel for 5 months (February-July). Samples for analytical determinations of exposure concentrations were taken over a 24-h period (before exchange of media until 24h later before next exchange of media) at month 1 for the second series (and month 1, 3 and 5 for the first series). Measured initial concentrations were very close to nominals, but concentrations declined between renewals. Results were therefore expressed in terms of median (not time-weighted) measured concentrations, which were between 39.0 % and 48.3 % of nominal levels. At 20 °C, BPA-exposed snails produced significantly more clutches and eggs compared to controls starting at the lowest test concentrations of 0.106 µg/L (measured, nominal: 0.25 µg/L). As a NOEC cannot be calculated, EC_{10} values were estimated to be 0.0148 µg/L (95 % confidence interval 0.00607– 0.0362) and 0.018 µg/L (95 % confidence interval 0.062-0.525 µg/L) for egg and clutch production, respectively.

Similar effects were already observed in the first (incomplete) exposure series I at 22 °C starting from concentrations of 0.0079 µg/L (0.05 µg/L nominal) (calculated EC_{10}: 0.0139 respectively 0.0146 µg/L measured). Here, 210 mature snails were exposed in groups to 0 – 0.05 – 0.1 – 0.25 – 0.5 and 1 µg/L BPA and positive control 0.01 µg/L EE2, for 6 months (september- march) at 22+/- 1 °C and samples of 30 snails collected every month for analysis.
At 27 °C in exposure series II, none of the treatment groups produced significantly more clutches, or eggs per female, than the control. A significant increase in egg production was only detected if measured in terms of cumulative egg number at 1 and 5 µg/ L (nominal) BPA. Here, the NOEC for egg production was 0.205 µg/L (measured, EC_{10}: 0.998 µg/L (95 % confidence interval 0.161-6.200 µg/L)) and the NOEC for clutch production was >1.990 µg/L (EC_{10}: 2.090 µg/L; 95 % confidence interval 0.796-5.460 µg/L).

The temperature-related differences in NOECs are seen as a direct consequence of the lower egg production in controls observed at 20 °C (~500 eggs/female over the 5-month period). "Superfemales" with malformations of gonads (enlarged accessory glands, gross malformations and pallial oviduct) were already observed in the first exposure series at 22 °C at 1 µg/L (nominal). Also at 20 °C (series II), females with oviduct malformations were found with an incidence of 4.8 %, 8.0 %, 14.8 % and 11.5 % at 0.25, 0.5, 1, and 5 µg BPA/L (nominal), but not at 27 °C. Mortality was increased in groups experiencing oviduct malformation (around 10 deaths per treatment group at 20 °C, compared to 3 in the controls).

The study of (Oehlmann et al., 2006) is well-documented and reproduced at lower temperatures (20° and 22 °C). The effects on egg production were observed during a seasonal period of low spawning behaviour with a natural low egg production. The increased egg production is associated with malformations of gonads and increased mortality compared to controls at increasing test concentrations. Due to the statistical and analytical challenges, two subsequent attempts to recalculate effect concentrations have been made: (van der Hoeven, 2005) assumed a linear concentration response relationship and estimated a EC_{10} of 2.1 µg/L (nominal), while Ratte (2009) estimated an **EC_{10} of 0.038 µg/L (meas TWA)** for the parameter egg production based on measured concentrations. Definite effects with a **LOEC of 0.25 µg/L nominal (median measured 0.106 µg/L, TWA 0.028 µg/L)** for effects on egg and clutch production rate represent the "best case", with effects potentially occurring even below and a NOEC certainly below.

Another study series with *Marisa cornuarietis* was conducted by Forbes et al. (2007a and b, Forbes et al. 2008) under a flow-through exposure regime and GLP standard for 181 days (6 months) using another strain originating from a tropical lake. The test method was previously established during a 12 month period without BPA exposure (see Auf der Heide et al. 2006 and Selck et al. 2006) and preliminary tests conducted at test concentrations of 0.1-1-16-160 and 640 µg/L at 25 °C for 3 months (see Warbritton et al. 2007a and Forbes et al. 2007a and b). Here no effects on egg hatchability, fecundity and growth rate could be discerned. In the definite test, nominal test concentrations of 0.1 – 1 – 25 and 640 µg BPA/L were applied using 3 replicates and tests were conducted at 25 °C. The evaluated endpoints comprised mortality, adult fecundity, hatchability and juvenile growth. The lowest NOEC was 25 µg/L nominal (measured 15.5 µg/L) both for juvenile growth (after 90 days) and for fecundity (after 181 days) at 25 °C. The results were confirmed in an additional experiment at 22 °C for one single test concentration (25 µg/L) after 84 days (see Forbes et al. 2008, Warbritton et al. 2007b). The study was conducted during seasonal conditions of high spawning behaviour with high/maximum egg production rates and may therefore have masked effects. It differs considerably with regard to test conditions from Oehlmann et al. 2006.

Sieratowitz et al. (2011) exposed ***Potamopyrgus antipodarum*** to 5 – 10 – 20 and 40 µg/L BPA for 28 days at different temperatures (7, 16, 25 °C). Chemical analyses were performed and experiments were conducted during pre-validation according to the test guideline proposal but examining temperature dependencies. At 16 °C a NOEC of 20 µg/L (19.4 meas), whereas at 7 and 25 °C **NOECs of 5 µg/L (meas: 4.6 µg/L)**, were estimated for the endpoint increased embryo production. The study is well-documented, valid and meets the quality criteria of the TG as conducted during pre-validation of TG 243.

Jobling et al. 2004 (corrected version) exposed *Potamopyrgus antipodarum* to 1 – 5 - 25 and 100 µg/L BPA nominal for 90 days in a semi-static system with 50 % of the dosed water being replaced every four days. Embryo production was significantly increased in comparison to controls after 63 days at 5 and 25 µg/L, while it decreased at 100 µg/L. A **NOEC of 1 µg/L (nominal)** was derived. As no analysis of the exposure solutions was performed, the study is not fully valid but supports a low NOEC for this species (as was also concluded by EU RAR).

Also Benstead et al. (2008), discussed in the transitional RAR of UK (ECHA 2009), report a significant increase in embryo numbers of *Potamopyrgus antipodarum* after 28d exposure at concentrations starting at the lowest test concentration of **0.2 µg/L (LOEC, nominal, measured: 0.168 µg/L**). Test concentrations were 0.2 – 2 and 20 µg/L nominal. Hence, a NOEC could not be derived. Athough the study had some drawbacks with respect to analytics (i.e. BPA was detected in the controls (5 times lower than test concentrations with effects), it supports stimulatory effects at low effect concentrations.

The observed effects on egg production in snails are supported by further studies with snails and are

considered adverse. Also for the marine snail *Nucella lapillus* Oehlmann et al. (2000) observed an enhanced oocyte development and enlarged sex glands at low concentrations (NOEC < 1 µg/L nominal, no analytical confirmation). And for the marine sea snail *Haliotis diversicolor supertexta* Zhou et al. (2011) estimated a NOEC for embryo development of 0.05 mg/L. For the same species Liu et al. (2011) estimated an EC10 of 0.016 mg/L for embryo development and larval malformations and EC50s 0.18 and 1.02 µg/L for reaching trochophore stage and metamorphosis, nominal, but analytics confirmed -3+8 %). Benstead et al. (2010) reported an 56d NOEC of 0.2 mg/L for *Planeorbis corneus* on reproduction.

Further invertebrates (Echinodermata, Porifera, Cnidaria, Rotifera)

For echinoderms, an 72h-EC10 of 0.42 mg/L for *Paracentrotus lividus* (Özlem and Hatice 2008) and an 96h EC50 of 0.227 mg/L (Roepke et al. 2005) and a NOEC of 0.71 m/L (Kiyomoto et al. 2006) for *Strongylocentrotus purpuratus* were reported.

Effects on the freshwater sponge (Porifera) *Heteromyenia sp.* were reported by Hill et al. (2002) and already considered in the EU RAR with a 9d NOEC of 1.6 mg/L (nominal, analytics for highest test conc.) with respect to growth.

For the cinidarian *Hydra vulgaris* a NOEC of 42 µg/L (nominal, analytics done) was estimated for the structure and physiology of polyps growth-related end point (Pascoe et al. 2002). For *Hydra oligactis*, a NOEC for suppression of testis formation of 500 µg/L is available (Fukuhori et al. 2005).

A 48-h NOEC of 1.8 mg/L (measured) is available for the rotifer *Brachionus calyciflorus* for the endpoint population increase (Mihaich et al., 2009)).

Summary for aquatic invertebrates

Snails are the most sensitive group, where valid results are available. The increase in egg production was observed in several experiments and at least two species. The LOEC of 0.25 µg/L nominal (median measured 0.106 µg/L, TWA 0.028 µg/L) for effects on egg and clutch production rate represents a reliable "best case". Copepods are also sensitive, but no analytics were conducted.

11.5.3 Chronic toxicity to algae or other aquatic plants

Chronic toxicity to algae and other aquatic plants was evaluated in the Risk Assessment Report of Bisphenol A, which has been copied here in italic letters (European Commission, 2010).

Alexander et al. (1985b; 1988) […] describes the test methods and test concentrations, and this test was considered valid for use in the PNEC derivation. In addition to the EC_{50} values reported, the percentage inhibition of cell count and cell volume is reported for the concentrations tested. From these data it is possible to derive an EC_{10} using probit analysis. The calculated 96 hour EC_{10} values are 1.36 mg/L based upon cell count and 1.68 mg/L based upon cell volume.

Springborn Bionomics Inc. (1985c) (also published in Alexander et al. (1988)) report 96-hour EC_{50} values, based upon cell count and chlorophyll content, of 1.0 mg/L and 1.8 mg/L, respectively for the marine alga Skeletonema costatum. The test report describes the test methods and test concentrations were measured. The method used to estimate the effect concentrations was non-linear interpolation. The percentage inhibition of cell count and chlorophyll content is reported for the concentrations tested. These original data have been analysed by the rapporteur [of the risk assessment report (European Commission, 2010)] *using probit analysis in accordance with the OECD Guideline. The resulting EC_{50} for cell count is 1.1 mg/L, and that for chlorophyll content is 1.4 mg/L. It is also possible to derive EC_{10} values using the probit analysis. The calculated 96-hour EC_{10} values are 0.69 mg/L based on chlorophyll content and 0.40 mg/L based upon cell count.*

Putt (2003) reports a 7-d frond density, biomass and growth rate NOEC of 7.8 mg/L for the duckweed Lemna gibba. The static-renewal study was performed to GLP according to OECD Guideline 221 and

analytical measurement of bisphenol-A showed that test concentrations remained between 79-100 % of nominal. The test report describes the test methods and test concentrations.

In summary, the 96h-EC_{10} of 1.36 mg/L for Ps.subcaptitata was considered valid in the risk assessment report and used in PNEC derivation for freshwater primary producers. For saltwater primary producers, *the 96h-EC_{10} of 0.40 mg/L for S. costatum* was *considered valid for the use in the derivation of a saltwater PNEC.*

11.5.4 Chronic toxicity to other aquatic organisms

There are different chronic tests on toxicity to amphibians, which has been evaluated in the Risk Assessment Report and the SVHC Support Document of Bisphenol A (European Commission, 2010) (ECHA, 2017b).

The No observed effect concentrations (NOECs) range from 0.0073 mg/L to 0.5 mg/L for *Xenopus laevis* depending on test design and endpoint.

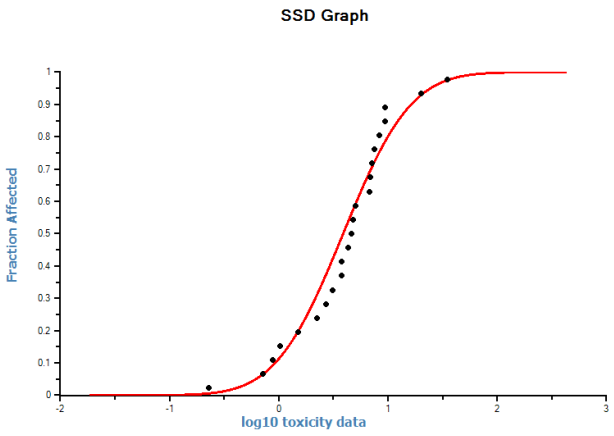
11.6 Comparison with the CLP criteria

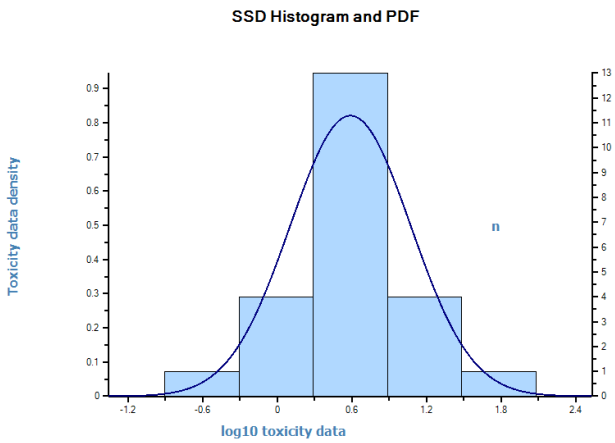
11.6.1 Acute aquatic hazard

The lowest valid EC_{50} for classification is **0.885 mg/L** for the invertebrate *Acartia clausi* (Tato et al., 2018) (deterministic approach).

According to the CLP Guidance, in case of very large data sets according to ECHA Guidance R.10, statistical techniques (e.g. HC_5 derivation via a SSD) can be used to estimate the aquatic toxicity reference value for classification (equivalent to using the lowest EC_{50}), when the criteria for applying the Species Sensitivity Distribution (SSD) approach (probabilistic approach) are met. For BPA sufficient species (>10) and taxonomic groups (>8) are available to meet the criteria for applying the Species Sensitivity Distribution (SSD) approach. The acute freshwater and marine water ecotoxicity values displayed in bold in the table in section 12.4 above (table 10) were used for the SSD analysis. For *Daphnia magna* a geomean of 9.47 mg/L (nominal, 1 study measured) calculated from 8 studies was used for the 48h EC50.

The SSD model assumes normal distribution of species sensitivities – for acute ecotoxicity this may be assumed as the endocrine mode of action of BPA rather exerts effects in long-term ecotoxicity studies. The data followed a normal distribution according to the three goodness-of-fit tests (Kolmogorov-Smirnov, Anderson-Darling and Cramer-von Mises).





"Goodness of fit" for the SSD acute EC_{50} values for all taxonomic groups were calculated with the *E_TX* 2.1 software (Van Vlaardingen, 2014).

Anderson-Darling test for normality				
Sign. level	Critical	Normal?		
0.1	0.631	Accepted		
0.05	0.752	Accepted	AD Statistic:	0.46223129
0.025	0.873	Accepted	n:	23
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:	0.68502791
0.025	0.995	Accepted	n:	23
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:	0.07925451
0.025	0.148	Accepted	n:	23
0.01	0.179	Accepted		

A HC_5 of **0.60 mg/L** was obtained with lower and upper limits of 0.29 and 1.01 mg/L, respectively.

This value is very similar to the value derived using the deterministic approach based on the lowest effect concentration, i.e. the most sensitive species EC_{50} of **0.885 mg/L**. Both values are below 1 mg/L and lead to a classification as Aquatic Acute 1 with an M-factor of 1.

Table 12: Comparison with criteria for acute aquatic hazards

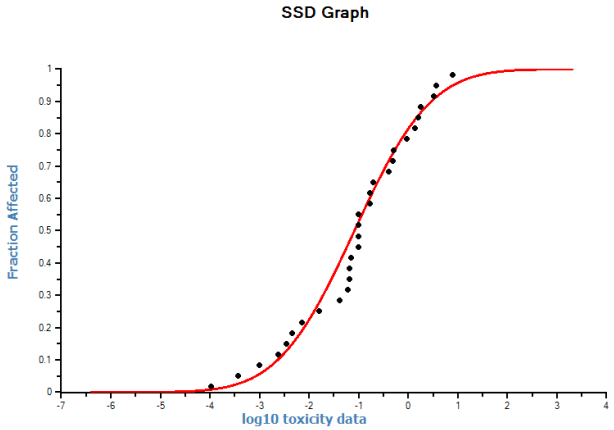
	Criteria for acute environmental hazards	**Bisphenol A**	**Conclusion**
Acute Aquatic Toxicity	Cat. 1: $LC_{50}/EC_{50}/ErC_{50} \leq 1$ mg/L	Fish: 96h-LC_{50}= 4.6 mg/L (n) (*Pimephales promelas*) Invertebrates: 48h-LC_{50}= 0.885 mg/L (m) (*Acartia clausi*) Algae: 96h-ErC_{50}= 3.73 mg/L (m) (*Navicula incerta*) SSD: HC_5 = 0.60 mg/L	**Aquatic Acute 1, M= 1**

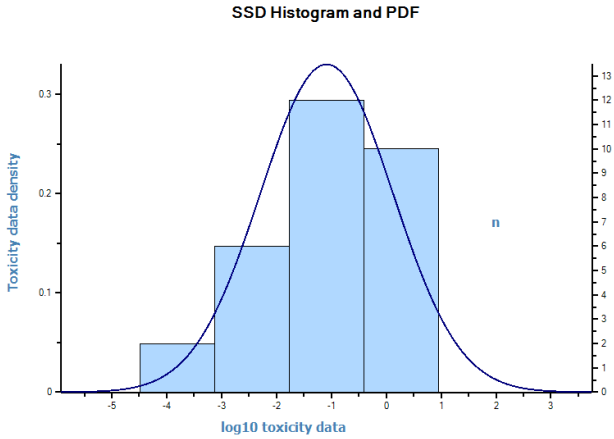
11.6.2 Long-term aquatic hazard (including bioaccumulation potential and degradation)

For the most sensitive species in some studies effects occurred even at the lowest test concentrations. Therefore, not for all studies definite NOECs were determinable. It would not be appropriate to take only the studies into account, in which these definite NOEC were derivable. This would not represent the properties of Bisphenol A and therefore underestimate the effects, as the studies with effects even at the lowest test concentration are reliable. Using the lowest effect concentrations from a valid test would result in a LOECof 0.000372 mg/L for *Danio rerio* based on mean-measured concentrations (or a NOEC < 0.000372 mg/L) and 0.000106 mg/L for *Marisa cornuarities* based on median measured concentrations. ECHA Guidance R.10 specifies in table R.10-1 how to derive a NOEC from a LOEC if the effect is between 10 and 20 % (NOEC can be calculated as LOEC/2.). As there was more than 20 % effect in the *Danio*-study (35 %), this was no possibility for NOEC derivation. As described in chapter 11.5.2 it would also be possible to use the EC_{10} 0.000038 mg/L (meas TWA) derived from a statistical reevaluation by Ratte (2009) instead of the LOEC. Both above mentioned values are above 0.0001 mg/L and below 0.001 mg/L. Therefore, for rapidly degradable substances a classification of Aquatic Chronic 1 with a M-factor of 10 applies.

Similar to the approach used for the acute aquatic hazard, for the long-term aquatic hazard a probabilistic approach (SSD) is shown below. According to ECHA Guidance R.10, for a reliable SSD especially the comparability of test conditions and different endpoints for long-term toxicity as well as specific modes of action and the differences between taxa need to be considered. The SSD model assumes a normal distribution of species sensitivities. The resulting HC_5 is 0.00805 mg/L, using the effect values in bold see Table 11. Note: For some species there are studies were no NOEC is available as there were effects even at the lowest concentration tested. In this case, when the use of the other NOECs available for the species would not cover the whole “picture”/proberties of Bisphenol A, the LOEC is used and the HC5 means a optimistic hazard concentration. According to ECHA Guidance R.10 NOEC values below the 5 % of the SSD (HC5) need to be discussed, as this could be an indication that a particular sensitive group exists, implying that some of the underlying assumptions for applying the statistical extrapolation method may not be met. This is the case for *D. rerio* and *M. cornuarities* (LOECs= 0.000372 and 0.000106 mg/L, respectively).

Therefore, for classification the lowest valid effect concentration (LOEC- see above) is used, resulting in a classification of Aquatic Chronic 1 with an M-factor of 10.





"Goodness of fit" for the SSD acute EC_{50} values for all taxonomic groups were calculated with the *ETX* 2.1 software (Van Vlaardingen, 2014).

Anderson-Darling test for normality				
Sign. level	Critical	Normal?		
0.1	0.631	Accepted		
0.05	0.752	Accepted	AD Statistic:	0.46289058
0.025	0.873	Accepted	n:	30
0.01	1.035	Accepted		

Kolmogorov-Smirnov test for normality				
Sign. level	Critical	Normal?		
0.1	0.819	Rejected		
0.05	0.895	Accepted	KS Statistic:	0.87261095
0.025	0.995	Accepted	n:	30
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:	0.08106453
0.025	0.148	Accepted	n:	30
0.01	0.179	Accepted		

A HC_5 of 0.00805 mg/L was obtained with lower and upper limits of 0.00017 and 0.00253 mg/L, respectively.

Table 13: Comparison with critera for long-term aquatic hazards

	Criteria for environmental hazards	**Bisphenol A**	**Conclusion**
Rapid Degradation	Half-life hydrolysis < 16 days Readily biodegradable in a 28-day test for ready biodegradability (> 70 % DOC removal or > 60 % theoretical oxygen demand, theoretical carbon dioxide)	hydrolysis negligible >78.2 % after 28 days (O_2 consumption) => readily biodegradable	**Rapidly degradable**
Bioaccumulation	Log Kow ≥ 4 BCF ≥ 500	Log Kow = 3.4 BCF ≤ 144	**Not bioaccumulative (low potential for bioconcentration)**
Aquatic Toxicity	Rapidly degradable substances: Cat. 1: NOEC ≤ 0.01 mg/L Cat. 2: NOEC ≤ 0.1 mg/L Cat. 3: NOEC ≤ 1 mg/L	Fish: 300d-LOEC= 0.000372 mg/L (mean measured) (*Danio rerio*) Invertebrates: 150d LOEC= 0.00025 mg/L (nominal; median-measured: 0.000106 mg/L) (*Marisa cornuarietis*) Algae: 96h-E_rC_{10}= 0.40 mg/L (n.a.) (*Skeletonema costatum*)	**Aquatic Chronic 1, M= 10** *(based on fish-LOEC and invertebrate-LOEC)*

11.7 CONCLUSION ON CLASSIFICATION AND LABELLING FOR ENVIRONMENTAL HAZARDS

The most protective valid short-term toxicity concentration resulting in fifty percent effect is the 48h-LC_{50} of 0.885 mg/L (measured) for *Acartia clausi*. This results in a classification of Bisphenol A as Aquatic Acute 1; H400 (M-factor of 1).

Bisphenol A is rapidly degradable and has a low acutal bioaccumulation. The most protective valid long-term toxicity no (in this case: lowest) observed effect concentration is 0.000372 mg/L (mean measured) for *Danio rerio*. This is supported by a further valid lowest observed effect concentration for *Marisa cornuarietis* of 0.000106 mg/L (median-measured). A determination of NOECs were not feasible, the LOECs represent a “best case”. This results in a classification of Bisphenol A as Aquatic Chronic 1; H410 (M-factor of 10).

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