

# **SUBSTANCE EVALUATION CONCLUSION**

**as required by REACH Article 48  
and  
EVALUATION REPORT**

**for**

**4,4'-Isopropylidenediphenol**

**EC No 201-245-8**

**CAS No 80-05-7**

**Evaluating Member State(s):** Germany

Dated: May 2017

## **Evaluating Member State Competent Authority**

### **BAuA**

Federal Institute for Occupational Safety and Health  
Division 5 - Federal Office for Chemicals  
Friedrich-Henkel-Weg 1-25  
D-44149 Dortmund, Germany

### **Year of evaluation in CoRAP: 2012**

Before concluding the substance evaluation a Decision to request further information was issued on: 20 December 2013

Based on the registration updates provided by the registrants and further information supplied during the follow-up phase, the evaluating Member State concluded the evaluation without the need for further information requirements according to Article 46(1).

### **Further information on registered substances here:**

<http://echa.europa.eu/web/guest/information-on-chemicals/registered-substances>

## DISCLAIMER

This document has been prepared by the evaluating Member State as a part of the substance evaluation process under the REACH Regulation (EC) No 1907/2006. The information and views set out in this document are those of the author and do not necessarily reflect the position or opinion of the European Chemicals Agency or other Member States. The Agency does not guarantee the accuracy of the information included in the document. Neither the Agency nor the evaluating Member State nor any person acting on either of their behalves may be held liable for the use which may be made of the information contained therein. Statements made or information contained in the document are without prejudice to any further regulatory work that the Agency or Member States may initiate at a later stage.

## Foreword

Substance evaluation is an evaluation process under REACH Regulation (EC) No. 1907/2006. Under this process the Member States perform the evaluation and ECHA secretariat coordinates the work. The Community rolling action plan (CoRAP) of substances subject to evaluation, is updated and published annually on the ECHA web site<sup>1</sup>.

Substance evaluation is a concern driven process, which aims to clarify whether a substance constitutes a risk to human health or the environment. Member States evaluate assigned substances in the CoRAP with the objective to clarify the potential concern and, if necessary, to request further information from the registrant(s) concerning the substance. If the evaluating Member State concludes that no further information needs to be requested, the substance evaluation is completed. If additional information is required, this is sought by the evaluating Member State. The evaluating Member State then draws conclusions on how to use the existing and obtained information for the safe use of the substance.

This Conclusion document, as required by Article 48 of the REACH Regulation, provides the final outcome of the Substance Evaluation carried out by the evaluating Member State. The document consists of two parts i.e. A) the conclusion and B) the evaluation report. In the conclusion part A, the evaluating Member State considers how the information on the substance can be used for the purposes of regulatory risk management such as identification of substances of very high concern (SVHC), restriction and/or classification and labelling. In the evaluation report part B the document provides explanation how the evaluating Member State assessed and drew the conclusions from the information available.

With this Conclusion document the substance evaluation process is finished and the Commission, the Registrant(s) of the substance and the Competent Authorities of the other Member States are informed of the considerations of the evaluating Member State. In case the evaluating Member State proposes further regulatory risk management measures, this document shall not be considered initiating those other measures or processes. Further analyses may need to be performed which may change the proposed regulatory measures in this document. Since this document only reflects the views of the evaluating Member State, it does not preclude other Member States or the European Commission from initiating regulatory risk management measures which they deem appropriate.

---

<sup>1</sup> <http://echa.europa.eu/regulations/reach/evaluation/substance-evaluation/community-rolling-action-plan>

## Contents

<b>PART A. CONCLUSION</b> .....	<b>7</b>
<b>1. CONCERN(S) SUBJECT TO EVALUATION</b> .....	<b>7</b>
<b>2. OVERVIEW OF OTHER PROCESSES / EU LEGISLATION</b> .....	<b>7</b>
<b>3. CONCLUSION OF SUBSTANCE EVALUATION</b> .....	<b>9</b>
<b>4. FOLLOW-UP AT EU LEVEL</b> .....	<b>10</b>
4.1. Need for follow-up regulatory action at EU level.....	10
4.1.1. Harmonised Classification and Labelling .....	10
4.1.2. Identification as a substance of very high concern, SVHC (first step towards authorisation)	10
4.1.3. Restriction .....	11
4.1.4. Other EU-wide regulatory risk management measures.....	11
<b>5. CURRENTLY NO FOLLOW-UP FORESEEN AT EU LEVEL</b> .....	<b>11</b>
5.1. No need for regulatory follow-up at EU level.....	11
5.2. Other actions .....	11
<b>6. TENTATIVE PLAN FOR FOLLOW-UP ACTIONS (IF NECESSARY)</b> .....	<b>11</b>
<b>PART B. SUBSTANCE EVALUATION</b> .....	<b>12</b>
<b>7. EVALUATION REPORT</b> .....	<b>12</b>
7.1. Overview of the substance evaluation performed .....	12
7.2. Procedure .....	16
7.3. Identity of the substance .....	16
7.4. Physico-chemical properties .....	17
7.5. Manufacture and uses .....	18
7.5.1. Quantities .....	18
7.5.2. Overview of uses .....	18
7.6. Classification and Labelling .....	24
7.6.1. Harmonised Classification (Annex VI of CLP) .....	24
7.6.2. Self-classification .....	25
7.7. Environmental fate properties .....	25
7.7.1. Degradation .....	25
7.7.2. Environmental distribution .....	25
7.7.3. Bioaccumulation .....	26
7.8. Environmental hazard assessment .....	26
7.8.1. Aquatic compartment (including sediment).....	26
7.8.2. Terrestrial compartment .....	30
7.8.3. Microbiological activity in sewage treatment systems.....	30
7.8.4. PNEC derivation and other hazard conclusions .....	30
7.8.5. Conclusions for classification and labelling.....	31
7.9. Human Health hazard assessment .....	31
7.9.1. Toxicokinetics.....	31
7.9.2. Acute toxicity and Corrosion/Irritation .....	34
7.9.3. Sensitisation.....	34
7.9.4. Repeated dose toxicity.....	35

7.9.5. Mutagenicity.....	35
7.9.6. Carcinogenicity .....	35
7.9.7. Toxicity to reproduction (effects on fertility and developmental toxicity) .....	36
7.9.8. Hazard assessment of physico-chemical properties.....	36
7.9.9. Selection of the critical DNEL(s)/DMEL(s) and/or qualitative/semi-quantitative descriptors for critical health effects .....	36
7.9.10. Conclusions of the human health hazard assessment and related classification and labelling .....	40
7.10. Assessment of endocrine disrupting (ED) properties .....	41
7.10.1. Endocrine disruption – Environment .....	41
7.10.2. Endocrine disruption - Human health .....	42
7.10.3. Conclusion on endocrine disrupting properties (combined/separate) .....	43
7.11. PBT and VPVB assessment .....	43
7.12. Exposure assessment .....	43
7.12.1. Human health .....	43
7.12.2. Environment.....	48
7.12.3. Combined exposure assessment.....	51
7.13. Risk characterisation .....	51
7.14. References .....	58
7.15. Abbreviations .....	62

## Part A. Conclusion

### 1. CONCERN(S) SUBJECT TO EVALUATION

4,4'-isopropylidenediphenol (bisphenol A; BPA) was originally selected for substance evaluation in order to clarify concerns about:

- Suspected Endocrine Disruptor for the environment
- Exposure/Wide dispersive use
- Consumer use
- High aggregated tonnage

During the evaluation an additional concern was identified:

- Dermal Absorption

### 2. OVERVIEW OF OTHER PROCESSES / EU LEGISLATION

A Risk Assessment Report for BPA was prepared by the United Kingdom in the context of Council Regulation (EEC) No. 793/93 on the evaluation and control of existing substances.

Later on evaluations were performed by the Scientific Committee on Occupational Exposure Limits (SCOEL 2014), the Scientific Committee on Emerging and Newly-Identified Health Risks (SCENIHR 2015), the European Food Safety Authority (EFSA 2015) and The Netherlands, RIVM (2014, 2015).

A proposal to restrict the use of BPA in thermal paper under REACH Annex XVII was submitted by France in January 2014. This proposal aims to address the risks for human health of pregnant workers and consumers exposed to BPA contained in thermal paper they may handle. The final background document taking into account the opinions of RAC and SEAC has been published in December 2015. The restriction has been adopted on 12 December 2016. BPA shall not be placed on the market in thermal paper in a concentration equal to or greater than 0.02% by weight after 2 January 2020.

Since the start of the evaluation, a harmonised classification of BPA for reproductive toxicity (Repr. 1B) has been adopted.

The intention of France to identify BPA as a substance of very high concern (SVHC) due to its CMR and ED properties was published in February 2016 and an Annex XV dossier to identify BPA according to Art. 57c) as an SVHC due to its properties as a reproductive toxicant has been submitted in August 2016. Unanimous agreement by the Member State Committee on the identification of BPA as an SVHC according to art. 57c was reached at the MSC-51 meeting.

With respect to Human Health, the substance evaluation in February 2013 based its main sources of information on

- the Chemical Safety Report (CSR) of the lead registrant, dated **2012-10-04**
- the initial (2003) and the updated (April 2008) European Risk Assessment Reports,
- the Transitional Dossier (November 2008), and
- EFSA Scientific Opinion on BPA (2010) and the Report of Joint FAO/WHO Expert meeting (2010) including according background papers.

Since February 2013, updated toxicological assessments utilizing more sophisticated approaches in risk assessment have become available (SCOEL 2014, SCENIHR 2015, EFSA 2015, ECHA (2015) and RIVM (2014, 2015). In particular, EFSA (2015) and ECHA (2015) used the Benchmark dose approach instead of determination of a no-observed adverse effect level when deriving a point of departure for risk assessment although the key study identified for that purpose was the same as the one used by the German MSCA for the evaluation in 2012-2013 and by EFSA (2015) and ECHA (2015).

Therefore, the eMSCA decided to perform human health related risk assessment and DNEL derivation in this conclusion document in accordance with the evaluations performed by EFSA (2015) and ECHA (2015), i.e. by using the Benchmark dose approach. For convenience, the EFSA (2015) and the ECHA (2015) evaluations are recommended for further reading and understanding.

Recently, EFSA evaluated two reports by RIVM (RIVM (2014, 2015) and specifically reviewed the toxicity of BPA on the immune system in light of two 2014 publications by Ménard et al. on immunotoxicity of BPA (EFSA, 2016). EFSA concluded that the results from the two studies were not sufficient to call for a revision of the t-TDI. However, EFSA announced the start of a review of all the scientific evidence published after 2012 and relevant for BPA hazard assessment in 2017 (EFSA, 2016). Thus, DNEL-derivations in this report based on kidney effects detected in the study by Tyl et al., 2008 have a provisional nature and might be subject for revision in the near future. In addition, the lead registrant referred to a recent *in vivo* dermal toxicokinetic study in humans from which some non-peer-reviewed information is available. Preliminary findings had been submitted during public consultation of the restriction proposal for BPA in thermal paper. Final results from this *in vivo* study might give a different figure on dermal absorption of BPA in humans than that obtained from the requested *in vitro* study prepared in the context of this SEv process on BPA.

Therefore, with respect to Human Health, all outcomes and conclusions reported in this document are based on the available information at the time of the substance evaluation and might be subject of change in the near future.



### 3. CONCLUSION OF SUBSTANCE EVALUATION

The evaluation of the available information on the substance has led the evaluating Member State to the following conclusions, as summarised in the table below.

**Table 1**

<b>CONCLUSION OF SUBSTANCE EVALUATION</b>	
<b>Conclusions</b>	<b>Tick box</b>
Need for follow-up regulatory action at EU level	X
Harmonised Classification and Labelling	
Identification as SVHC	X
Restrictions	
Other EU-wide measures	
No need for regulatory follow-up action at EU level	

## 4. FOLLOW-UP AT EU LEVEL

### 4.1. Need for follow-up regulatory action at EU level

#### Human Health:

The eMSCA has re-evaluated the RCR for bisphenol A using newly derived DNEL values as described in section 7.9.9, the results of RCR calculation are presented in section 7.12.1.2. According to this re-evaluation it is concluded by the member state that use of bisphenol A in thermal paper is not safe for the consumer. Furthermore, the use of articles made of PVC and larger articles made of polycarbonate is not safe for the consumer. Based on total exposure of the consumer the eMSCA concludes that the use of small articles made of polycarbonate and articles made of epoxy resins is safe. However, for dermal exposure the RCR for all articles made of polycarbonate exceeds the value of 1. Additionally, the RCR for dermal exposure towards larger articles made of epoxy resins also exceeds the value of 1.

It should be noted, however, that the DNEL is based on a conservative calculation. The restriction proposal for BPA in thermal paper has been legally implemented in December 2016. Therefore, the eMSCA concludes that no additional measure is currently required for bisphenol A in thermal paper regarding the protection of consumers as this restriction addresses the risk to human health appropriately.

In light of the risks identified regarding the additive use of BPA in articles made from PVC by consumers, the eMSCA supports the SVHC identification of bisphenol according to article 57c proposed by the French authorities and agreed upon unanimously by the MSC. It is expected that an authorisation of bisphenol A will address the possible risks in the use of bisphenol A in articles made of PVC. It should be noted that currently no description of safe use exists in the relevant registrations or downstream user reports regarding the use of BPA in the processing of PVC (cf. Section 7.2).

The eMSCA will evaluate the necessity of further action regarding human health in the follow-up of the SVHC identification process and the evaluation of the results of the two-year study by the U.S. National Toxicology Program scheduled for 2017.

#### Environment:

In the eyes of the eMSCA, the available data on endocrine effects of BPA in the environment are sufficient to conclude on BPA being an endocrine disruptor for the environment according to the WHO/ICPS definition. Therefore, further regulatory measures are relevant to address this hazard property of BPA.

#### 4.1.1. Harmonised Classification and Labelling

Since the start of the evaluation, a harmonised classification for reproductive toxicity (Repr. 1B) has been adopted for fertility. No additional classification is suggested based on the outcome of this evaluation. However, the eMSCA notes that endocrine disrupting effects for the environment cannot be captured by harmonised classification and labelling.

#### 4.1.2. Identification as a substance of very high concern, SVHC (first step towards authorisation)

BPA has already been proposed as an SVHC according to REACH article 57c) due to its classification as a reproductive toxicant with a second proposal to address endocrine disrupting properties for human health in a follow-up SVHC dossier. In view of the eMSCA, the available data is sufficient to conclude on the endocrine disrupting effects in the environment and possibly identify BPA as SVHC according to article 57f.

### 4.1.3. Restriction

The restriction of bisphenol A in thermal paper has been recently adapted. The use of BPA in thermal paper will be subject to a REACH restriction after formal adoption and a transitional period of 36 months. The eMSCA concludes that no additional action is required to address the risk of BPA in thermal paper once the restriction is in effect.

### 4.1.4. Other EU-wide regulatory risk management measures

Not applicable.

## 5. CURRENTLY NO FOLLOW-UP FORESEEN AT EU LEVEL

### 5.1. No need for regulatory follow-up at EU level

Not applicable.

### 5.2. Other actions

Not applicable.

## 6. TENTATIVE PLAN FOR FOLLOW-UP ACTIONS (IF NECESSARY)

**Table 2**

<b>FOLLOW-UP</b>		
<b>Follow-up action</b>	<b>Date for intention</b>	<b>Actor</b>
Updating of RMO Analysis	01/2017-06/2017	Germany
Possible SVHC identification according to article 57f – endocrine effects for the environment	Depending on outcome of RMOA	Germany

## Part B. Substance evaluation

### 7. EVALUATION REPORT

#### 7.1. Overview of the substance evaluation performed

4,4'-isopropylidenediphenol (bisphenol A; BPA) was originally selected for substance evaluation in order to clarify concerns about:

- Suspected Endocrine Disruptor for the environment
- Exposure/Wide dispersive use
- Consumer use
- High aggregated tonnage

**Table 3**

<b>EVALUATED ENDPOINTS</b>	
<b>Endpoint evaluated</b>	<b>Outcome/conclusion</b>
Endocrine disruption	<p>There is sufficient scientific evidence for an endocrine mode of action on aquatic organisms such as fish, amphibians as well as certain invertebrate species. Available studies are sufficient to conclude that Bisphenol A results in adverse effects due to its endocrine mode of action (i.e. is an Endocrine Disruptor according to the WHO/IPCS definition) and that these effects seem to be of equivalent concern according to Art 57 (f) REACH regulation.</p> <p>Due to its endocrine disrupting properties and the correlated specific uncertainties for deriving a safe concentration in environmental media, a risk-based approach is not appropriate to assess the environmental hazards of Bisphenol A. To be able to justify this and conclude on Bisphenol A to be an endocrine disrupter for the environment, there is no need for further data.</p>
Environmental exposure assessment / high aggregated tonnage	<p>Evaluation concluded 2013 with request for further data. In the lead registration dossier the exposure assessment was significantly improved with the update of the registration dossiers. However, due to the complex use and supply chain structure and some still remaining uncertainties in the assessment (e.g. in tonnages) it is not possible to decide without doubts which are the relevant pathways of emission to the environment. No further data are requested.</p>
Consumer exposure	<p>The eMSCA performed a risk assessment of the relevant consumer uses which were described in the registration dossiers at the beginning of the evaluation process. While some consumer uses are no longer</p>

	<p>supported by the majority of registrants, the eMSCA has identified certain uses which may pose a risk applying a conservative estimation.</p> <p>A revision of the registration dossiers to properly reflect the conclusions of the eMSCA regarding consumer uses of articles containing BPA should be conducted in order to safeguard the demonstration of safe use for the relevant articles.</p>
Dermal Absorption	<p>A new study on dermal absorption of BPA has been performed as a result of the information requirements of the BPA substance evaluation decision. The new data was used by the eMSCA to refine the corresponding risk assessment (cf. Section 7.9.1) of consumer uses considered relevant during the evaluation.</p>

The initial grounds of concerns from the justification document for inclusion in the CoRAP 2012 were the following (The order of the respective concerns has been adapted):

**Concern 1:**

As described in the updated risk assessment report, information on toxicity towards snails indicates that effects on this organism group might have been underestimated.

**Concern 2:**

Several studies indicate that Bisphenol A is an endocrine disruptor resulting in adverse effects at very low concentrations (at least low µg/L range) in aquatic organisms due to the endocrine mode of action. Risk calculated by PEC/PNEC ratios might underestimate the concern for the environment due to the endocrine disrupting mechanism of action.

**Concern 3:**

Some studies indicate that degradation in sewage plant might have been overestimated. This might result in underestimation of exposure e.g. by the use of recycled toilet paper. Recycled paper may contain Bisphenol A due to fractions of thermal paper used for recycling in which Bisphenol A acts as developer.

**Concern 4:**

As summarized in the updated risk assessment report, environment monitoring data especially for sediment concentrations indicate that exposure might have been underestimated.

**Concern 5:**

Production volume as well as exposure estimates were based on production volumes considering past EU 15 member states only. Current registrations include those from member states that joint later indicating that exposure might be higher than calculated in the EU risk assessment.

It was further stated in the justification:

Aspects described above indicate that current registration dossiers might underestimate risk for the environment. This is supported by a first check of one of the lead registration dossiers revealing that overall production volume and exposure assessment was based on data provided in EU 2010 and that some exposure scenarios such as emission from recycled toilet paper were not considered. Due to the number of registrants the actual exposure might be higher than estimated in the single registration dossiers and PEC/PNEC ratios might be exceeded.

The German CA considers a substance evaluation of Bisphenol A as necessary to check if concerns described above are addressed appropriately in current registration dossiers. In addition substance evaluation should reveal if – due to the high number of registration dossiers and the high production volume by each registrant – exposure is underestimated.

Based on a preliminary check, both exposure assessment as well as effect assessment especially with regard to aquatic toxicity (pelagic and sediment) needed to be evaluated.

### **Conclusions (environment)**

From an environmental point of view the analysis of the concerns revealed the following results:

#### **Concern 1:**

Snails are the most sensitive organism group affected by Bisphenol A. Effect concentrations in the low  $\mu\text{g/L}$  range (2.1  $\mu\text{g/L}$ ) were already assigned during the EU risk assessment (EU RAR 2008). New calculations of the respective data indicate even much lower effect concentrations for snails (recalculated EC10 of 0.038  $\mu\text{g/L}$ ). The low effect concentrations are supported by studies with other mollusc species. The available studies give evidence for effects at low concentrations, which need to be considered for a hazard assessment.

In view of the high number of studies already conducted with snails, it seems not to be justified to request a further testing.

#### **Concern 2:**

There is sufficient scientific evidence for an endocrine mode of action on aquatic organisms such as fish, amphibians as well as certain invertebrate species. Available studies are sufficient to conclude that Bisphenol A results in adverse effects due to its endocrine mode of action (i.e. is an Endocrine Disruptor according to the WHO/IPCS definition) and that these effects seem to be of equivalent concern according to Art 57 (f) REACH regulation.

Due to its endocrine disrupting properties and the correlated specific uncertainties for deriving a safe concentration in environmental media, a risk-based approach is not appropriate to assess the environmental hazards of Bisphenol A.

To be able to justify this and conclude on Bisphenol A to be an endocrine disrupter for the environment, there is no need for further data.

#### **Concern 3:**

Results from tests on ready biodegradability indicate that degradation might vary strongly with the environmental conditions, and especially the microbiotic community present. Studies with adapted inoculum demonstrate that a degradation of Bisphenol A is possible if microorganisms are adapted. In reliable tests conducted with non-adapted inoculum Bisphenol A is not ready degradable. Microorganisms in industrial sewage treatment plants of manufacturers and (downstream-) users may be adapted to Bisphenol A. However, Bisphenol A is ubiquitously used and may enter surface waters directly or via smaller sewage treatment plants with unadapted microorganisms. It cannot be generally concluded that Bisphenol A is readily degraded in the environment. Therefore, Bisphenol A may be assessed as not ready biodegradable for the environment. Since it is not expected that further studies on degradation might change the situation, no additional information is required to conclude on the concern.

#### **Concern 4:**

Data from existing monitoring programs (mainly in Germany) and scientific publications across Europe of the years 2007-2012 were evaluated in the context of a study report (Fischer et al., 2014). Bisphenol A is ubiquitously and regularly found in all environmental compartments (freshwater, marine water, soil, biota, sediment, sewage sludge, air/dust). Data is mainly available for the aquatic compartment. Here, measured concentrations are in the  $\text{ng/L}$  and up to  $\mu\text{g/L}$  range. This gives evidence for continuous emissions of Bisphenol A in surface waters. It remains still unclear to which extent certain uses are responsible for the emissions into the environment. It is most probable that the continuous presence

of Bisphenol A in relevant concentrations is caused by the aggregated emission of different sources due to the high number of uses.

**Concern 5:**

As an outcome of the substance evaluation further information on environmental exposure was requested to clarify suspected risk and to identify the main source of environmental exposure to conclude on the best risk management measure. For detailed description see the decision published on ECHA website.

In response to the request, registrants deleted several uses from the lead dossier, updated the lead dossier in December 2014 and 2015 (compare chapter 7.5.2) and modelled the emissions of BPA into the environment in the frame of a substance flow analysis (SFA) and regionalized pathway analysis (RPA) in 2015. In parallel the Epoxy Resin Committee provided exposure assessments for their main uses (<http://www.epoxy-europe.eu/en/resource/documents/>).

In the lead registration dossier the exposure assessment was significantly improved with the update of the registration dossiers. However, due to the complex use and supply chain structure and some still remaining uncertainties in the assessment (e.g. in tonnages) it is not possible to decide without doubts which are the relevant pathways of emission to the environment.

The substance flow analysis / regional pathway analysis (SFA / RPA) provided by Registrants during substance evaluation comes to the conclusion that emission to the environment result mainly from consumer uses. Bisphenol A is mainly emitted to surface water. Effluent from municipal and industrial waste water treatment plants are important sources. However, it was not shown which consumer uses contribute most to the emissions to the environment.

No further exposure data are requested within the substance evaluation procedure.

No further data on endocrine disruption resulting in adverse effect was requested as eMSCA is of the opinion that enough data is publicly available to conclude on the concern.

Most registrants provided an update of their registration dossier. Main change in the registration dossier was the deletion of uses of Bisphenol A as additive. Furthermore, the Bisphenol A consortium provided a modelling study to identify sources of environmental exposure.

Within the scope of the update, the epoxy resin industry in particular provided extensive reflections on the environmental exposure of its main application fields.

In parallel to the substance evaluation the JRC has drafted a dossier for the derivation of an environmental quality standard value.

The eMSCA concluded that emission into the environment occurs. According to the SFA/RPA and the other documents provided consumer uses and professional uses are made responsible for the emission without distinction being made in the various uses.

*Further concerns and annotations with respect to the CSR and IUCLID:*

PNEC derivation: According to ECHA (questions and answers 10.7.2012, question 10), the SEV is not meant to achieve a harmonization or changes of the PNEC values, with the exception if values are not derived properly. According to Annex I 0.5, the registrant needs to justify if PNECs are derived by another method than during previous assessments such as in the EU RAR (2008). The method used as well as the selected studies for the SSD deviate from the EU RAR (2008). The registrant did not provide a justification. Moreover, assessment factors were not applied properly: for PNEC water an assessment factor of 1 seems not to be justified as no mesocosm or field data is included. Please refer to chapter 7.1.2 of the SEV report for further details.

## 7.2. Procedure

**Note:** This evaluation report takes into account publications and available data on BPA up to November 2013. Publications made available after this date have not been taken into account to derive the conclusions given herein. Data as requested from the registrant was considered in this document.

BPA was included in the first Community Rolling Action Plan (CoRAP) for evaluation by Germany in 2012. The evaluation process was started in March 2012 and evaluation was concluded within 12 months with the issuing of a draft decision requesting further information from the registrants pertaining to environmental exposure and dermal absorption of BPA. The decision<sup>2</sup> was finalised by the Member State Committee in November 2013 and consequently taken by ECHA. The decision required the concerned registrants of BPA to update their registration dossiers until 20 December 2015 with use-specific information leading to environmental exposure as well as information from a skin absorption study with specifications given in the decision. An update of the lead registration and joint chemical safety report as well as a portion of joint registrations was received until December 2015 and in some cases with considerable delay in 2016.

The eMSCA assessed the available information and concluded on the evaluated concerns without requiring further information from the registrants.

The eMSCA further notes that as of December 2016 not all registration dossiers which have been subjected to the evaluation decision have been updated to reflect the use-specific information described in the comprehensive update of the lead dossier and therefore require adaption to avoid continued non-compliance of the affected dossiers regarding incomplete or erroneous supporting of uses. The uses concerned by this non-compliance are especially additive uses of BPA in which it does not seem to be used as a monomer:

- Use of BPA in thermal paper
- Use of BPA as an additive for the processing and use of PVC
- Use of BPA in professional and consumer articles made of PVC

For these uses, currently no description of safe use exists across the entirety of registrations and chemical safety reports, especially with regard to the information requirements regarding these uses contained in the substance evaluation decision. The eMSCA considers that a persistence of these uses in the supply chains of registrants of BPA would contradict the current registration situation of the joint dossier and constitute a breach of compliance of the responsible registrants or downstream users.

## 7.3. Identity of the substance

**Table 4**

<b>SUBSTANCE IDENTITY</b>	
<b>Public name:</b>	<a href="#">4,4'-Isopropylidenediphenol</a>
<b>EC number:</b>	201-245-8
<b>CAS number:</b>	80-05-7
<b>Index number in Annex VI of the CLP Regulation:</b>	604-030-00-0

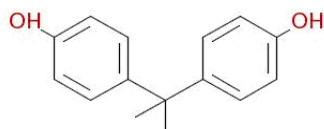
<sup>2</sup> "Decision on substance evaluation pursuant to article 46(1) of Regulation (EC) No 1907/2006 for 4,4'-isopropylidenediphenol (Bisphenol A), CAS No 80-05-7 (EC No 201-245-8)" accessible via <https://echa.europa.eu/documents/10162/84dbe057-2950-487a-8c72-ae0aacf215>



<b>Molecular formula:</b>	C <sub>15</sub> H <sub>16</sub> O <sub>2</sub>
<b>Molecular weight range:</b>	228.28 g/mol
<b>Synonyms:</b>	<i>Bisphenol A</i>

Type of substance       Mono-constituent       Multi-constituent       UVCB

**Structural formula:**



## 7.4. Physico-chemical properties

**Table 5**

OVERVIEW OF PHYSICOCHEMICAL PROPERTIES	
Property	Value
Physical state at 20°C and 101.3 kPa	<i>white solid</i>
Vapour pressure	<i>4.12E-09 hPa at 25 °C</i>
Boiling point	<i>360 °C at 1013 hPa with decomposition 155°C at 17 hPa with potential decomposition</i>
Surface tension	<i>4,4'-isopropylidenediphenol is a solid substance that has no structure with expected/predicted surface activity, nor surface activity is a desired property of the substance. Therefore, no testing for surface tension is required for 4,4'-isopropylidenediphenol.</i>
Water solubility	<i>300 mg/L at 25 °C</i>
Partition coefficient n-octanol/water (Log Kow)	<i>Log Kow: 3.4 at 21.5 °C and pH 6.4</i>
Flammability	<i>idem</i>
Explosive properties	<i>idem</i>
Oxidising properties	<i>idem</i>
Granulometry	<i>most of the granules are &gt;1 mm in diameter.</i>
Stability in organic solvents and identity of relevant degradation products	<i>Data waiving - 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.</i>
Dissociation constant	<i>pKa: 11.3</i>
Viscosity	<i>Data waiving - In accordance with section 1 of REACH Annex XI, a study does not need to be</i>

	<i>conducted as the substance is a solid at ambient temperatures.</i>
Thermal stability	<i>The substance is stable. There are no structural groups indicating corrosive behaviour to metals. The substance melted at 150 °C in the Grewer test.</i>

## 7.5. Manufacture and uses

### 7.5.1. Quantities

**Table 6**

AGGREGATED TONNAGE (PER YEAR)				
<input type="checkbox"/> 1 – 10 t	<input type="checkbox"/> 10 – 100 t	<input type="checkbox"/> 100 – 1000 t	<input type="checkbox"/> 1000- 10,000 t	<input type="checkbox"/> 10,000-50,000 t
<input type="checkbox"/> 50,000 – 100,000 t	<input type="checkbox"/> 100,000 – 500,000 t	<input type="checkbox"/> 500,000 – 1000,000 t	<input checked="" type="checkbox"/> > 1000,000 t	<input type="checkbox"/> Confidential

### 7.5.2. Overview of uses

#### Information from registrations

The ECHA dissemination web site provides the following information on uses which however may be based on inactive or revoked registrations, thereby leading to a difference between the disseminated use spectrum and revised currently active registration dossiers: The substance is used in polymers (product category). The substance has an industrial use resulting in manufacture of another substance (use of intermediates). The substance is used for the formulation of mixtures and/or re-packaging and building & construction work (sector of use). The substance is used for the manufacture of plastic products, chemicals, machinery and vehicles and electrical, electronic and optical equipment. The substance can be found in complex articles, with no release intended: machinery, mechanical appliances and electrical/electronic products (e.g. computers, cameras, lamps, refrigerators, washing machines) and vehicles. The substance can be found in products with material based on: plastic (e.g. food packaging and storage, toys, mobile phones) and paper (e.g. tissues, feminine hygiene products, nappies, books, magazines, wallpaper).

The production of polycarbonate and epoxy resin are the most important uses of BPA. According to information from the EU RAR, 865,000 tonnes/year are used for the production of polycarbonate and approximately 200,000 tonnes/year of BPA is used in the production of epoxy resins [EU RAR 2010].

It should be noted that only specific uses of BPA are supported within the scope of the current REACH registration (cf. Table 10).

#### Information from UBA research project (Fischer et al., 2014)

In Western Europe the main use is the production of PC (75% of total BPA), followed by the second largest use in epoxy resin production (17 % of total BPA use). Besides that, BPA has been used in a range of other application (incl. use in thermal papers). All these 'other' applications represented around 2 % of the total BPA use whereas the use of BPA in thermal papers only accounts for 0.16 % of the total BPA consumption in 2005/2006.

In the SPIN database (database on the use of substances in preparations in the Nordic countries) BPA is listed in the following use categories using the 62 use categories (UC) included in the register: with the highest reported tonnages lubricants and additives, construction material, adhesives and binding agents, paints, lacquers and varnishes, process regulators and with minor tonnages surface treatment, softeners, hydraulic fluids

and additives, fillers, stabilizers, anti-static agents, insulating materials, intermediates, viscosity adjustors, non-agricultural pesticides and preservatives, reprographic agents. According to the SPIN database BPA or BPA containing products are used in the following branches: construction activities, vehicles, manufacture of chemicals and chemical products, rubber and plastic products, metals and metal products, electrical equipment, wood and wood products, furniture, machinery, transport equipment, computer, electronic and optical products, paper and paper products, non-metallic mineral products, civil engineering, extraction of crude petroleum and natural gas, air transport.

### Polycarbonate

The production of polycarbonate is the largest use of BPA. Based on information from Plastic Europe the different end uses of polycarbonate products are summarised in the following table (Plastic Europe, 2012 and PE, 2012b).

**Table 7**

USE OF BPA IN POLYCARBONATE		
%	Application Class	Application
23	Optical Media	compact discs, CD ´s, DVD ´s, HD-DVD ´s, Blue-Ray Discs, Holography Discs, Innovative Data Storage Technology, forgery-proof holographic shadow pictures in ID cards
21	Electrical and Electronics	housing for cell phones, alarm devices, SLR cameras, electrical razors, hairdryers, steam irons, mixers, computers, monitors, TVs, copiers, printers, telephones, microwaves, coffee makers, front panels for electric cookers, electrical kettles, transparent front panels for vending machines, interior lighting panels for trains and airplanes, backlight units for TVs, housing for switch modules, distributor boxes, fuses, battery power stations, sockets, electrical meters, illuminated rotary switches, plug connectors, switches, sockets, plugs, lamp holders, fax machines, pagers, circuit breakers, cable sockets, displays, relays, LED ´s, safety switches, fluorescent lightning diffusers, fridges
27	Construction	sheets for roofing, conservatory glazing, architectural glazing, greenhouse glazing, safety glazing, rooflights, cover for solar panels, noise reduction walls for roads and train tracks, carport covers, glazing for bus stop shelter, road signs, internal safety shields for stadiums, housing and fitting for halogen lightning systems, front panels for advertising posters, sign boards (e.g. fuel stations), large advertising displays, dust & water-proof luminaries for streetlights and lamp globes, diffusing reflectors for traffic lights
12	Automotive	fixed side windows, transparent and retractable roof modules, windstops and convertibles, rear windows, transparent rear body parts, headlamp lenses, headlamp, tail light, indicator reflectors, foglamps, interior light covers, high-mount brake lights, housing for licence-plate lights, bumpers, radiator and ventilation grills, dashboards, rear light reflectors, coverings, moulded mirror housings, turn signals
2,5	Bottles and Packaging	reusable water bottles, unbreakable, reusable milk bottles, cutlery, food containers, drinking water

		generators, pitchers, water carboys, storage containers, tableware, water cooler bottles
2,5	Medical and Healthcare	blood oxygenators, cardiotomy reservoirs, dialysers, respirators, dentists' operating lamps, breastpumps, inhaler housings, prescription spectacles, i.v. connectors, scalpel cases, laparoscope handles, contact lens holders, syringe tops, medical packaging film, ampoules, three-way stopcocks and stopcocks manifolds, tweezers with integrated lighting, single-use operating instruments, eyeglass lenses
3,5	Leisure and Safety	Leisure: ski goggles, sun glasses, transparent building blocks in toys, mouthpieces for musical instruments, compass housings, binocular housings, seats for sleighs ballpoint pen chasings, transparent roof modules in caravans, instrumentation housings in boats, suitcase shells. Safety: safety goggles, protective visors for welding or handling of hazardous substances, protective visors for motorbikes or snowmobiles, motorbike and cycle helmets, fencing helmets, safety shields for policemen, guards to protect from moving machine parts, blends mainly used in automotive and electrical and electronics
5		Domestic Appliances
3		Others

### Epoxy resins

Epoxy resin production is the second largest use of BPA in the EU. There are a number of different epoxy resins, which vary depending upon the starting materials. However, diglycidyl ethers of BPA derived from BPA and epichlorohydrin are among the most widely used epoxy resins (EU RAR 2003). 90 % of the world production (1.7 million tonnes in 2008) of epoxy is produced based on BPA (BmVBS 2012). For use the resins must be cross-linked with a curing agent or hardener. The choice of curing agent is of paramount importance in designing an epoxy resin for a given application. The major reactive groups in the resin can react with many other groups so that many types of chemical substances can be used as curing agents. The bisphenol A derived epoxy resins are most frequently cured with acid anhydrides, aliphatic and aromatic amines and polyaminoamides, depending on the desired end properties. Some curing agents will cross-link the resin at ambient temperature while others require the application of heat. Some of the desired properties are superior electrical properties, chemical resistance, heat resistance, and adhesion. Epoxy resins are a family of synthetic resins, including products which range from viscous liquids to high melting point solids. Epoxy resins are selected because of their corrosion protection, thermal stability and mechanical strength and are used primarily as coatings for consumer and industrial applications, such as food and drinks cans and protective coatings for automotive and marine uses, electrical and electronic laminates, adhesives and paving applications, protective coatings, structural composites, electrical laminates, electrical applications and adhesives (EU RAR 2003, PE 2006, Geens et al. 2011). An overview on the use of epoxy resins is given in the following table.

**Table 8**

<b>USE OF BPA IN EPOXY RESINS</b>		
<b>%</b>	<b>Application Class</b>	<b>Application</b>
20	Marine and Protective Coatings	water ballast tanks, underwater ship hulls, cargo tank linings, offshore oil drilling platforms, supporting steel structures, sea containers, steel bridges, storage tanks (metal and concrete), power plant scrubbers, electric motors, engines, machinery, drinking water distribution pipes (metal and concrete), gas pipes
18	Powder Coatings	construction panels (cladding, metal roofing, ceiling, garage doors), radiators, rebars (concrete reinforcement), gardening tools and equipment, engine blocks, automotive parts, steel furniture, steel racks, frames beds, office furniture (shelves, metal desks, filling cabinets), pipes, valves and fittings
16	Electrical and Electronics	potting / encapsulation electronic parts (transformers, inductors), printed circuit boards
15	Civil Engineering	flooring (industrial / public buildings), food / catering industry, chemical plants, pharmaceutical industry, hospitals), mortars grouting (tile and brick linings), fillers, crack repair, coatings concrete bridges (seal against water and de-icing chemicals), coatings secondary containment walls (ground water protection), anti-skid coatings for park desks
11	Can and Coil Coatings	Can: food and drink cans / can ends, menue trays, food trays, craps and closure, crown cork, drums, pails, general line cans (oil, hairspray), collapsible tubes (toothpaste, cream)
	Can and Coil Coatings	Coil: construction panels (cladding, metal roofing, ceilings, garage doors), cookers, mobile homes, caravans, heat – ventilation- air conditioning equipment, office furniture (metal desks, shelves, filing cabinets, cupboards), fridges and freezers, dishwashers, washing machines, dryers, household appliances (e.g. vacuum cleaners)
9	Automotive Coatings	waterborne primers for cars, buses, railcars
5	Composites	rackets (tennis, badminton, squash), hockeysticks and golf clubs, ski, ski poles, snowboards, surfboards, boats, canoes, hang gliders, helmets, lightweight bicycles, pipes, valves and fittings, storage tanks, containers, gas bottles, windmill blades, scrubbers, pultruded structural parts (rods, bars, shafts, beams, grating), cars parts (body panels, cabin, spoiler, leaf springs, drive shafts), railcars, boats, yachts, aviation (aircraft), aerospace, military (helicopters)
4	Adhesives	DIY repair kits (adhesives, fillers), structural adhesives for buildings and constructions, adhesives for cars, boats, aircrafts
2	Photocure	printing inks, wood coatings, paper and board varnish incl. food packaging, coatings for plastics and primed metals

**Other polymers**

BPA is also used in the production of a number of other polymers and resins including phenoplast resins, phenolic resins, and unsaturated polyester resins.

**BPA formaldehyde resins or phenoplast resins** are based on the reaction products of a phenol (BPA) and formaldehyde. After dilution with water, they are used for the impregnation of paper or coating of wood fibres in the manufacturing of high pressure laminated compact panels. These phenoplast resins may be used in parts for electrical applications; electrical parts for electronics, aviation, radio engineering; antifrictional parts and constructive and insulating parts [Geens et al. 2011].

**Unsaturated polyesters resins** based on BPA include BPA fumarates and BPA dimethylacrylates. Propoxylated BPA fumarate unsaturated polyester resin provides good resistance against highly corrosive environments and is therefore used as storage tanks and process vessels. Glass reinforced composite resins are used in the manufacture of boats, swimming pools and translucent roof sheet. Ethoxylated BPA dimethacrylate is a cross-linker for anaerobic adhesives and dental compounds [Geens et al. 2011].

**Polysulfone** is a thermoplastic polymer synthesized by the condensation of BPA and bis(4-chlorophenyl)sulfone. It is used due to its toughness and stability at high temperatures. It offers a higher heat resistance and better hydrolytic stability than Polycarbonate (PC) polymers and preserves its good mechanical properties when exposed to steam and other sterilization techniques. It can be used as a highly transparent, sterilizable, long-term dishwasher safe and impact resistant alternative for PC.

**Polyacrylate** dental composite resins consist of a mixture of monomers and are most commonly based on bisphenol-A glycidyl methacrylate (bis-GMA). In addition to bis-GMA, these resins contain other monomers to modify the properties, e.g. bisphenol-A dimethacrylate (bis-DMA). Although BPA is not used itself in composite resins, it might be present as an impurity of these monomers. Once sealants are applied to tooth structures, they are polymerized in situ through a chemical curing process or photoactivation [Geens et al. 2011].

**Table 9**

USE OF BPA IN OTHER POLYMERS		
Polymer	Application Class	Application
Polysulfone	Membranes	hemodialysis, drinking and ultra-pure waters, gas separation, food & beverage concentration, dairy
	Medical and Healthcare	surgical trays, nebulizers, humidifiers
	Food service	microwave cookware, beverage and food dispensers, milking machine parts
	Plumbing	hot water fittings, manifolds, mixer tape cartridges
Polyacrylates	Medical and Healthcare	Dental composite resins (BPA as impurity)
Polyetherimide		Electronic and Electrical, Automotive, aircraft industries, microwave applications
Unsaturated polyesters	Bottles and Packaging	BPA fumarates: storage tanks, process vessels
	Adhesives, Medical and Healthcare	BPA dimethylacrylates: adhesives, dental compounds
Benzoxazines	Composites, Coatings, Adhesives, Encapsulant 's Manufacturing	Variety of uses, capability to exhibit the thermal and flame retardant properties of phenolics along with mechanical performance and molecular design flexibility

## PVC

BPA is used in soft PVC. Three different uses have been described in the EU RAR [EU RAR 2010]: as an anti-oxidant in PVC processing, as a constituent of an additive package used in PVC processing, and as an antioxidant in the production of plasticisers used in PVC processing. According to a communication by the Bisphenol A REACH consortium representing a significant fraction of BPA registrants, this use is not an identified use anymore. Nevertheless, there are no information from downstream users available about use of BPA in their production nor downstream user CSRs which have been notified at ECHA.

### Thermal paper

The use in thermal paper is not an identified use in the lead dossiers. Nevertheless, some registrants still support this use. Furthermore, downstream user from thermal paper industry state that they still use bisphenol A in their production process. However, so far these reports have not been notified to ECHA.

The table below lists the currently disseminated uses for BPA on ECHA's page (duplication of similar uses in the listing has been avoided).<sup>3</sup>

**Table 10**

<b>REGISTERED USES FOR BPA CURRENTLY DISSEMINATED</b>	
	<b>Use(s)</b>
<b>Manufacture</b>	Industrial Use of Bisphenol A as Laboratory Reagent Manufacture of Bisphenol A Industrial Manufacturing of Bisphenol A
<b>Formulation</b>	Industrial Repackaging Professional Repackaging Formulation of epoxy resin hardeners Industrial use of BPA as anti-oxidant for processing PVC* Formulation of preparations Industrial use of BPA in epoxy resin hardeners Industrial use of BPA for manufacturing thermal paper*
<b>Uses at industrial sites and uses as intermediate</b>	Industrial use of BPA for manufacturing polymers Industrial use of BPA for manufacturing chemicals Manufacture of epoxy resins Manufacture of epoxy resin hardeners Industrial use of BPA for manufacturing thermal paper (including paper recycling)* Industrial Use of BPA for Blending of polycarbonate Industrial Use of epoxy resin hardeners Industrial Use of BPA as anti-oxidant for processing PVC Use of BPA as laboratory reagent Manufacture of coating materials
<b>Uses by professional workers</b>	Professional use of BPA in epoxy resin hardeners Professional use of BPA as anti-oxidant for processing PVC* Professional use of thermal paper* Professional use of articles made of PVC Professional repackaging of BPA Use of epoxy resin hardeners
<b>Consumer Uses</b>	Consumer use of thermal paper Consumer use of articles made of PVC Consumer use of articles made of polycarbonate Consumer use of articles of epoxy resins
<b>Article service life</b>	Professional and consumer use, indoor and outdoor, of articles made of polycarbonate Professional and consumer use of thermal paper* Professional and consumer use of articles made of PVC*

For the uses marked with a star, currently no description of safe use exists in the registrations.

<sup>3</sup> <https://echa.europa.eu/de/registration-dossier/-/registered-dossier/15752/3/1/7> ECHA dissemination page last accessed on 21 April 2017.



A more streamlined spectrum of supported and described uses was implemented in a comprehensive update of the joint chemical safety report during the evaluation which discontinued the description and support of "additive" uses of BPA, e.g. in PVC or thermal paper (cf. Table 10).

**Table 11**

<b>REGISTERED USES OF BPA CURRENTLY SUPPORTED BY THE JOINT CSR</b>	
	<b>Use(s)</b>
<b>Manufacture</b>	Manufacture of BPA
<b>Formulation</b>	Industrial repackaging of BPA Professional repackaging of BPA Formulation of epoxy resin hardeners
<b>Use at industrial sites</b>	Manufacture of polycarbonate Blending of polycarbonate Industrial manufacture of articles made of polycarbonate Manufacture of epoxy resins Manufacture of coating materials Use of epoxy resin hardeners Manufacture of other substances Use of BPA as laboratory reagent
<b>Use by professional worker</b>	Use of epoxy resin hardeners
<b>Service life (professional worker)</b>	Professional indoor and outdoor use of articles made of polycarbonate
<b>Service life (consumers)</b>	Consumer indoor and outdoor use of articles made of polycarbonate

## 7.6. Classification and Labelling

### 7.6.1. Harmonised Classification (Annex VI of CLP)

The following Annex VI entry for BPA was implemented in the 9<sup>th</sup> Adaption to Technical Progress based on a CLH proposal by France.

**Table 12**

<b>HARMONISED CLASSIFICATION ACCORDING TO ANNEX VI OF CLP REGULATION (REGULATION (EC) 1272/2008)</b>							
<b>Index No</b>	<b>International Chemical Identification</b>	<b>EC No</b>	<b>CAS No</b>	<b>Classification</b>		<b>Spec. Conc. Limits, M-factors</b>	<b>Notes</b>
				<b>Hazard Class and Category Code(s)</b>	<b>Hazard statement code(s)</b>		
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		



## 7.6.2. Self-classification

- In the registration(s), the following hazard class is notified in addition to the legal classification:

Aquatic Chronic 2	H411
-------------------	------

- The following hazard classes are in addition notified among the aggregated self-classifications in the C&L Inventory (The hazard classes marked with \* have only been listed once by a single notifier).

Aquatic Chronic 3	H412
Ox. Sol. 3	H272
Asp. Tox. 1	H304*
Muta. 1B	H340*
Carc. 1B	H350*

## 7.7. Environmental fate properties

### 7.7.1. Degradation

The physical and chemical properties of Bisphenol A suggest that hydrolysis and photolysis is likely to be negligible (EU RAR, 2003 and 2008). In the registration the same data and conclusion are presented as in the EU RAR 2008 and the eMSCA can support this conclusion.

Many studies on the degradation behaviour of Bisphenol A exist. Evaluation of the data presented in the registration and Gehring (2004) has shown that the outcomes on degradation are contradictory. Results from tests on ready biodegradability indicate that degradation might vary strongly with the environmental conditions, and especially depend on the microbiotic community available. Studies with adapted inoculum demonstrate that a degradation of Bisphenol A is possible if such inoculum is available. In reliable tests conducted with non-adapted inoculum Bisphenol A is not ready degradable. Therefore, Bisphenol A may be assessed as not readily biodegradable for the environment. As the registrant assesses Bisphenol A as readily degradable in general, exposures to the environment may be underestimated. Microorganisms in industrial sewage treatment plants of manufacturers and (downstream-) users may be adapted to Bisphenol A. However, Bisphenol A is ubiquitously used and may enter surface waters directly or via smaller sewage treatment plants with unadapted microorganisms. In some environmental compartments and particularly in sediments, existing evidence suggests that Bisphenol A may not readily biodegrade (see Bakker et al., 2014). Therefore, it cannot be generally concluded that Bisphenol A is readily degraded in the environment. Since it is not expected that further studies on degradation might change the situation, no additional information is required.

### 7.7.2. Environmental distribution

It is assumed that Bisphenol A absorbs to sewage sludge due to its potential to moderately absorb to solids (EU RAR Bisphenol A (2003), 2008, chapter 3.1.3.3, page 26) (BUA substance report no. 203, Bisphenol A, chapter 6.3, page 40). The application of sewage sludge at least from municipal sewage treatment plants can lead to an entry of Bisphenol A into soil.

### 7.7.3. Bioaccumulation

Not considered in this substance evaluation.

## 7.8. Environmental hazard assessment

### 7.8.1. Aquatic compartment (including sediment)

As it is not area of concern and does not influence the overall decision, this chapter was only evaluated on a screening level.

For the selection of studies to assess the toxicity for aquatic organisms and populations the registrant only refers to studies designated as reliable without restriction. A large number of studies (75) on further fish and invertebrate species were not included in Sections 6.1, 6.2, 6.3 of the technical IUCLID dossier but are listed in IUCLID as additional ecotoxicological information (IUCLID Section 6.6). These studies are not further considered and referred to in the CSR.

#### Fish

For the chronic toxicity to fish, the joint registration dossier refers to a NOEC value of 16 µg/L as the lowest effect concentration based on a fully reliable multi-generation study with *Pimephales promelas* (Caunter et al. 2000 in ECHA 2016). A separate evaluation for salt water species is performed in the registration dossier referring to a NOEC value of 66 µg/L in a 116d fish life cycle toxicity test with *Cyprinodon variagatus* (sheepshead minnow) as the lowest effect concentration.

The European risk assessment report (EU RAR 2008) provides further studies assessed as "valid with restriction" for additional species which were not considered in the registration dossier. Effect concentrations reported for these species are in the range of 100 – 3640 µg/L. One test performed by Lahnsteiner et al. (2005) with *Salmo trutta* provides evidence, that lower concentrations can affect fish populations as ovulation was completely inhibited at 1.75 µg/L. Though this study was a key study of the risk assessment provided by ENVIRONMENT CANADA, the study was assessed as being of low quality by the registrant. One additional study, not considered by the registrant, became available during this evaluation providing evidence that effects on *Danio rerio* populations might have been underestimated in previous studies. Keiter et al. (2012) reported a NOEC (growth) of 10 µg/L after 90 d postfertilization for the F1 generation in a multi-generation test. The table below contains a comparison of studies and chronic toxicity (NOEC) values freshwater fish, which were used as basis for PNEC derivation by the registrant, respectively the EU RAR 2008 as well as further studies not considered so far. Only the most sensitive tests per species are reported.

**Table 13**

COMPARISON OF STUDIES AND NOEC VALUES FOR FRESH WATER FISH					
Species	Endpt NOEC [µg/L]	Test/Endpoint	Reference	Reliability	Annotation (Critical issue for PNEC-derivation)
<i>Used by registrant for PNEC derivation</i>					
<i>Pimephales promelas</i>	16	Multi-generation/reproduction:	Caunter et al. (2000) in ECHA (2016)	1	
<i>Cyprinodon variagatus</i>	66	FLC / reproduction	York, 2010	1	
<i>Tests covered in the Registration dossier and the RAR but not used for PNEC derivation</i>					

<i>Onc. Mykiss</i>	3640	28-d juvenile growth test growth	Bayer (1999)	4-cited in RAR 2010	Test duration not sufficient to cover endocrine effects
<i>Oryzias latipes</i>	247	Multi-generation mortality/ growth	Japan Ministry of Environment (2004)	4-cited in RAR 2010	
<i>Poecilia reticulata</i>	500	30-d mortality	Kinnberg and Toft (2003)	2	- Test duration and endpoints covered not sufficient to cover endocrine effects. - hints that effects on sperm maturation occur at lower conc.
<i>Tests covered in the RAR but not reported in the registration dossier</i>					
<i>Danio rerio</i>	750	Full life cycle test	Segner et al. (2003a)	2	
<i>Salmo trutta</i>	2.4	103-d / complete inhibition of ovulation in females:	Lahnsteiner et al. (2005)	3	
<i>Additional tests</i>					
<i>Danio rerio</i>	10	180-d FFLC-test / VTG induction F2 Generation (90 + 180 dpf):	Keiter et al. (2012)	2	

Based on the data available the lowest NOEC for fish seems to be 10 µg/L (Keiter et al. (2012)). Although tests with other species do not provide lower NOEC values, they provide valuable information with regard to the species-sensitivity-distribution (SSD) and should be used if the PNEC is derived by SSD (see chapter 7.1.2). In addition, several studies indicate that Bisphenol A acts as an endocrine disruptor in fish in low concentrations (see chapter 7.4).

The following evidence suggesting that effects might start at lower concentrations should be considered for PNEC derivation and risk characterisation:

- Although the endpoint assessed by Lahnsteiner et al. (2005) is usually not used in risk assessment as the study is considered to be of lower quality, results should be considered in the overall weight of evidence during PNEC derivation as it indicates that Salmoidae might be more sensitive than other species tested.
- For some species the tests available do not include endocrine sensitive life stages and endpoints and thus these tests might underestimate the toxicity of Bisphenol A for these species.

## Aquatic invertebrates

### Molluscs

For chronic aquatic toxicity to freshwater invertebrates, the Lead-CSR refers to a NOEC of 25 µg/L for the endpoints mortality, adult fecundity, hatchability and juvenile growth of the freshwater snail *Marisa cornuarietis* as lowest effect concentration based on studies of documented in Forbes et al. (2007). However, the study was performed with a tropical strain not showing seasonal spawning behavior.

Overall, the Lead CSR deviates from the EU risk assessment (RAR 2008) with respect to the consideration and interpretation of available studies. Additional studies give evidence for lower effect concentrations for snails:

In a study by Oehlmann et al (2006) with *Marisa cornuarietis* an increase in egg production was observed at all test concentrations (0.25 - 5 µg/L nominal) in a semi-static test. Results of other tests performed by Oehlmann et al (2000, 2001) support the finding that

snails might be affected at concentrations below 1 µg/L and indicate that they are caused by an overproduction of eggs during a seasonal period with natural low egg production (i.e. effects are not observed during the seasonal reproduction period when egg production is natural high). Shortcomings of the studies by Oehlmann et al. (2000, 2006) and Schulte-Oehlmann et al. (2001) have been discussed extensively (RAR 2008). They include the test design (breeding groups instead of breeding pairs), the decrease in test concentration between renewal cycles making it difficult to estimate the real concentration and the statistical analysis performed.

As effects were observed already at the lowest test concentration (LOEC ≤ 0.25 µg/L) NOEC values may not be derived. Results of an EC<sub>10</sub> value seem to be highly dependent on the statistical method used: While Oehlmann et al (2006) calculated an EC<sub>10</sub> of 0.0148 µg/L nominal based on a Weibull distribution, van der Hoeven et al (2005) cited in Oehlmann et al. (2008) recalculated an EC<sub>10</sub> of 2.1 µg/L based on a linear regression. Based on a similar method an expert opinion on behalf of the German Federal Environment Agency (UBA) (Ratte 2009) recalculated EC<sub>10</sub> values of 0.038 µg/L nominal and 0.0053 µg/L real, based on time weighted average concentrations.

In summary, although the study documented in Forbes et al. (2007) is standardized to a higher degree, it may have missed effects as it does not cover a potential increase of egg production during a season of low spawning behavior. Studies by Oehlmann et al (2000, 2006) and Schulte-Oehlmann et al. (2001) indicate that effects may start at ≤ 0.25 µg/L (nominal) and EC<sub>10</sub> values may be as low as 0.0053 µg/L (Ratte 2009, TWA).

The low effect concentrations observed for *Marisa cornuarietis* are supported by other studies with snails, e.g.:

- For the mud snail *Potamopyrgus antipodarum* Jobling et al. (2003, corrected 2004) estimated a NOEC for the parameter embryo production of 1 µg/L and significant effects at 5 µg/L (nominal, no analytical confirmation). Actual concentrations might be lower.
- In sediment, Duft et al. (2003) observed a stimulation of embryo production and estimates a NOEC of < 1µg/kg.
- For the marine snail *Nucella lapillus* Oehlmann et al. (2000) estimated a NOEC < 1 µg/L (nominal, no analytical confirmation).
- For the marine sea snail *Haliotis diversicolor* Liu et al. (2011) estimated EC<sub>5</sub> values of 0.18 and 1.02 µg/L for embryo toxicity (nominal, analytics -3+8%).
- Further studies with several snail species have been conducted by Benstead et al. 2008 (reported in ECHA 2008) or were reported in a transitional dossier under the REACH legislation provided by UK (2008) (ECHA 2008). Although all of them show severe drawbacks they also provide hints that other snail species might be sensitive too.

Based on the available data the EU RAR (EC 2010) concluded, that there is a need for further information due to uncertainties over the potential effects of Bisphenol-A on snails. However, already a high number of studies have been conducted with snails. The available studies give evidence for effects at low concentrations, which cannot be "overwritten" by further studies and need to be considered for a hazard assessment. Further studies might support this evidence or give indications for further effects, but can hardly give unequivocal results or a proof. At the moment it seems not to be justified to request a further testing unless a closely controlled, and statistically robust partial life cycle reproduction test method which covers the sensitive endpoints is available (which in the best case also covers endocrine mediated effects).

## Crustaceans and Insects

For crustaceans the lead registrant refers to a study of Caspers (1998) with a NOEC of >3160 µg/L (measured) for *Daphnia magna* as selected key study, supported by further studies with *Daphnia magna* with a NOEC of 1000 µg/L (nominal) for reproduction reported by Brennan et al. (2006) and an NOEC of 1300 µg/L (nominal, no analytical confirmation) reported by Mu et al. (2005). For *Gammarus pulex*, a NOEC of 1500 µg/L for the parameter mortality is referred to as supporting study of the registrant. For marine invertebrates, the registrant refers to a crustacean species as most sensitive

organism, selecting a study with *Americamysis bahia* of Testing Laboratory 2010 reported in ECHA (2016) as key study with a NOEC of 170 µg/L.

Analysis of available data provided in the EU risk assessment indicate that effect concentrations for *D. magna* and *G. pulex* might be lower than reported in the registration dossier:

- Although no effect on reproduction was observed by Brennan et al. (2006) they estimated LC<sub>50</sub> values of 806 µg/L for the first generation of *Daphnia magna* and a lower LC<sub>50</sub> value of 600 µg/L and LC<sub>10</sub> of 200 µg/L for the second generation.
- Watts et al. (2001) reports effects on precopulatory behaviour of *Gammarus pulex* at a concentration of 830 µg/L.

In addition results for further species are reported in the EU risk assessment report (EU RAR 2008), some of which are more sensitive than *D. magna* and *G. pulex*:

- Low effect concentrations are reported by Ladewig et al. (2006) for *Gammarus fossarum* in a 103 d pulse-dose exposure scenario in artificial indoor streams. An EC 10 of 17 µg/L (nominal, confirmed analytics 101-122%) is estimated for the proportion of reproductive females in the fourth brood and an EC 10 of 5 µg/L for a decrease in brood size in the fourth brood, although for the first three broods they observed an increase in brood sizes at the highest Bisphenol A concentration.
- Tatarazako et al. (2002) reports a NOEC of 900 µg/L for the reproduction of *Ceriodaphnia dubia*.
- A NOEC of 490 µg/L for reproduction of *Hyallela azteca* is reported by Testing Laboratory 2006 (cited in EC 2010).
- The RAR 2008 reports several studies with the lowest NOEC of 100 µg/L for *Chironomus riparius* (Watts 2003).

All these tests provide valuable information and should be used if the PNEC is derived by SSD.

## Algae and aquatic plants

Toxicity to algae and aquatic plants was not evaluated in detail as it is not an area of concern and does not influence the overall decision.

## Sediment organisms

The lead registration uses NOEC 22 mg/kg for freshwater sediment (*Lumbriculus variegates*, Staples et al. 2015 and ECHA 2016) and 32 mg/kg for marine sediment (*Leptocheirus plumulosus*, Staples et al. 2015 and ECHA 2016). One additional test with *Chironomus riparius* (Picard et al. 2010c) is reported showing that the species is less sensitive.

The effect values reported are lower than the one reported in the EU RAR (EC 2010), which is 36 mg/kg (direct spiked sediment) for *Corophium volutator* (Testing Laboratory 1999 cited in ECHA 2016). But the EU RAR (EC 2010) reports one additional study with the snail *Potamopyrgus antipodarum* with effect concentrations as low as 1 µg/kg (Duft et al. 2003) which, although it should be taken with care, indicates that snails may be more sensitive than other aquatic invertebrates such as insects or annelids.

## Other aquatic organisms

**Amphibians**

For the chronic toxicity to amphibians, the joint registration dossier refers to a NOEC value of 500 µg/L for *Xenopus laevis* after 90 d of exposure based on larval survival, adult growth and sex ratio as the lowest effect concentration (Pickford et al. 2003).

In addition, the EU risk assessment reports a second study with *Xenopus laevis* with a lower effect concentration of 7.3 µg/L for sex ratio and reproduction after 120 days of exposure (geometric mean of two experiments) (Levy et al. 2004). As worked out in the RAR 2008 it is not clear, why the results of Pickford et al. (2000 and 2003) and Levy et al. (2004) are different. The experimental design is not the same in the test but as also the true NOEC is uncertain. In the RAR 2010 a geometric mean was used, pointing towards concentrations of 60.4 µg/L for sex ratio and reproduction.

For the PNEC derivation (via SSD) the registrant refers to the value of 500 µg/L and the EU RAR (2008) to the value of 7.3 µg/L.

**7.8.2. Terrestrial compartment**

Toxicity and PNEC derivation in the terrestrial compartment was not evaluated in detail as it is not an area of concern and does not influence the overall decision.

**7.8.3. Microbiological activity in sewage treatment systems**

This chapter was not evaluated because it is not an area of concern and does not influence the overall decision. The Lead-registrant refers to a NOEC of 320 mg/L (Fabig 1988).

**7.8.4. PNEC derivation and other hazard conclusions****Table 14**

<b>PNEC DERIVATION AND OTHER HAZARD CONCLUSIONS</b>		
<b>Hazard assessment conclusion for the environment compartment</b>	<b>Hazard conclusion</b>	<b>Remarks/Justification</b>
Freshwater	CSR: 18 µg/L EU RAR (2008): 1.5 µg/L UQN: 0.24 µg/L	EMSCA did not derive PNECs as risk-based assessment it is not appropriate for the substance. However, the UQN value is used for an assessment of the risk characterisation of the registrant.
Marine water	CSR: 16 µg/L EU RAR (2008): 0.15 µg/L UQN: 0.24 µg/L	
Intermittent releases to water	CSR: 10 µg/L EU RAR (2008): -	
Sediments (freshwater)	CSR: 220 µg/kg dw	

	EU RAR (2008): a) 24 µg/kg wet weight (63 µg/kg dry weight) b) 36 µg/kg dry weight	
Sediments (marine water)	CSR: 440 µg/kg dw EU RAR (2008): 2.4 µg/kg ww (6.3 µg/kg dw)	
Sewage treatment plant	CSR: 320 mg/L	

### 7.8.5. Conclusions for classification and labelling

Environmental classification and labelling: The proposed self-classification of the registrants does not seem to cover the effects observed for aquatic organisms at very low concentrations (ng-µg/L range). There are different self-classifications from "Not classified" to Aquatic Chronic 2. It is furthermore necessary to achieve a common and sound classification for all. In the eyes of the eMSCA, the available ecotoxicity data for Bisphenol A is sufficient to propose a harmonised classification and labelling of Aquatic Chronic 1 to BPA (based on a NOEC of 2.4 µg/L for reduced egg production in *Salmo trutta*) (Lahnsteiner et al., 2005). However the substance is also proposed to be identified as SVHC based on ED properties of BPA to the environment and therefore later on included in the Candidate List. Therefore the eMSCA does not consider that it is a priority to propose an environmental harmonised classification of BPA for the time being. This priority may need to be revisited once the SVHC process is finalised. Registrants are anyway recommended to use the self-classification as Aquatic Chronic 1 in their registration dossiers.

## 7.9. Human Health hazard assessment

### 7.9.1. Toxicokinetics

#### Oral and inhalation absorption

Studies performed in different species (rats, mice, monkeys, humans) demonstrate that BPA is rapidly and completely absorbed after oral administration. Therefore, 100 % oral absorption is taken for DNEL derivation. There are no data on the toxicokinetics of BPA after inhalation exposure. Based on systemic effects observed in a repeat-dose inhalation study, the high partition coefficient and the fact that first-pass metabolism would not take place after inhalation uptake, a 100 % absorption was assumed in the EU RARs. Therefore, 100 % absorption via inhalation is taken for DNEL-derivation.

#### Dermal absorption

Since publication of the EU-RARs on BPA (in which 10 % dermal absorption was assumed based on conclusions from the available data and from a study which was considered unreliable for the determination of dermal absorption), further studies on the dermal absorption of BPA have been performed, not all of them according to standard guidelines. The overall weight of evidence of the available studies indicated that dermal exposure absorption might be as high as 50 %. However, based on deficiencies of the available dermal absorption studies a dermal absorption study specifically addressing possible pitfalls was requested in a Decision.

The results of the dermal absorption study were provided in 2015 (Testing Laboratory 2015).

The study was performed according to the OECD principles of Good Laboratory Practice and was compliant with OECD TG 428 and SCCS/1358/10 as requested in the Decision.

The percutaneous absorption of  $^{14}\text{C}$  radiolabelled BPA (ring-labelled) was investigated in split-thickness skin (350–400  $\mu\text{m}$  thick) prepared from human abdominal skin obtained from donors aged 33 to 46 years. Metabolic competence of skin, solubility of BPA in the receptor fluid (tissue culture medium DMEM containing ca. 1% [v/v] ethanol and 2 mM UDPGA (Uridine 5'-diphosphoglucuronic acid) and 40  $\mu\text{M}$  PAPS (3'-phosphoadenosine-5'-phosphosulfate)) and skin barrier integrity were checked prior to the measurement of percutaneous absorption.

Percutaneous absorption was determined at 4 different concentrations of BPA (2.4, 12.0, 60.0 and 300 mg/l) using flow-through diffusion cells. Receptor fluid was collected for Donor 1 at 0.5, 1, 2, 4, 6, 8, 10, 12 and 24 h post dose. Receptor fluid was collected for Donors 2-4, at 0 and 1 h post dose and then in two-hourly fractions from 2 to 24 h post dose. All the receptor fluid samples were analysed by liquid scintillation counting (LSC). At 24 h post dose, the flow through cells and skin samples were washed, skin samples were dried by applying commercial hand wash soap and all washing fluids were analysed by LSC. Stratum corneum was removed from the skin samples by using 20 successive tape strips. Epidermis and dermis were then separated, each sample was solubilized and analysed by LSC. One skin sample per donor of the highest concentration (300 mg/l) was analysed for metabolism by HPLC-UV (levels of radioactivity in the other test preparation was too low to enable determination of metabolism). For determination of percutaneous absorption, each test concentration was applied to a total of 12 skin samples from 4 donors (i.e. 3 skin samples/donor).

Amongst the different fractions analysed by LSC, radioactivity detected in epidermis, dermis, receptor fluid, receptor fluid rinse and receptor chamber wash is considered as the amount dermally absorbed according to the guidelines followed. In that sense, the term **amount dermally absorbed** is used in the present document.

Results:

a) Metabolism of BPA in human skin

Results from two different experiments with viable skin samples over 24 h demonstrated that metabolism of BPA was possible in the skin. In experiments with viable skin disks (tape-stripped split-thickness) incubated in receptor-fluid solution, 7–20 % of the applied BPA was metabolized. In the diffusion-cell experiments, up to 14 and 19 % of the radioactivity in the dermis and receptor fluid, respectively, was related to metabolized BPA. For the dermis and receptor fluid (including receptor fluid rinse and receptor chamber wash) combined, 6–11 % of the radioactivity was related to metabolized BPA. Metabolites observed in the radio-chromatograms had retention times consistent with BPA-glucuronide and BPA-sulfate, and also more polar compounds. It might be assumed, but was not analytically verified, that these polar compounds are mixed sulfate/glucuronide bis-conjugate metabolites.

b) Dermal penetration of radiolabelled BPA in test preparations containing 2.4, 12.0, 60.0 and 300 mg/l BPA.

As deviation from the test protocol (inclusion of cells with less resistance than 10.9 k $\Omega$ ) was noted for cell 37 (12 mg/l). As rationale for inclusion it was mentioned that no further skin sample was available from that donor. The lower electrical resistance observed in this sample indicates poorer barrier integrity and hence potential for greater absorption; therefore, including the sample is considered as conservative approach for a risk assessment and this deviation was deemed to have no impact upon the integrity of the study. The eMSCA agrees to accept this deviation from the test protocol.

Apart from one cell of the lowest concentration, the recovery (= mass balance) fell within the acceptable range (i.e. between 85 and 115 %). Across the different compartments, the percentage of the applied dose for all four test concentrations was 1.68–6.62 % for the receptor fluid (including receptor fluid rinse and receptor chamber wash), 3.28–6.19 % for the dermis, 10.38–11.91 % for the epidermis, and 7.31–10.25 % for the stratum corneum. The table below gives an overview of the amount dermally absorbed, i.e. on in vitro dermal absorption values in terms of the relative and absolute amount dermally



absorbed (amounts in epidermis, dermis and receptor fluid) of  $^{14}\text{C}$ -BPA 24 hr post-dose using skin samples from four human volunteers and three different concentrations of  $^{14}\text{C}$ -BPA (n = 12 per concentration).

**Table 15**

<b>IN VITRO DERMAL ABSORPTION VALUES</b>				
<b>BPA Concentration [mg/l]</b>	<b>% of Applied Dose</b>		<b>ng equiv./cm<sup>2</sup></b>	
	<b>Amount absorbed (mean)</b>	<b>SD of mean absorbed</b>	<b>Amount absorbed (mean)</b>	<b>SD of mean absorbed</b>
2.4	20.04	6.24	5.07	1.70
12	19.28	8.54	24.07	10.81
60	16.10	7.01	103.41	46.83
300	15.92	8.14	510.6	263.45

A high variability in the amount dermally absorbed was observed between skin samples for each of the testing concentrations investigated as evidenced by high standard deviations. The guidelines followed recommend to use the mean plus two standard deviations in case of high variability. Resulting amounts observed when using the respective means plus two standard deviations is given in the table below.

**Table 16**

<b>OBSERVED AMOUNTS FOR DERMAL ABSORPTION</b>		
<b>BPA Concentration [mg/l]</b>	<b>Mean absorbed + 2 SD [% of Applied Dose]</b>	<b>Mean absorbed + 2 SD [ng equiv./cm<sup>2</sup>]</b>
2.4	32.52	8.47
12	36.36	48.14
60	30.12	197.07
300	32.2	1037.5

In the revised CSA the lead registrant used a rounded value of 30 % dermal absorption for DNEL-derivation. The eMSCA concurs with this value and considers it as a conservative (worst-case) value.

In summary, as a result from the new information provided in following the draft decision, the following absorption percentages are taken for DNEL-derivation:

Oral: 100 %

Inhalation: 100 %

Dermal: 30 % (worst case)

For real life situations, however, several further aspects have to be taken into account:

The parameter "amount dermally absorbed" overestimates the amount that can become systemically available **within the time period of 24 h**. It covers portions related to systemic and local availability. The amount contained in the epidermis is not immediately systemically available, because *in vivo* only the dermis is perfused by blood. Under *in vitro* conditions, the dermis is no longer blood-perfused and therefore contributes to the overall diffusive barrier established by the skin sample.

The epidermis of "thin" skin (not that from the palms and soles of the feet) has a thickness of 75–150 µm which gives a hint about the share of the dermis in the split-thickness skin samples which had a thickness of 350–400 µm. In comparison, the dermal absorption study by Demierre et al. (2012), which had been considered as key study by EFSA (2015) and ECHA (2015), used 200-µm thick skin samples. Because of the thinner skin samples, representing a lower diffusion barrier, the Demierre study found a higher fraction of the applied dose (test concentration: 194 mg/L) in the receptor fluid (8.6 %) after 24hr in comparison to the present dermal absorption study (1.98 % for the comparable test concentration of 300 mg/L). Differences in skin-sample thickness and compartment proportions between the Demierre study and the present dermal absorption study also contribute to explain the different proportions of the applied dose located in the stratum corneum (34.9 vs. 10.25 %) and in the epidermis and dermis combined (0.6 % vs. 13.94 %). So from the present knowledge, without additional information from an *in vivo* study in humans, it cannot be decided which of the two *in vitro* dermal penetration studies gives a better approximation of the dermal absorption under *in vivo* conditions and whether a dermal absorption factor of 10 % or 30 % is more appropriate to the real-life dermal exposure situation in humans.

It should be noted that the lead registrant referred to a recent *in vivo* dermal toxicokinetic study in humans from which some non-peer-reviewed information is available. Preliminary findings had been submitted during public consultation of the restriction proposal for BPA in thermal paper indicating a cumulative urinary excretion of total BPA of 0.5 – 3.8 % of the applied dose (applied dose: 100 µg/kg administered for 8 hours). Final results from this *in vivo* study might give a different figure on dermal absorption of BPA in humans.

### 7.9.2. Acute toxicity and Corrosion/Irritation

The acute toxicity of BPA is low. The oral and dermal LD<sub>50</sub> values are higher than 2000 mg/kg. A 6-hr exposure to 170 mg/m<sup>3</sup> (highest concentration attainable) produced no deaths in rats.

BPA is neither corrosive nor irritating to skin, but irritating to eyes. It has a limited potential for respiratory irritation. The classification according to Annex VI of regulation (EC) No. 1272/2008 is Eye dam 1 H318.

### 7.9.3. Sensitisation

BPA is currently classified according to Annex VI of regulation (EC) No. 1272/2008 as Skin Sens 1 H317. Animal data are available for classic skin sensitisation which do not allow a subcategorization.

Re-evaluation of all data may be considered if new data become available that allow a conclusion on the potential of sensitisation and the classification as subcategory 1A or 1B.

#### **7.9.4. Repeated dose toxicity**

As summarized by ECHA (2015), "the toxicity of BPA has been extensively reviewed in the recent past, amongst others in the EU by the European Chemicals Bureau resulting in the EU Risk Assessment Report (ECB 2007), by the European Food Safety Authority (EFSA 2015), by the Scientific Committee on Occupational Exposure Limits (SCOEL 2014) and by the Scientific Committee on Emerging and Newly-Identified Health Risks (SCENIHR 2015)." Based on an extended robust database on repeat-dose general toxicity, effects on kidney and liver have been used for hazard characterization. RAC agreed to use a BMDL<sub>10</sub> (benchmark dose lower confidence limit of 10%) of 8960 µg/kg bw/day based on a 10% increase in the mean relative kidney weight (an indication for systemic toxicity) in male mice of the F0 generation in Tyl et al. (2008) as calculated by EFSA (2015) for hazard characterisation.

The BMDL<sub>10</sub> of 8960 µg/kg bw/d is used as a starting point for DNEL derivation for systemic toxicity.

It should be kept in mind that further effects after repeated administration of BPA had been reported such as effects on brain and behaviour, effects on the female reproductive system, effects on metabolism and obesity, immunotoxicity and effects on mammary glands (EFSA, 2015; ECHA, 2015). Although RAC concluded that these effects should be accounted for in hazard, risk and health impact assessments, data were not considered sufficient in order to establish dose-response relationships. Therefore, in agreement with EFSA (2015), RAC decided to account for these effects by an additional assessment factor of 6 in DNEL-derivation (see section 7.9.9).

An additional assessment factor of 6 will thus also be used in this SEv conclusion document.

It should be kept in mind, that based on a recent report by RIVM (RIVM, 2015), EFSA has been mandated to examine the results of the RIVM report and specifically review the toxicity of BPA on the immune system in light of two 2014 publications by Ménard et al. on immunotoxicity of BPA (<http://www.efsa.europa.eu/en/press/news/160426a>). In addition, it has to be kept in mind that EFSA committed to the re-evaluation of BPA when a two-year study by the U.S. National Toxicology Program becomes available in 2017. Thus, appropriateness of the selected point of departure (PoD) for risk assessment based on kidney effects detected in the study by Tyl et al., 2008 will be subject for rediscussion after completion of ongoing studies/evaluations.

#### **7.9.5. Mutagenicity**

In agreement with EFSA (2015) the eMSCA concludes that BPA is not likely to pose a genotoxic hazard to humans based on the available information.

#### **7.9.6. Carcinogenicity**

It is acknowledged that EFSA (2015) by using a WoE approach considered BPA likely to induce proliferative changes in the mammary gland but for other tissues (e.g. prostate or testis) available evidence is too limited to reach a conclusion.

It should be noted that a currently ongoing long-term study in rats might enable a better evaluation of BPA-induced proliferative effects in mammary gland and in other tissues (<http://ntp.niehs.nih.gov/testing/status/agents/ts-10034-y.html>).

### **7.9.7. Toxicity to reproduction (effects on fertility and developmental toxicity)**

See section 7.9.4

### **7.9.8. Hazard assessment of physico-chemical properties**

Not assessed in this evaluation.

### **7.9.9. Selection of the critical DNEL(s)/DMEL(s) and/or qualitative/semi-quantitative descriptors for critical health effects**

#### **Oral DNEL, systemic, general population**

A BMDL(10) of 8960 µg/kg/day was calculated by EFSA (2015) for changes in the mean relative kidney weight in a two generation toxicity study in mice (Tyl et al., 2008). This value has been taken by EFSA as a starting point for their TDI calculation and by ECHA (2015) as starting point for the DNEL derivation. The value is also used by the eMSCA for DNEL derivation for systemic effects.

ECHA (2015) has also agreed to use the Human Equivalent Dose (HED) approach as used by EFSA (2015) instead of a (default) assessment factor for toxicokinetics. The HED represents the multiples of the dose (D) in an animal species by a specified route and life-stage that a human would require to obtain an equivalent AUC from oral administration. Based on a human equivalent dose factor (HEDF) of 0.068 (derived by comparison of an oral mouse AUC with an oral human AUC (derived by PBPK modelling) replacing the default factor of 7 for toxicokinetic differences (allometric scaling) between mice and humans an HED of 609 µg/kg bw/d was obtained from the BMDL(10) of 8960 µg/kg/day.

Using an assessment factor of 2.5 for toxicodynamics and an assessment factor of 10 for interindividual differences in the general population yields a DNEL of 24 µg/kg bw/d (609 µg/kg bw/d divided by 10 x 2.5). Based on a WoE analysis performed by EFSA (2015), ECHA (2015) concluded that the available data indicate that kidney effects are not the most critical effects of BPA. Whereas the data on other adverse effects do not allow to identify a sufficiently robust starting point, the WoE analysis by EFSA (2015) indicates that they could occur starting from a HED of 100 µg/kg bw/day, i.e. at a 6-fold lower level than the HED for kidney effects. Consequently, a DNEL (and also the temporary TDI as derived by EFSA) accounting for these effects would be 6-fold lower than a DNEL based on kidney effects alone. Thus, an additional assessment factor of 6 was used for DNEL and t-TDI-derivation. This results in an oral DNEL of 4 µg/kg bw/day for the general population.

It should be kept in mind, that based on a recent report by RIVM, EFSA has been mandated to examine the results of the RIVM report and specifically review the toxicity of BPA on the immune system in light of two 2014 publications by Ménard et al. on immunotoxicity of BPA. In addition, it has to be kept in mind that EFSA committed to the re-evaluation of BPA when a two-year study by the U.S. National Toxicology Program becomes available in 2017. Thus, DNEL-derivations in this sections based on kidney effects detected in the study by Tyl et al., 2008 have a provisional nature and might be subject for revision in the near future.

#### **Dermal DNEL, systemic, general population**

A new in-vitro dermal penetration studies has been provided in the context of this SEv. As discussed in section 7.9.1 (toxicokinetics), a dermal absorption percentage of 30 % was derived based on the results of this study.

In order to derive AUC figures for humans after dermal exposure, ECHA (2015) utilized information from two PBPK studies (Mielke et al., 2011 and Yang et al., 2013) in order to calculate dermal AUCs for a dermally absorbed dose of 100 µg/kg bw.

It was calculated by ECHA (2015) that an oral dose of 100 µg/kg/d corresponds to an oral AUC of 29.2 nMol x h/L according to the Mielke model. In mice, an oral dose of 100 µg/kg bw/d yields an AUC of 0.244 nMol x h/L. By using an external dose level of external dermal dose of 0.542 µg/kg bw per day (finger contact to thermal paper once a day) and a dermal absorption figure of 10 % (leading to a dermally absorbed dose of 0.0542 µg/kg bw per day), a dermal AUC of 0.19 nMol x h is obtained. By scaling to a dermally absorbed dose of 100 µg/kg/d human dermal AUCs of 350.6 and 329.5 nmol x h/L were obtained from the Mielke and Fisher/Yang models, respectively assuming linear kinetics.

Taking the dermal absorption figure of 30 % as obtained from the study described in section 7.9.1 instead of 10 % dermal absorption, an external dermal dose of 0.542 µg/kg bw/d leads to a dermally absorbed dose of 0.1626 µg/kg bw/d and a resulting dermal AUC of 0.57 nMol x h. By scaling to a dermally absorbed dose of 100 µg/kg/d, a human dermal AUC of 350.6 nMol x h is obtained from the Mielke model (only the Mielke model was available) assuming linear kinetics.

Thus, a dermal absorption percentage of 30 % instead of 10 % results in the same human dermal AUC value and, consequently, in the same value for the DNEL dermally absorbed.

According to ECHA (2015) the dermally absorbed DNEL is calculated as follows:

$$\text{DNEL dermally abs.} = \left( \frac{\text{BMDL}_{10/\text{Mouse / Tyl}}}{\frac{\text{AUC dermal abs. Human}}{\text{AUC Oral abs. Mouse}}} \right) / \text{AF (2.5 x 10 x 6)}$$

The dermal human AUC of 350.6 nMol x h is divided by the mouse oral AUC of 0.244 nMol x h yields a conversion factor of 1436.9.

The BMDL(10) of 8960 µg/kg/day as point of departure for DNEL derivation is converted to a human equivalent dermal (HED<sub>dermal</sub>) dose by using this conversion factor (8960 µg/kg/day / 1436.9) resulting in a HED<sub>dermal</sub> of 6.24 µg/kg bw/d.

The total assessment factor applied to HED<sub>dermal</sub> is 150 for the general population (2.5 for toxicodynamic interspecies differences, 10 for interindividual (human) variability and 6 as the already discussed additional factor). The resulting DNEL for the dermally absorbed dose in the general population is **0.042** µg/kg bw/d.

ECHA (2015) suggested that the dermal DNEL of roughly 0.05 µg/kg bw/d (based on the calculated value of 0.04 µg/kg bw/d) should be rounded to 0.1 µg/kg bw/d, because a dermal biotransformation (i.e. inactivation) of 50 % due to skin metabolism was assumed (however, there was a lack of reliable data on the extent of BPA metabolism in skin).

The new in vitro dermal absorption study described in section 7.9.1 of this document, however, indicated that metabolism takes place in human skin samples, but that the extent of metabolism is around 10 %. Therefore, the eMSCA suggests to keep the **dermal DNEL** for the general population at 0.042 µg/kg bw/d (rounded: **0.05 µg/kg bw/d**).

In the recent update of the CSR the lead registrant used an alternative approach based on pharmacokinetic principles and allometric scaling to calculate the dermal systemic DNEL. The registrant used this alternative approach because the data (from Doerge et al., 2011) used by EFSA (2015) to calculate the AUC for adult mice orally dosed with 100 µg/kg were associated with a high degree of uncertainty. EFSA (2015) had derived an AUC value of 0.244 nM×h and had specified an uncertainty range of 0.108–1.257 nM×h.

Based on the relationship between systemic clearance (CL), dose and AUC (AUC = dose/CL) and on the allometric scaling of clearance with body weight (BW, kg) (CL = a × BW<sup>b</sup>), a regression analysis was performed using data from several toxicokinetic studies with oral dosing in different species to derive estimates for the scaling parameters a. By using this method, the registrant determined parameter a as 36.5 L/h and b as 0.92). Although in principle, this procedure can be considered acceptable, the data presented on the CSR do not allow to reproduce the calculations performed by the registrant.

The resulting predicted oral AUC for mice dosed with 100 µg/kg bw was 2.9 nM×h, i.e. roughly by a factor of 10 higher compared to the EFSA/ECHA (2015) value described above.

Based on the Mielke et al. (2011) study, a dermal AUC 697 pg/ml x h was calculated for an external dose of 0.97 µg/kg/d assuming 100 % dermal absorption. Scaling to an external dose of 100 µg/kg bw yields a dermal AUC of 314 nM×h. This is divided by 3 to cover 30 % dermal absorption leading to a dermal AUC of 94.2 nM×h.

From the oral BMDL of 8960 µg/kg bw/d the corrected starting point was calculated by the following equation:

$$8960 \mu\text{g/kg bw/d} \times 2.9/94.2 = 275.8 \mu\text{g/kg/d}$$

The corrected starting point was then divided by an overall assessment factor of 150 (essentially the same as used in the EFSA/ECHA (2015) evaluations) yielding a dermal DNEL of **1.84** µg/kg bw/d.

Due to the lower oral AUC used in the industry approach, a higher dermal DNEL was calculated. It is noted that the oral AUC for mice as predicted from pharmacokinetic principles and allometric scaling is also associated with a great uncertainty due to the scattering of the experimental data points around the predicted relationship (cf. page 130 of Industry dossier).

### **Inhalation DNEL, systemic, general population**

Starting point: a NOAEC of 10 mg/m<sup>3</sup> air was derived from a subchronic (13 week) inhalation study performed in the rat based on (Testing Laboratory, 1988) based on decreased body weights in males and females and decreased absolute liver weights in males, increased alkaline phosphatase in females and increased urea nitrogen in males at 10 mg/m<sup>3</sup> BPA) (Testing Laboratory, 1988).

100 % inhalation absorption is assumed for animals and humans. The first pass effect is not of relevance here. As animals were exposed 6 hrs/5d/week over 13 weeks and for human population, 24 h exposure is assumed, the corrected starting point according to the REACH guidance (Figure R. 8-2) is 1.79 mg/m<sup>3</sup> (10 mg/m<sup>3</sup> × 0.25 (6h/d/24h/d) × 0.71 (5days/7days) = 1.79 mg/m<sup>3</sup>).

The exceptions are the scenarios PVC articles and thermal paper for consumers. The exposure time is 8 h (10 mg/m<sup>3</sup> × 0.75 (6h/d/8h/d) × 0.71 (5days/7days)) yielding an inhalation DNEL of 5.36 mg/m<sup>3</sup>.

Assessment factors:

- Interspecies differences: 10
- Intraspecies differences for Consumers/man exposed via environment (MvE): 10

- differences in duration of exposure: 2 (extrapolation from subchronic to lifetime)
- dose-response and endpoint specific/severity issues: 1
- quality of the database: 1

Overall Assessment factor: 200

Long-term inhalation DNEL for chronic-systemic effects:  $1.79 \text{ mg/m}^3 / 200 = 0.01 \text{ mg/m}^3$   
(rounded value)

Exception PVC articles and thermal paper:  $5.36 \text{ mg/m}^3 / 200 = 0.03 \text{ mg/m}^3$

### **Inhalation DNEL, local, general population**

Starting point: a NOAEC of  $10 \text{ mg/m}^3$  air was derived from a subchronic (13 week) inhalation study performed in the rat based on reversible epithelial hyperplasia and chronic inflammation in the nasal cavity in males and females at  $50 \text{ mg/m}^3$  (Testing Laboratory, 1988). As animals were exposed 6 hrs/5d/week over 13 weeks and for human population, 24 h exposure is assumed, the corrected starting point according to the REACH guidance (Figure R. 8-2) is  $1.79 \text{ mg/m}^3$ .

100 % inhalation absorption is assumed for animals and humans. The first pass effect is not of relevance here. As animals were exposed 6 hrs/5d/week over 13 weeks and for human population, 24 h exposure is assumed, the corrected starting point according to the REACH guidance (Figure R. 8-2) is  $1.79 \text{ mg/m}^3$  ( $10 \text{ mg/m}^3 \times 0.25$  (6h/d/24h/d)  $\times 0.71$  (5days/7days) =  $1.79 \text{ mg/m}^3$  ( $10 \text{ mg/m}^3 \times 0.25$  (6h/d/24h/d)  $\times 0.71$  (5days/7days) =  $1.79 \text{ mg/m}^3$ ).

The exception are the scenarios PVC articles and thermal paper for consumers. The exposure time is 8 h ( $10 \text{ mg/m}^3 \times 0.75$  (6h/d/8h/d)  $\times 0.71$  (5days/7days)) yielding an inhalation DNEL of  $5.36 \text{ mg/m}^3$ .

Assessment factors:

- Interspecies differences: 2.5
- Intraspecies differences for Consumers/man exposed via environment (MvE): 10
- differences in duration of exposure: 2 (extrapolation from subchronic to lifetime)
- dose-response and endpoint specific/severity issues: 1
- quality of the database: 1

Overall Assessment factor: 50

Long-term inhalation DNEL for chronic-systemic effects:  $1.79 \text{ mg/m}^3 / 50 = 0.036 \text{ mg/m}^3$   
(rounded value)

Exception PVC articles and thermal paper:  $5.36 \text{ mg/m}^3 / 50 = 0.107 \text{ mg/m}^3$

**Table 17**

<b>CRITICAL DNELS/DMELS FOR THE GENERAL POPULATION</b>					
<b>Endpoint of concern</b>	<b>Type of effect</b>	<b>Critical study(ies)</b>	<b>Corrected dose descriptor(s) (e.g. NOAEL, NOAEC)</b>	<b>DNEL/ DMEL</b>	<b>Justification/ Remarks</b>
<i>Oral: Repeat dose systemic effects</i> <sup>1)</sup>	Effects on mammary gland, reproductive, neurobehavioural, immune and metabolic systems	See ECHA 2015	609 µg/kg bw/d	4 µg/kg bw/d	See ECHA 2015
<i>Dermal: Repeat dose systemic effects</i> <sup>1)</sup>	Effects on mammary gland, reproductive, neurobehavioural, immune and metabolic systems	See ECHA 2015	609 µg/kg bw/d	0.05 µg/kg bw/d	See ECHA 2015
<i>Inhalation: Repeat dose systemic effects</i>	decreased body weights in males and females; decreased absolute liver weights in males, increased alkaline phosphatase in females and increased urea nitrogen in males	Testing Laboratory, 1988	NOAEC of 10 mg/m <sup>3</sup> air;	0.01 mg/m <sup>3</sup>  Exception: PVC articles and thermal paper: = 0.03 mg/m <sup>3</sup>	
<i>Inhalation: repeat dose local effects</i>	reversible epithelial hyperplasia and chronic inflammation in the nasal cavity	Testing Laboratory, 1988	NOAEC of 10 mg/m <sup>3</sup> air;	0.036 mg/m <sup>3</sup>  Exception: PVC articles and thermal paper: = 0.107 mg/m <sup>3</sup>	

1) In accordance with the lead registrant's suggestion, oral and dermal systemic values for short-term and long-term exposure should be the same.

### **7.9.10. Conclusions of the human health hazard assessment and related classification and labelling**

The eMSCA considers the existing harmonised classification and labelling as appropriate regarding the effects of BPA on the human health.



## 7.10. Assessment of endocrine disrupting (ED) properties

### 7.10.1. Endocrine disruption – Environment

With the update of the joint registration dossier in December 2015 an additional document was attached which addressed endocrine-disrupting properties of BPA. Endocrine properties for the environment were until then not addressed in the registration. With this the registrant concludes that Bisphenol A shows weak endocrine activity but they do not characterise the substance as an endocrine disruptor for environmental species.

Assessing all available data, the eMSCA does not follow the conclusion of the registrant but concludes that available data is sufficient with regards to the environment to identify BPA as an endocrine disruptor according to the WHO/IPCS definition.

For Bisphenol A there is scientific evidence from good quality studies that the substance causes **endocrine mediated adverse effects** in several taxa.

In fish, BPA acts as an oestrogen agonist/androgen antagonist as well as via a thyroidal mode of action.

- *In vitro* data unambiguously shows that BPA binds to vertebrate (and fish) oestrogen receptors in the low µg/L range and modulates gene expression. BPA also competitively inhibits androgenic activity of a known AR agonist. In addition, the thyroidal mode of action is supported by *in vitro* studies demonstrating a thyroid receptor binding in vertebrate cells.
- The endocrine mode of action is substantiated by *in vivo* data. Diagnostic for the oestrogenic mode of action are the observed Vitellogenin induction, changes in gonadal staging, testis ova, and reduced male secondary sex characteristics. The thyroidal mode of action is substantiated by an accelerated embryonic development in *O. latipes*, which was shown to be blocked by amiodorone.
- Adverse effects such as a skewed sex ratio were observed. A direct link between the oestrogenic mode of action *in vivo* (e.g. VTG induction, testis, ova) and adverse effects (sex ratio, reduced egg production) is provided for *O. latipes*, *D. rerio* and very likely for *P. promelas*. For six other fish species, adverse endocrine mediated effects were demonstrated. Additional effects, which are known to be sensitive towards and oestrogenic mode of action, are for example growth, behaviour, and fertilisation success. In addition, the thyroid-mediated effects (accelerated development, earlier hatching and smaller individuals) are to be considered adverse.

In amphibians, BPA is proposed to act as a thyroid antagonist as well as an oestrogen agonist.

- *In vitro* studies with amphibian and mammal cells demonstrate that BPA is able to replace and inhibit T3 and thus acts as a thyroid antagonist. The *in vitro* studies demonstrating a binding to oestrogen receptor in vertebrates provide evidence in amphibians.
- The endocrine mode of action is also substantiated by *in vivo* data. Diagnostic for a thyroid mode of action in amphibians is the accelerated/asynchronous development or an abnormal histopathology, which could be demonstrated. The oestrogenic mode of action is substantiated by a skewed sex ratio, a delay of development and the ability to induce Vitellogenin.
- With respect to the thyroidal mode of action, a direct link between the *in vitro* and *in vivo* data for the TH-induced and spontaneous inhibition of metamorphosis was shown for *R. rugosa*, *X. laevis* and *X. tropicalis*. These lead to a delayed development and disturbed life-cycle and may definitively be considered adverse. For the oestrogenic mode of action, a direct link is provided between Vitellogenin induction through binding to the estrogen receptor and changes of the sex ratio and reproduction for *X. laevis* and 3 other species, which need to be considered adverse.

In invertebrates, BPA also affects steroid hormone regulated pathways and is proposed to act as anti-ecdysteroid in arthropods such as insects and crustaceans, and to exert oestrogen-like effects in molluscan species. In addition, effects on further invertebrates (Echinodermata, Porifera, Cnidaria) are possibly endocrine mediated as effects are similar than for known (xeno-) oestrogens.

- For molluscs, the endocrine mode of action (*in vitro*, biomarkers *in vivo*) is substantiated by oestrogen receptor binding, mRNA expression and increased Vitellogenin or Vitellogenin-like protein levels in 3 species. The oestrogen-like mode of action is linked to characteristic effects on egg production and comitigation by known anti-oestrogens in two species *in vivo*, as well as the induction of superfemales, malformations of genital tissues, which are also known for Oestradiol in four species as well as embryo malformations in 2 species. The reproduction and development related disturbances need to be considered adverse.
- For insects, there is *in vitro* evidence for an antagonistic receptor binding and mRNA expression from studies with *Drosophila* and *Chironomus*. The mode of action is supported by similar effects as known for other (xeno-)oestrogens (nonylphenol (NP), octylphenol (OP), ethinylestradiol (EE2)), such as for example also the characteristic mouthpart deformities in *Chironomus*. For the two insect species the adverse *in vivo* effects comprise a delayed development, reduced fecundity and decreased emergence as well as increased weight/growth.
- For crustaceans, the presumed action as anti-ecdysteroid is supported by comitigation experiments with known ecdysteroids in crustaceans. Due to the close relationship to insects, a binding to the ecdysteroid receptor is assumed. In crustaceans, ecdysteroid-mediated pathways are possibly also indirectly disturbed via an action on methylfarnesoates. Adverse *in vivo* effects are associated with embryo malformations, a developmental delay and an altered reproductive outcome (enhanced or reduced due to embryotoxicity). In isopods, altered ecdysteroid levels were linked to a skewed sex ratio towards females, embryo malformations and an enhanced molting.
- For further invertebrate species, no receptor studies are available, but underlying endocrine modes of action supported by comparison to effects of known (xeno-) oestrogens (NP, OP, EE2). Adverse *in vivo* effects comprise embryo malformations, alterations of development and reproduction in Porifera (embryo abnormalities as known for NP, growth), Echinodermata (similar developmental effects as known for OP and E2, but not EE2, spermiotoxicity, growth), Cnidaria (effects on polyp structure similar to EE2, development) and Annelida (delayed metamorphosis, population growth).

The analysis of results for fish and amphibians according to the OECD Guidance Document for Endocrine Disrupters (OECD 2012) reveals that Bisphenol A needs to be considered as endocrine disrupter. It also fulfils the WHO/IPCS definition of an endocrine disrupter and the recommendations from the European Commission's Endocrine Disrupter Expert Group (JRC 2013) for a substance to be identified as endocrine disrupter. Bisphenol A acts via multiple modes of endocrine action in different taxa, disrupting steroid- and thyroid mediated processes. The endocrine mediated effects observed in fish, amphibians and several invertebrate taxa after exposure to Bisphenol A are considered to adversely affect population stability and recruitment. The endocrine-mediated effects already occurred well below 1 µg/L or in the low µg/L range and thus at lower concentrations than acute, systemic or narcotic toxicity.

### 7.10.2. Endocrine disruption – Human health

See also section 7.9.4. Based on a thorough evaluation of so far available data EFSA concluded in 2015 that "Many effects induced by BPA appear to be tissue-, sex- and concentration-specific. For several BPA-induced effects "windows of exposure" have been reported. Due to the complexity of BPA's interaction with different hormone receptors

and signalling pathways is the German MSCA found it challenging in 2013 to establish which specific endocrine mechanism triggers a certain in vivo effect of BPA.

Meanwhile a SVHC identification has been submitted by France suggesting BPA as a Human Health endocrine disrupter according Art. 57 f based on currently available data.<sup>4</sup>

More clarity might be obtained in the near future from the NIEHS/FDA CLARITY-BPA research program (see e.g. <http://www.sciencedirect.com/science/article/pii/S0890623815300071> and Heindel et al., 2015) might become available in the near future.).

### **7.10.3. Conclusion on endocrine disrupting properties (combined/separate)**

The eMSCA concludes that available data is sufficient to identify BPA as an endocrine disruptor for the environment.

## **7.11. PBT and VPVB assessment**

This chapter was not evaluated because it is not area of concern and does not influence the overall decision.

## **7.12. Exposure assessment**

### **7.12.1. Human health**

Worker

Consumer

During the SEv procedure four relevant consumer exposure scenarios were identified, discussed and assessed:

- Consumer use of thermal paper
- Consumer use of articles made of PVC
- Consumer use of articles made of polycarbonate
- Consumer use of articles of epoxy resins

#### Preface

The exposure estimations were carried out in accordance with the ECHA guidance on Information Requirements and Chemical Safety Assessment, Chapter R.15: Consumer exposure estimation, Version 2 (ECHA, April 2010). Assessments of exposure levels for the consumers were performed during the evaluation period of SEv-procedure (that means in 2012) with the tool ECETOC Targeted Risk Assessment Programme, Version 2.0 (ECETOC, 2009). Deviations from these estimates were justified by appropriate studies. The values used are based on an intense discussion with the lead registrant, who in consequence updated his chemical safety report (October 2012). Due to this process and the resulting documents the following assessment was conducted.

---

<sup>4</sup> ECHA website: Section on BPA: [https://echa.europa.eu/proposals-to-identify-substances-of-very-high-concern-previous-consultations/-/substance-rev/16002/term?\\_viewsubstances\\_WAR\\_echarevsubstanceportlet\\_SEARCH\\_CRITERIA\\_EC\\_NUMBER=201-245-8&\\_viewsubstances\\_WAR\\_echarevsubstanceportlet\\_DISS=true](https://echa.europa.eu/proposals-to-identify-substances-of-very-high-concern-previous-consultations/-/substance-rev/16002/term?_viewsubstances_WAR_echarevsubstanceportlet_SEARCH_CRITERIA_EC_NUMBER=201-245-8&_viewsubstances_WAR_echarevsubstanceportlet_DISS=true)

## Consumer use of thermal paper

EC (2008a, p. 23 HS) has concluded that the use of thermal paper is considered to result in negligible potential for consumer exposure in comparison with other sources.

For this use AC 8 (Paper articles), especially the subcategory "Printed paper" covering papers, magazines and books, is relevant.

### Oral exposure

The oral route is not relevant.

### Dermal exposure

The consumer use of thermal paper has been evaluated in two important publications, done by Biedermann (2010) and Lassen (2011).

Lassen (2011) expects that consumers handle thermal paper up to 4.6 times per day using 8 fingers. Biedermann (2010) has shown that typically 1.13 µg of BPA are present on the skin of each finger (if thermal paper is touched with dry fingers). In comparison results of Lassen (2011) shows an average of 1.38 µg of BPA present on the skin of each finger (if thermal paper is touched with dry fingers).

In the publication of Biedermann (2010) additionally data on a specific quality of thermal paper were included. In this case Biedermann (2010) has demonstrated that 3 µg of BPA being present on the skin of each dry finger. Based on the assumptions of Lassen (2011) and the results of Biedermann (2010) the daily uptake can be calculated as follows:

$4.6 \text{ (times per day)} \times 8 \text{ (fingers)} \times 3 \text{ } \mu\text{g (BPA concentration on the skin of each finger)} = 110 \text{ } \mu\text{g.}$

Based on a body weight of 60 kg (110 µg:60 kg) a systemic exposure of  **$1.84 \times 10^{-3}$  mg/kg bw day** can be calculated.

This assessment is based on the relevant literature (Biedermann 2010 and Lassen 2011) and uses the conservative assessments of these authors for the estimates of consumer exposure. The calculation is based on 3µg BPA per fingertip as highest value of Biedermann (2010) and not on an average of 1,13 µg per fingertip. Additionally 8 fingertips (not only 2) and 4,6 contacts per day from Lassen (2011) were used for the calculation.

Based on data of Liao (2011) an average systemic exposure of  $1.08 \times 10^{-6}$  mg/kg bw day can be calculated for a body weight of 60 kg . Using the data for the 95% percentile a systemic exposure of  $3.35 \times 10^{-5}$  mg/kg bw day is obtained. This value is by a factor of 50 below the systemic exposure of  $1.84 \times 10^{-3}$  mg/kg bw day as based on Biedermann (2010) and Lassen (2011).

Based on the data in Geens (2012a) an average systemic exposure of  $2.75 \times 10^{-5}$  mg/kg bw day can be calculated for a body weight of 60 kg. This value which is by a factor of 70 below the systemic exposure of  $1.84 \times 10^{-3}$  mg/kg bw day as based on Biedermann (2010) and Lassen (2011).

### Inhalative exposure

#### Operational conditions:

Duration-time: 8h/day

Frequency of use: 365 days per year

Concentration: < 3 %

risk management measures related to consumers: no

This consumer use is an indoor use.

#### Model settings:

Molecular weight :228.29 g/mol

Vapour pressure:  $4.12 \times 10^{-9}$  hPa

Amount of product used per application: < 50 g

Product ingredient fraction by weight : 0.03

The inhalative exposure was calculated by ECETOC TRA :  $4.57 \times 10^{-3}$  (mg/kg bw day) equivalent to  $2.50 \times 10^{-2}$  mg/m<sup>3</sup>.

#### Total Exposure of consumers in AC 8

Member State concludes that the total exposure of consumers in AC 8 due to thermal paper was  **$6.41 \times 10^{-3}$  mg/kg bw day.**

#### **Consumer use of articles made of PVC**

EC (2008a, p. 23 HS) concluded that the use of articles made of PVC is considered to result in negligible potential for consumers exposure.

For this use the categories AC 2 (Machinery, mechanical appliances, electrical/electronic articles) and AC 13 (Plastic articles) are relevant.

It is not possible to calculate exposure by use of electrical/electronic articles (AC 2) with ECETOC TRA.

ECETOC (2009, p. 80) explain as follows: "Consumer use may not be totally ruled out for the category but there is a lack of adequate information for estimating a relevant value of consumer exposure at the present time."

In AC 13 it is necessary to differentiate 3 subcategories:

- Plastics –larger articles, covering a plastic chair, PVC-flooring or a lawn mover
- Plastics – small articles, covering a ball pen or a mobile phone.
- Toys

#### Operational conditions:

Duration-time: 8h/day for larger and small plastic articles and  
24h/day for toys (as a worst case scenario for children)

Frequency of use: 365 days per year

Concentration: < 0.2 %

amount of product: < 1 KG

risk management measures related to consumers: no

#### Model settings:

Molecular weight :228.29 g/mol

Vapour pressure:  $4.12 \times 10^{-9}$  hPa

Amount of product used per application:1000 g

Product ingredient fraction by weight : 0.002

#### AC 13 (Plastic, larger articles)

Oral exposure: route not relevant – reasoning: Oral exposure does not occur as part of the intended product use (ECETOC,2009, p.87)

Dermal systemic exposure (mg/kg bw day):  $2.92 \times 10^{-1}$

Inhalative exposure (mg/m<sup>3</sup>):  $1.00 \times 10^{-1}$

Inhalative exposure (mg/kg bw day): $1.83 \times 10^{-2}$

#### AC 13 (Plastic, small articles)

Oral exposure (mg/kg bw day):  $2.00 \times 10^{-3}$

Dermal systemic exposure (mg/kg bw day): $1.19 \times 10^{-3}$

Inhalative exposure (mg/m<sup>3</sup>):  $1.00 \times 10^{-1}$

Inhalative exposure (mg/kg bw day): $1.83 \times 10^{-2}$

#### AC 13 (Toys)

Oral exposure (mg/kg bw day): $2.00 \times 10^{-3}$

Dermal systemic exposure (mg/kg bw day):  $1.11 \times 10^{-1}$

Inhalative exposure:ECETOC TRA gives no data - reasoning: Formulations contain negligible amounts of volatiles or particulate matter- no inhalation exposure, (ECETOC,2009, p.87)

Total exposure of consumers in AC 13 (concentrations in mg/kg bw day)AC 13 (Plastic, larger articles) :  **$3.10 \times 10^{-1}$** AC 13 (Plastic, small articles) :  **$2.15 \times 10^{-2}$** AC 13 (Toys)  **$1.13 \times 10^{-1}$** **Consumer Use of Articles made of Polycarbonate**

For this use the categories AC 1 (Vehicles), AC 2 (Machinery, mechanical appliances, electrical/electronic articles) and AC 13 (Plastic articles) are relevant.

Operational conditions:

Duration-time: &lt;24h/day (as a worst case scenario)

Frequency of use: 365 days per year

Concentration of substance &lt; 100 ppm (maximum); the typical concentration is &lt; 10 ppm

Risk management measures related to consumers: no

Model settings:

Molecular weight : 228.29 g/mol

Vapour pressure:  $4.12 \times 10^{-9}$  hPa

Product ingredient: 100 ppm

Fraction by weight :  $1.00 \times 10^{-4}$ Long-term exposure

It is not possible to calculate exposure by use of vehicles (AC 1) and use of machinery and mechanical appliances and electrical/electronic articles (AC 2) with ECETOC TRA. ECETOC (2009, p. 80) explain as follows: "Consumer use may not be totally ruled out for the category but there is a lack of adequate information for estimating a relevant value of consumer exposure at the present time."

AC 13 (Plastic, larger articles)

Oral exposure: route not relevant (ECETOC, 2009, p.87)

Dermal systemic exposure (mg/kg bw day):  $1.46 \times 10^{-2}$ Inhalative exposure (mg/m<sup>3</sup>)  $3.86 \times 10^{-5}$ Inhalative exposure (mg/kg bw day):  $7.06 \times 10^{-6}$ AC 13 (Plastic, small articles)Oral exposure (mg/kg bw day):  $1.67 \times 10^{-4}$ Dermal systemic exposure (mg/kg bw day):  $5.95 \times 10^{-5}$ Inhalative exposure (mg/m<sup>3</sup>):  $3.86 \times 10^{-5}$ Inhalative exposure (mg/kg bw day)  $7.06 \times 10^{-6}$ Total exposure of consumers in AC 13 (concentrations in mg/kg bw day)AC 13 (Plastic, larger articles) :  **$1.47 \times 10^{-2}$** C 13 (Plastic, small articles) :  **$2.38 \times 10^{-5}$** Refinement of dermal exposure estimation

The study of Mercea (2009) shows that the release of BPA from polycarbonate does not correlate with the content of free Bisphenol A. The release of BPA is inhibited due to incorporation in the polymer matrix. Mercea (2009) reported that BPA only occurs if polycarbonate is subject to significant thermal, chemical or mechanical stress. For most articles made of polycarbonate any consumer contact is rather short and limited to skin contact. Typical examples for articles made of polycarbonate are casings of mobile phones and keypads.

The refinement done by the lead-registrant was based on a worst case scenario:

As an example for AC 13 (Plastic, larger articles) a chair made of polycarbonate was used. An adult consumer would have permanent dermal contact to the polycarbonate

chair for 24 hours/day at a surrounding temperature of 40 °C. This temperature was selected to cover the same conditions as in a study with sweat simulant. In this study polycarbonate films were exposed to sweat simulant for 24 hours at 40 °C. The refinement was done with the highest release (business confidential data) of BPA from the films in this study. The relevant skin contact area in accordance with ECETOC (2012) is half of the default whole body skin surface area:  $17.500 \text{ cm}^2 : 2 = 8.750 \text{ cm}^2$ . Considering a conservative default body weight of 60 kg the worst case dermal exposure of consumers from a polycarbonate chair was **0.57 µg/kg bw/day equivalent to 0.00057 mg/kg bw/day**.

### Consumer Use of Articles made of Epoxy Resins

For this use the categories AC 1 (Vehicles), AC 2 (Machinery, mechanical appliances, electrical/electronic articles) and AC 13 (Plastic articles) are relevant. Epoxy resins are produced by mixing BPA and epichlorohydrin. The reaction product is a basic monomer unit of epoxy resin called BADGE (or DGEBA), CAS No 25068-38-6. BADGE has been subject to a substance evaluation by Denmark in 2015. The evaluation is currently still ongoing.

The Epoxy Resin Committee states that epoxy resins in liquid form can contain a maximum of 10 ppm of residual unreacted BPA. For solid epoxy resins the maximum amount is 65 ppm of BPA.

[http://www.epoxy-europe.eu/uploads/Modules/Resources/epoxy\\_erc\\_bpa\\_whitepapers\\_summarypaper.pdf](http://www.epoxy-europe.eu/uploads/Modules/Resources/epoxy_erc_bpa_whitepapers_summarypaper.pdf)

Notwithstanding the above consumer use of articles made of epoxy resins was evaluated as described in the preface.

#### Operational conditions:

Duration-time: <24h/day (as a worst case scenario)  
 Frequency of use: 365 days per year  
 Concentration of substance : < 10 ppm  
 Risk management measures related to consumers: no

#### Model settings:

Molecular weight : 228.29 g/mol  
 Vapour pressure:  $4.12 \times 10^{-9}$  hPa  
 Product ingredient: 10 ppm  
 Fraction by weight :  $1.00 \times 10^{-5}$

#### Long-term exposure

*It is not possible to calculate exposure by use of vehicles (AC 1) and use of machinery and mechanical appliances and electrical/electronic articles (AC 2) with ECETOC TRA. ECETOC (2009, p. 80) explain as follows: "Consumer use may not be totally ruled out for the category but there is a lack of adequate information for estimating a relevant value of consumer exposure at the present time."*

#### AC 13 (Plastic, larger articles)

Oral exposure: route not relevant (ECETOC, 2009, p.87)  
 Dermal systemic exposure (mg/kg bw day):  $1.46 \times 10^{-3}$   
 Inhalative exposure (mg/m<sup>3</sup>)  $3.86 \times 10^{-5}$   
 Inhalative exposure (mg/kg bw day):  $7.06 \times 10^{-6}$

#### AC 13 (Plastic, small articles)

Oral exposure (mg/kg bw day):  $1.67 \times 10^{-5}$   
 Dermal systemic exposure (mg/kg bw day):  $5.95 \times 10^{-6}$   
 Inhalative exposure (mg/m<sup>3</sup>):  $6.47 \times 10^{-6}$   
 Inhalative exposure (mg/kg bw day)  $1.18 \times 10^{-6}$

#### Total exposure of consumers (mg/kg bw day):

AC 13 (Plastic, larger articles)  **$1.47 \times 10^{-3}$**

AC 13 (Plastic, small articles)

**2.38 x 10<sup>-5</sup>**

Independent of these current uses EC (2003) has identified the following consumer uses for epoxy resin hardeners:

- Marine antifouling paints (content of epoxy resin in paint: 40%, content of residual BPA in epoxy resin: 10 ppm)
- wood varnish (content of epoxy resin in paint: 40%, content of residual BPA in epoxy resin: 10 ppm)
- wood fillers (content of epoxy resin: 20%, content of residual BPA in epoxy resin: 10 ppm)
- adhesives (content of residual BPA in epoxy resin: 10 ppm)

Based on data from EC (2003) the dermal exposure (mg/kg bw day) can be calculated as follows:

- Marine antifouling paints:  $4.83 \times 10^{-4}$
- Wood varnish:  $6.00 \times 10^{-5}$
- Wood fillers :  $1.50 \times 10^{-4}$
- Adhesives:  $1.67 \times 10^{-5}$

### 7.12.2. Environment

As a result of the substance evaluation further information on environmental exposure was requested. For detailed description see the decision published on ECHA website.

In response to the request, registrants deleted several uses from the lead dossier, updated the lead dossier in December 2014 and 2015 (compare chapter 7.5.2) and modelled the emissions of BPA into the environment in the frame of a substance flow analysis (SFA) and regionalized pathway analysis (RPA) in 2015. In parallel the Epoxy Resin Committee provided exposure assessments for their main uses (<http://www.epoxy-europe.eu/en/resource/documents/>).

Response to the request and update of the registration dossier

a) Exposure assessment for the terrestrial compartment (soil and groundwater)

As both exposure pathways for emission to soil and groundwater – the application of sewage sludge and the deposition of Bisphenol A from air – were not considered in the registration dossier, the registrant added the required scenarios.

The Registrants stated that for the updated registration dossier for each covered scenario an exposure assessment for air, soil and water was included. In accordance with REACH guidance document R 16 the possible emission of Bisphenol A to groundwater was covered via the assessment "man via environment" and possible exposure via drinking water. In the updated dossier for each covered scenario an individual waste exposure assessment was included to elucidate the releases from municipal landfill sites. For deposition via air to soil, the Registrants used in each scenario a worst case assessment assuming that the total Bisphenol A volume emitted to air is directly deposited to the terrestrial compartment, not taking into account degradation.

EMSCA concludes that the exposure scenarios cover basically the required information. However, not all input parameters are understandable. The assessment of emission from sludge application is still not clear and therefore it is unclear how the concentration in groundwater was assessed. Regarding the assessment for air it is unclear if it was distinguished between BPA in air and BPA aggregated to dust. However, the eMSCA considers that no further information needs to be requested for the scope of this evaluation.

b) Exposure assessment for life cycle steps missing in the registration dossier

Subsequent life cycle steps for the manufacture of chemicals and for the manufacture of laboratory reagents and for the waste stage of all uses was requested.



Registrant included waste stage scenarios but did not include scenarios following the manufacture of chemicals (in the updated dossier the scenario is named "manufacturing of other substances") and manufacturing of laboratory reagents. The registrant states that the manufacturing and the waste stage from the manufacturing process were assessed and that a subsequent service life of the Bisphenol A used for the process is not relevant as any residual Bisphenol A would become either a constituent or an impurity of the new manufactured substance. According to the assumptions of the Registrants the life cycle of Bisphenol A used for the manufacturing ends with the end of the manufacturing process. Further regulatory measures will be based on the information available.

- c) Exposure assessment for industrial manufacturing of Bisphenol A and industrial use of Bisphenol A for manufacturing of polycarbonate

The registrants were requested to clarify the tonnages and explain the selection of the worst case site.

The registrant revised the scenario, used recent tonnage data for the PEC calculation and provided up to date emission data for all Bisphenol A manufacturing sites which are also the manufacturing sites for polycarbonate. Registrants provided explanations how the relevant dataset for the risk assessment was identified as well as how the calculation were performed.

The requests are met with the information provided.

- d) Industrial, professional and consumer use of articles made of polycarbonate

The registrants were requested to develop exposure scenarios for industrial, professional, and consumer use of articles made of polycarbonate including the service life and waste stage for indoor and outdoor uses, provide recent information on tonnages and justify the input parameters for the exposure scenario.

The registrants provided a differentiated life cycle concept in the updated registration dossier distinguishing between indoor and outdoor uses for professional and consumer uses (ES 7 to ES 10). The updated EU tonnages were used in the assessment. The registrants assessed for a dataset of polycarbonate samples (in total more than 3000 measurements) regarding the residual content of Bisphenol A in the polymer. The measurements included unprocessed and processed polycarbonate samples as well as polycarbonate articles. In each use scenario where polycarbonate is assessed a conservative residual Bisphenol A content at that live cycle step was considered.

The industrial life cycle of PC was split in the steps: industrial manufacture of PC; industrial blending of PC; industrial manufacture of PC articles. For each of these steps a life cycle and a waste assessment are provided. For the industrial use of manufactured polycarbonate articles the Registrants states that a separate assessment of this life cycle step was not relevant as a) PC articles in EU are not manufactured for a specific industrial use only, b) an assignment of the "industrial article" volume is not possible, c) in the case that an article is used in an industrial setting there are no indications that this will lead to different emissions of residual Bisphenol A to the environment than during a usage in a professional or consumer setting. Therefore, the Registrants assessed the total volume of EU manufactured PC articles for the professional and consumer usage.

In the updated registration dossier the Registrants assessed the outdoor and indoor uses separately to account for the individual use condition on the emission of the residual monomer content to the environment. Both, a life cycle assessment and a waste assessment was provided to distinguish emissions to waste water treatment plants and subsequent surface water.

For each of the five EU polycarbonate manufacturing sites Registrants provided information on Bisphenol A emission from the respective STP. Registrants state that sewage sludge from each of the industrial STP of these sites is either incinerated or

stored at dedicated landfill sites and is not applied on agricultural soil. Registrants assess releases via this pathway as not applicable.

The distinction in indoor and outdoor uses for professional and consumer uses is helpful to assess the risk for the environment. Registrants choose the following uses as worst case scenarios: Professional and consumer indoor use: washing of PC bottles; professional and consumer outdoor use: polycarbonate sheets which are used for greenhouse construction for example. However, it stays unclear which articles are produced exactly for professional and consumer uses. Therefore it is not possible to assess, if the selected scenarios for professional and consumer uses reflect in all cases the use with the highest emission having in mind the above-mentioned range of uses.

No further information will be requested in the frame of substance evaluation.

e) Industrial and professional repackaging of Bisphenol A

Registrants were requested to detail this exposure assessment.

Registrant provided worst case calculations for release to air from these uses.

The requests are met. No further information will be requested in the frame of substance evaluation.

f) Industrial use of Bisphenol A for manufacture of epoxy resins

The registrant was requested to update their calculations as the numbers for the assessment seem to be outdated. Furthermore, Registrant were requested to clarify the contribution of small-volume sales for emission to the environment.

Registrants provided assessment based on updated tonnages and emission data from the sites. Registrant states that the emission data do not distinguish the source (manufacturing or conversion to BADGE). Based on updated volume and emission data a worst case release fraction was calculated and used for a generic scenario. The scenario is based on the highest volume reported by Epoxy manufacturers.

Regarding small-volume sales Registrants state that there is no significant contribution to emission to the environment from selected point sources (i.e. smaller epoxy manufacturers) as monitoring data and the modelling study (regionalized pathway analysis and substance flow analysis) may show.

No further information will be requested in the frame of substance evaluation.

g) Industrial, professional and consumer use of articles made of epoxy resin

Registrant was requested to provide exposure scenarios for industrial and professional use of articles made of epoxy resin including the service life and waste stage and to clarify the boundaries to the scenario manufacture of coating materials. Furthermore Registrants are requested to clarify consumer uses.

Registrants state that as the majority of articles made with epoxy resins (e.g. coated articles etc.) are made from a substance other than Bisphenol A (DGEBA). This is the reason why the uses are not formally covered in the CSR. Nevertheless, Registrant provided a semi-quantitative assessment in the document "Approach for a lifecycle assessment of epoxy resins which include Bisphenol A" using various publically available data to estimate release from epoxy resin coatings during service life and in the waste stage. For example, the use of Epoxy Resin in water pipe rehabilitation is a use of other substances, such as DGEBA.

No further information will be requested in the frame of substance evaluation.

h) Use of Bisphenol A for the manufacture of epoxy resin hardeners, Use of Bisphenol A in epoxy resin hardeners

The Registrants were requested to detail their calculations and to provide consumer uses of Bisphenol A in epoxy resin hardeners.

Registrant did not provide information on consumer use of Bisphenol A based hardeners as this is a downstream use and no information indicating Bisphenol A based hardeners in consumer products are available to Registrants. The Registrants provided a description of the sequence of steps and the scenarios describing the production of epoxy hardeners. The volumes used in each step have been revised and updated.

No further information will be requested in the frame of substance evaluation.

Conclusion on findings of updated registration dossier: The exposure assessment was significantly improved with the update of the registration dossiers. However, due to the complex use and supply chain structure and some still remaining uncertainties in the assessment (e.g. in tonnages) it is not possible to decide without doubts which are the relevant pathways of emission to the environment.

The substance flow analysis / regional pathway analysis (SFA / RPA) provided by Registrants during substance evaluation comes to the conclusion that emission to the environment result mainly from consumer uses. Bisphenol a is mainly emitted to surface water. Effluent from municipal and industrial waste water treatment plants are important sources. However, it was not shown which consumer uses contribute most to the emissions to the environment.

### **Information from registrations**

According to ECHA dissemination website release to the environment of this substance is likely to occur from industrial use as an intermediate step in further manufacturing of another substance (use of intermediates), in the production of articles, formulation of mixtures and formulation in materials. Other release to the environment of this substance is likely to occur from indoor use in long-life materials with low release rate (e.g. flooring, furniture, toys, construction materials, curtains, foot-wear, leather products, paper and cardboard products, electronic equipment), outdoor use in long-life materials with low release rate (e.g. metal, wooden and plastic construction and building materials), indoor use and outdoor use resulting in inclusion into or onto a materials (e.g. binding agent in paints and coatings or adhesives).

According to the Epoxy Resin Committee (ERC) the main uses are use of epoxy resin in energy, construction, transport sectors (cars, ships, planes), food packaging and drinking water applications, applications in home and leisure (paint and coatings, floorings, sports), electronics (<http://www.epoxy-europe.eu/en/applications/>). These uses account for emission of at least approximately 750 kg BPA per year. However, not all uses and all life cycle steps were considered in this calculation by the ERC.

### **7.12.3. Combined exposure assessment**

Not part of the evaluation.

## **7.13. Risk characterisation**

The calculations of exposure and its DNEL derivation based on parameters in the registration was presented in the sections above. In the following section these values are used by the eMSCA for the calculation of risk characterization ratios.

### **Risk characterisation for consumers**

The following four relevant consumer exposure scenarios were identified, discussed and assessed previously in section 7.12.1.2:

- Consumer use of thermal paper
- Consumer use of articles made of PVC
- Consumer use of articles made of polycarbonate
- Consumer use of articles of epoxy resins

**Consumer use of thermal paper****Table 18**

<b>RCR FOR DERMAL EXPOSURE OF CONSUMERS FOR USE OF THERMAL PAPER</b>			
<b>Operation</b>	<b>Dermal exposure (mg/kg bw/day)</b>	<b>DNEL for dermal exposure (mg/kg bw/day)</b>	<b>Risk characterisation ratio for dermal exposure</b>
AC 8	$1.84 \times 10^{-3}$	$5.0 \times 10^{-5}$	37

The eMSCA concludes that the RCR for thermal paper and dermal exposure is clearly above 1.

**Table 19**

<b>RCR FOR INHALATIVE EXPOSURE OF CONSUMERS FOR USE OF THERMAL PAPER</b>			
<b>Operation</b>	<b>Inhalative exposure (mg/kg bw/day)</b>	<b>DNEL for inhalative exposure (mg/kg bw/day)</b>	<b>Risk characterisation ratio for inhalative exposure</b>
AC 8	$2.5 \times 10^{-2}$	$3.0 \times 10^{-2}$	0.833

The eMSCA concludes that the RCR for thermal paper and inhalative exposure is 0.833.

**Table 20**

<b>RCR FOR TOTAL EXPOSURE OF CONSUMERS FOR USE OF THERMAL PAPER</b>			
<b>Operation</b>	<b>Total exposure (mg/kg bw/day)</b>	<b>DNEL for total exposure (mg/kg bw/day)</b>	<b>Risk characterisation ratio for total exposure</b>
AC 8	$6.41 \times 10^{-3}$	$4.0 \times 10^{-3}$	1.60

The eMSCA concludes that the RCR for the consumer use of thermal paper is above 1.

**Consumer use of articles made of PVC**

The registrants have divided the article category 13 in three subcategories:

- Plastics – larger articles,
- Plastics – small articles and
- Toys.

**Table 21**

<b>RCR FOR ORAL EXPOSURE OF CONSUMERS FOR ARTICLES MADE OF PVC</b>			
<b>Operation</b>	<b>Oral exposure (mg/kg bw/day)</b>	<b>DNEL for oral exposure (mg/kg bw/day)</b>	<b>Risk characterisation ratio for oral exposure</b>
AC 13 larger article	Not applicable	$4.0 \times 10^{-3}$	Not derived
AC 13 small article	$2.0 \times 10^{-3}$	$4.0 \times 10^{-3}$	0.5
AC 13 toys	$2.0 \times 10^{-3}$	$4.0 \times 10^{-3}$	0.5

The eMSCA concludes that the RCR for PVC articles and oral exposure is 0.5.

**Table 22**

<b>RCR FOR DERMAL EXPOSURE OF CONSUMERS FOR ARTICLES MADE OF PVC</b>			
<b>Operation</b>	<b>Dermal exposure (mg/kg bw/day)</b>	<b>DNEL for dermal exposure (mg/kg bw/day)</b>	<b>Risk characterisation ratio for dermal exposure</b>
AC 13 larger article	$2.92 \times 10^{-1}$	$5.0 \times 10^{-5}$	5840
AC 13 small article	$1.19 \times 10^{-3}$	$5.0 \times 10^{-5}$	24
AC 13 toys	$1.11 \times 10^{-1}$	$5.0 \times 10^{-5}$	2220

The eMSCA concludes that the RCR for all PVC articles and dermal exposure is clearly above 1.

**Table 23**

<b>RCR FOR INHALATIVE EXPOSURE OF CONSUMERS FOR ARTICLES MADE OF PVC</b>			
<b>Operation</b>	<b>Inhalative exposure (mg/kg bw/day)</b>	<b>DNEL for inhalative exposure (mg/kg bw/day)</b>	<b>Risk characterisation ratio for inhalative exposure</b>
AC 13 larger article	$1.0 \times 10^{-1}$	$3.0 \times 10^{-2}$	3.33
AC 13 small article	$1.0 \times 10^{-1}$	$3.0 \times 10^{-2}$	3.33
AC 13 toys	No data		Not derived

The eMSCA concludes that the RCR for PVC articles and inhalative exposure is clearly above 1.

**Table 24**

<b>RCR FOR TOTAL EXPOSURE OF CONSUMERS FOR ARTICLES MADE OF PVC</b>			
<b>Operation</b>	<b>Total exposure (mg/kg bw/day)</b>	<b>DNEL for total exposure (mg/kg bw/day)</b>	<b>Risk characterisation ratio for total exposure</b>
AC 13 larger article	$3.1 \times 10^{-1}$	$4.0 \times 10^{-3}$	78
AC 13 small article	$2.15 \times 10^{-2}$	$4.0 \times 10^{-3}$	5.38
AC 13 toys	$1.13 \times 10^{-1}$	$4.0 \times 10^{-3}$	28

The eMSCA concludes that the RCR for consumer use of all PVC articles is clearly above 1.

### Consumer use of articles made of polycarbonate

The registrants have divided the article category 13 in two subcategories:

- Plastics – larger articles and
- Plastics – small articles.

**Table 25**

<b>RCR FOR ORAL EXPOSURE OF CONSUMERS FOR ARTICLES MADE OF PC</b>			
<b>Operation</b>	<b>Oral exposure (mg/kg bw/day)</b>	<b>DNEL for oral exposure (mg/kg bw/day)</b>	<b>Risk characterisation ratio for oral exposure</b>
AC 13 larger article	Not applicable	$4.0 \times 10^{-3}$	Not derived
AC 13 small article	$1.67 \times 10^{-4}$	$4.0 \times 10^{-3}$	0.042

The eMSCA concludes that the RCR for small polycarbonate articles and oral exposure is below 1.

The dermal exposure for larger articles made of polycarbonate was refined by the lead registrant.

**Table 26**

<b>RCR FOR DERMAL EXPOSURE OF CONSUMERS FOR ARTICLES MADE OF PC</b>			
<b>Operation</b>	<b>Dermal exposure (mg/kg bw/day)</b>	<b>DNEL for dermal exposure (mg/kg bw/day)</b>	<b>Risk characterisation ratio for dermal exposure</b>
AC 13 larger article	$1.46 \times 10^{-2}$	$5.0 \times 10^{-5}$	292
AC 13 larger articles, refinement	$5.7 \times 10^{-4}$	$5.0 \times 10^{-5}$	11.4

AC 13 small article	$5.95 \times 10^{-5}$	$5.0 \times 10^{-5}$	1.19
---------------------	-----------------------	----------------------	------

The eMSCA concludes that the RCR for all polycarbonate articles and dermal exposure is above 1.

**Table 27**

<b>RCR FOR INHALATIVE EXPOSURE OF CONSUMERS FOR ARTICLES MADE OF PC</b>			
<b>Operation</b>	<b>Inhalative exposure (mg/kg bw/day)</b>	<b>DNEL for inhalative exposure (mg/kg bw/day)</b>	<b>Risk characterisation ratio for inhalative exposure</b>
AC 13 larger article	$3.86 \times 10^{-5}$	$1.0 \times 10^{-2}$	0.0039
AC 13 small article	$3.86 \times 10^{-5}$	$1.0 \times 10^{-2}$	0.0039

The eMSCA concludes that the RCR for all polycarbonate articles and inhalative exposure is below 1.

**Table 28**

<b>RCR FOR TOTAL EXPOSURE OF CONSUMERS FOR ARTICLES MADE OF PC</b>			
<b>Operation</b>	<b>Total exposure (mg/kg bw/day)</b>	<b>DNEL for total exposure (mg/kg bw/day)</b>	<b>Risk characterisation ratio for total exposure</b>
AC 13 larger article	$1.47 \times 10^{-2}$	$4.0 \times 10^{-3}$	3.68
AC 13 small article	$2.38 \times 10^{-5}$	$4.0 \times 10^{-3}$	0.00595

The eMSCA concludes that the RCR for consumer use of small polycarbonate articles is below 1 and the RCR for consumer use of larger articles is above 1.

### **Consumer use of articles made of epoxy resins**

The registrants have divided the article category 13 in two subcategories:

- Plastics – larger articles and
- Plastics – small articles.

**Table 29**

<b>RCR FOR ORAL EXPOSURE OF CONSUMERS FOR ARTICLES MADE OF EPOXY RESINS</b>			
<b>Operation</b>	<b>Oral exposure (mg/kg bw/day)</b>	<b>DNEL for oral exposure (mg/kg bw/day)</b>	<b>Risk characterisation ratio for oral exposure</b>
AC 13 larger article	Not applicable	$4.0 \times 10^{-3}$	Not derived

AC 13 small article	$1.67 \times 10^{-5}$	$4.0 \times 10^{-3}$	0.0042
---------------------	-----------------------	----------------------	--------

The eMSCA concludes that the RCR for small epoxy resin articles and oral exposure is below 1.

**Table 30**

<b>RCR FOR DERMAL EXPOSURE OF CONSUMERS FOR ARTICLES MADE OF EPOXY RESINS</b>			
<b>Operation</b>	<b>Dermal exposure (mg/kg bw/day)</b>	<b>DNEL for dermal exposure (mg/kg bw/day)</b>	<b>Risk characterisation ratio for dermal exposure</b>
AC 13 larger article	$1.46 \times 10^{-3}$	$5.0 \times 10^{-5}$	29.2
AC 13 small article	$5.95 \times 10^{-6}$	$5.0 \times 10^{-5}$	0.119

The eMSCA concludes that the RCR for larger articles made of epoxy resins and dermal exposure is clearly above 1. Furthermore, eMSCA concludes that the RCR for small articles made of epoxy resins and dermal exposure is below 1.

**Table 31**

<b>RCR FOR INHALATIVE EXPOSURE OF CONSUMERS FOR ARTICLES MADE OF EPOXY RESINS</b>			
<b>Operation</b>	<b>Inhalative exposure (mg/kg bw/day)</b>	<b>DNEL for inhalative exposure (mg/kg bw/day)</b>	<b>Risk characterisation ratio for inhalative exposure</b>
AC 13 larger article	$3.86 \times 10^{-5}$	$1.0 \times 10^{-2}$	0.0039
AC 13 small article	$6.47 \times 10^{-6}$	$1.0 \times 10^{-2}$	0.000647

The eMSCA concludes that the RCR for all epoxy resin articles and inhalative exposure is below 1.

**Table 32**

<b>RCR FOR TOTAL EXPOSURE OF CONSUMERS FOR ARTICLES MADE OF EPOXY RESINS</b>			
<b>Operation</b>	<b>Total exposure (mg/kg bw/day)</b>	<b>DNEL for total exposure (mg/kg bw/day)</b>	<b>Risk characterisation ratio for total exposure</b>
AC 13 larger article	$1.47 \times 10^{-3}$	$4.0 \times 10^{-3}$	0.368
AC 13 small article	$2.38 \times 10^{-5}$	$4.0 \times 10^{-3}$	0.00595

The eMSCA concludes that the RCR for consumer use of articles made of epoxy resins is below 1.



**Risk characterization for the environment**

For risk assessment eMSCA choose the UQN derived in the course of the development of the UQN dossier (JRC unpublished) to assess the risk for freshwater and marine water.

Based on the exposure data Registrant provided there is a risk for freshwater and marine water as the resulting RCR values are close to or above 1, respectively for

- Manufacture of Bisphenol A (ES 1, contributing scenario 2: manufacture of Bisphenol A (sites with emission to fresh water; contributing scenario 3: waste treatment))
- Manufacture of polycarbonate (ES 4, contributing scenario 2: industrial use of monomers for manufacture of polycarbonate (sites with emission to marine water))
- Industrial repackaging of Bisphenol A (ES 2, contributing scenario 2: waste treatment)

Based on the data Registrant provided and taking into account the newly derived UQN there is a risk for freshwater for

- Manufacture of Bisphenol A (ES 1, contributing scenario 1: manufacture of Bisphenol A (sites with emission to fresh water))
- Industrial repackaging of Bisphenol A (ES 2, contributing scenario 1: industrial repackaging of Bisphenol A)
- Professional repackaging of Bisphenol A (ES 3, contributing scenario 1: professional repackaging of Bisphenol A; contributing scenario 2: waste treatment)
- Manufacture of polycarbonate (ES 4, contributing scenario 1: industrial use of monomers for manufacture of polycarbonate (sites with emission to freshwater); contributing scenario 3: waste treatment)
- The blending of polycarbonate (ES 5, contributing scenario 1: blending; contributing scenario 2: waste treatment)
- Industrial manufacture of articles made of polycarbonate (ES 6, contributing scenario 1: manufacture of articles; contributing scenario 2: waste treatment)
- Service life – professional indoor use of articles made of polycarbonate (ES 7, contributing scenario 1: wide dispersive professional indoor use of long-life articles with low release made polycarbonate; contributing scenario 2: waste treatment)
- Service life – professional outdoor use of articles made of polycarbonate (ES 8, contributing scenario 1: wide dispersive professional outdoor use of long-life articles with low release made polycarbonate; contributing scenario 2: waste treatment)
- Service life – consumer indoor use of articles made of polycarbonate (ES 9, contributing scenario 1: wide dispersive professional indoor use of long-life articles with low release made polycarbonate; contributing scenario 2: waste treatment)
- Service life – consumer outdoor use of articles made of polycarbonate (ES 10, contributing scenario 1: wide dispersive professional outdoor use of long-life articles with low release made polycarbonate; contributing scenario 2: waste treatment)
- Manufacture of epoxy resin (ES 11, contributing scenario 1: industrial intermediate use for manufacture of epoxy resin; contributing scenario 2: waste treatment)
- Manufacture of coating materials (ES 12, contributing scenario 1: industrial intermediate use for manufacture of coating materials; contributing scenario 2: waste treatment)
- Formulation of epoxy resin hardeners (ES 13, contributing scenario 1: formulation of epoxy resin hardeners; contributing scenario 2: waste treatment)

- Manufacture of epoxy resin hardeners (ES 14, contributing scenario 1: Manufacture of epoxy resin hardeners; contributing scenario 2: waste treatment)
- Use of epoxy resin hardeners (ES 15, contributing scenario 1: Industrial use of epoxy resin hardeners resulting in inclusion into or onto a matrix; contributing scenario 2: waste treatment)
- Use of epoxy resin hardeners (ES 16, contributing scenario 1: wide dispersive professional indoor use of epoxy resin hardeners resulting in inclusion into or onto a matrix; contributing scenario 2: waste treatment)
- Manufacture of other substances (ES 17, contributing scenario 1: industrial intermediate use for manufacture of other substances; contributing scenario 2: waste treatment)
- Use of Bisphenol A as laboratory reagent (ES 18, contributing scenario 1: industrial use of Bisphenol A as laboratory reagent; contributing scenario 2: waste treatment)

## 7.14. References

- Bakker J, te Biesenbeek JD, Boon PE, Bos P, van Broekhuizen FA, Geertsma R, Gaeraets L, de Jong W, Mennes W, Palmes NGM, Piersma A, Schuur G, Sijm D, van der Ven L, Verbist K, Wouters M, and Zeilmaker M (2014): Bisphenol A : Part 1. Facts and figures on human and environmental health issues and regulatory perspectives, date: 3.9.2014. RIVM National Institute for Public Health and the Environment.  
[http://www.rivm.nl/en/Documents\\_and\\_publications/Scientific/Reports/2014/september/Bisphenol\\_A\\_Part\\_1\\_Facts\\_and\\_figures\\_on\\_human\\_and\\_environmental\\_health\\_issues\\_and\\_regulatory\\_perspectives](http://www.rivm.nl/en/Documents_and_publications/Scientific/Reports/2014/september/Bisphenol_A_Part_1_Facts_and_figures_on_human_and_environmental_health_issues_and_regulatory_perspectives)
- Benstead, R, Routledge, E and Jobling, S (2008). Effects of Bisphenol-A on the fecundity of adult European gastropod snails during simulated Spring and Autumn conditions. Final report to Defra and the Environment Agency, October 2008. Environment Agency and Institute for the Environment, Brunel University, UK. Reported in ECHA (2008).
- Biedermann S, Tschudin P, Grob K (2010). Transfer of bisphenol A from thermal printer paper to the skin. *Analytical and Bioanalytical Chemistry*, 398: 571-576.
- Brennan SJ, Brougham CA, Roche, JJ, and Fogarty AM (2006) Multi-generational effects of four selected environmental oestrogens on *Daphnia magna*. *Chemosphere* 64 (1):49-55.
- Caspers, N. (1998) No estrogenic effects of Bisphenol-A in *Daphnia magna* Straus. *Bull. Environ. Contam. Toxicol.*, 61, 143-148.
- Caunter J, Williams T, Hetheridge M, Evans M (2000) Bisphenol A: Multigeneration study with the Fathead Minnow (*Pimephales promelas*). Unpublished Report. Testing laboratory: Brixham Environmental Laboratories. Report no.: BL6878/B.
- Committee for Risk Assessment (RAC) Committee for Socio-economic Analysis (SEAC) (2015) Opinion on an Annex XV dossier proposing restrictions on Bisphenol A. Available at: <http://echa.europa.eu/documents/10162/9ce0977b-3540-4de0-af6d-16ad6e78ff20>.
- Demierre A, Peter R, Oberli A, Bourqui-Pittet M (2012). Dermal penetration of bisphenol A in human skin contributes marginally to total exposure. *Toxicology Letters*, 213: 305 – 308.
- Duft M, Schulte-Oehlmann U, Weltje L, Tillmann M, and Oehlmann J (2003): Stimulated embryo production as a parameter of estrogenic exposure via sediments in the freshwater mudsnail *Potamopyrgus antipodarum*. *Aquatic Toxicology* 64 (4), 437-449. DOI: doi: DOI: 10.1016/S0166-445X(03)00102-4.
- EC (2008a). 4,4'-Isopropylidenediphenol (bisphenol-A). Updated European Union Risk Assessment Report, 3rd priority list, Volume 37.
- EC (2010) European Union Risk Assessment Report 4,4-ISOPROPYLENEDIPHENOL (Bisphenol-A) complete risk assessment in one document. Luxembourg: Office for Official Publications of the European Communities.
- ECETOC (2009) Addendum to ECETOC Targeted Risk Assessment Report No. 93, date: December. European Center for Ecotoxicology and Toxicology of Chemicals, Brussels, BE.  
<http://www.ecetoc.org/tra> (last accessed 2015-07-07).
- ECHA (2008) Annex XV Transitional Reports Bisphenol A. Available at: [https://echa.europa.eu/documents/10162/13630/trd\\_uk\\_bisphenol\\_a\\_en.pdf/d7a1ca84-3922-4f4f-b20d-d58241cd4216](https://echa.europa.eu/documents/10162/13630/trd_uk_bisphenol_a_en.pdf/d7a1ca84-3922-4f4f-b20d-d58241cd4216).
- ECHA (2016) Registration Dossier 4,4'-isopropylidenediphenol (<https://www.echa.europa.eu/web/guest/registration-dossier/-/registered-dossier/15752>) (last access date: 18.05.2017)
- EFSA (2010): Scientific Opinion on Bisphenol A: evaluation of a study investigating its neurodevelopmental toxicity, review of recent scientific literature on its toxicity and advice on the Danish risk assessment of Bisphenol A. *EFSA Journal* 8:1829.
- EFSA (2015): Scientific opinion on the risks to public health related to the presence of BPA (BPA) in foodstuffs. *EFSA Journal*, 13(1):3978.
- EFSA (2016) A statement on the developmental immunotoxicity of bisphenol A (BPA): answer to the question from the Dutch Ministry of Health, Welfare and Sport. *EFSA Journal*, 14(10):4580.
- FAO/WHO (2011) Joint FAO/WHO expert meeting to review toxicological and health aspects of bisphenol A: final report, including report of stakeholder meeting on bisphenol A. ISBN 978 92 14 156427 4.
- Fischer et al. (2014): Fischer, Benedikt, Milos Milunov, Yvonne Floredo, Peter Hofbauer and Anke Joas: Identification of relevant emission pathways to the environment and quantification of environmental exposure for Bisphenol A; Texte 41/2014, Umweltbundesamt ([https://www.umweltbundesamt.de/sites/default/files/medien/378/publikationen/texte\\_41\\_2014\\_identification\\_of\\_relevant\\_emission\\_pathways\\_of\\_bisphenol\\_a\\_0.pdf](https://www.umweltbundesamt.de/sites/default/files/medien/378/publikationen/texte_41_2014_identification_of_relevant_emission_pathways_of_bisphenol_a_0.pdf))
- Forbes, V.E., Selck, H., Palmqvist, A., Aufderheide, J., Warbritton, R., Pounds, N., Thompson, R., van der Hoeven, N., Caspers, N. (2007a) Does Bisphenol A induce super feminization in *Marisa*

- cornuarietis? Part I: Intra- and interlaboratory variability in test endpoints. *Ecotoxicol. Environ. Saf.*, 66, 309-318.
- Forbes, V.E., Aufderheide, J., Warbritton, R., van der Hoeven, N., Caspers, N. (2007b) Does Bisphenol A induce super feminization in *Marisa cornuarietis*? Part II: Toxicity test results and requirements for statistical power analysis. *Ecotoxicol. Environ. Saf.*, 66, 319-325.
- Geens T, Goeyens L, Covaci A. (2011) Are potential sources for human exposure to bisphenol-A overlooked? *Int. J. Hyg. Environ. Health* 214:339–347.
- Gehring M. (2004): Verhalten der endokrin wirksamen Substanz Bisphenol A bei der kommunalen Abwasserentsorgung., Technische Universität Dresden
- Geens T, Goeyens L, Kannan K, Neels H, Covaci A (2012a). Levels of bisphenol-A in thermal paper receipts from Belgium and estimation of human exposure. *Science of the Total Environment*. 435–436: 30–33.
- Heindel, J.J., Newbold, R.R. Bucher, J.R., Camacho, L., Delclos, K.B., Lewis, S.M., Vanlandingham, M., Churchwell, M.I., Twaddle, N.C., McLellen, M., Chidambaram, M., Bryant, M., Woodling, K., Gamboa da Costa, G., Ferguson, S.A., Flaws, J., Howard, P.C., Walker, N.J., Zoeller, R.T., Fostel, J., Favaroh, C., Schug, T.T. (2015): NIEHS/FDA CLARITY-BPA research program update. *Reproductive Toxicology* 58, 33 – 44.
- Jobling S, Casey D, Rodgers-Gray T, Oehlmann J, Schulte-Oehlmann U, Pawlowski S, Baunbeck T, Turner AP, and Tyler CR (2003) Comparative responses of molluscs and fish to environmental estrogens and an estrogenic effluent. *Aquatic Toxicol.* 65 (2):205-220.
- Jobling S, Casey D, Rodgers-Gray T, Oehlmann J, Schulte-Oehlmann U, Pawlowski S, Baunbeck T, Turner AP and Tyler CR (2003) Comparative responses of molluscs and fish to environmental estrogens and an estrogenic effluent. *Aquat. Toxicol.*, 65, 205-220.
- Jobling S, Casey D, Rodgers-Gray T, Oehlmann J, Schulte-Oehlmann U, Pawlowski S, Baunbeck T, Turner AP and Tyler CR (2004) Comparative responses of molluscs and fish to environmental estrogens and an estrogenic effluent. *Aquat. Toxicol.*, 66, 207-222. [Note: this is a corrected and reprinted version of Jobling et al. (2003)].
- Keiter S, Baumann L, Färber H, Holbech H, Skutlarek D, Engwall M, and Braunbeck T (2012) Long-term effects of a binary mixture of perfluorooctane sulfonate (PFOS) and Bisphenol A (BPA) in zebrafish (*Danio rerio*) *Aquatic Toxicol.* 118-119:116-129.
- Kinnberg K. and Toft G. (2003): Effects of estrogenic and antiandrogenic compounds on the testis structure of the adult guppy (*Poecilia reticulata*). *Ecotoxicol. Environ. Saf.* 54 (1), 16-24. <http://www.ncbi.nlm.nih.gov/pubmed/12547630>
- Ladewig V, Jungmann D, Köhler HR, Licht O, Ludwichowski KU, Schirling M, Triebkorn R, and Nagel R (2006) Effects of Bisphenol A on *Gammarus fossarum* and *Lumbriculus variegatus* in artificial indoor streams. *Toxicol. Environ. Chem.* 88 (4):649-664.
- Lahnsteiner F, Berger B, Kletzl M, and Weismann T (2005) Effect of Bisphenol A on maturation and quality of semen and eggs in the brown trout, *Salmo trutta f. fario*. *Aquat Toxicol* 75 (3):213-224.
- Lassen C, Mikkelsen S, Brandt U (2011). Migration of bisphenol A from cash register receipts and baby dummies. Danish Environmental Protection Agency. Survey of Chemical Substances in Consumer Products, No. 110 2011.
- Liao, C, Kannan, K (2011). Widespread Occurrence of Bisphenol A in Paper and Paper Products: Implications for Human Exposure. *Environ Sci Technol*, 45: 9372–9.
- Liu Y, Tam NF, Guan Y, Yasojima M, Zhou J, and Gao B (2011): Acute toxicity of nonylphenols and bisphenol A to the embryonic development of the abalone *Haliotis diversicolor supertexta*. *Ecotoxicology* 20 (6), 1233-1245. DOI: 10.1007/s10646-011-0672-7.
- Menard, S., Guzylack-Piriou, L., Lencina, C., Leveque, M., Naturel, M., Sekkal, S., Harkat, C., Gaultier, E., Olier, M., Garcia-Villar, R., Theodorou, V., and Houdeau, E. (2014a) Perinatal exposure to a low dose of bisphenol A impaired systemic cellular immune response and predisposes young rats to intestinal parasitic infection. *PLoS One* 9, e112752.
- Menard, S., Guzylack-Piriou, L., Leveque, M., Braniste, V., Lencina, C., Naturel, M., Moussa, L., Sekkal, S., Harkat, C., Gaultier, E., Theodorou, V., and Houdeau, E. (2014b) Food intolerance at adulthood after perinatal exposure to the endocrine disruptor bisphenol A. *Faseb j* 28, 4893–4900.
- Mercea P (2009). Physicochemical Processes Involved in Migration of Bisphenol A from Polycarbonate. *Journal of Applied Polymer Science*, 112: 579–593.
- Mielke, H., Partosch, F., Gundert-Remy, U. (2011) The contribution of dermal exposure to the internal exposure of bisphenol A in man. *Toxicology Letters*, 204, 190-198.
- Mu X, C. V. Rider, S. H. Gap, H. Hoy, and G. A. LeBlanc (2005) Covert signal disruption: Anti-ecdysteroidal activity of Bisphenol A involves cross talk between signaling pathways. *Environmental Toxicology and Chemistry* 24 (1):146-152.

- National Institute for Public Health and the Environment (2014) Bisphenol A: Part 1. Facts and Figures on human and environmental health issues and regulatory perspectives. RIVM Report 601351001. Available at: [http://www.rivm.nl/Documenten\\_en\\_publicaties/Wetenschappelijk/Rapporten/2014/september/Bisphenol\\_A\\_Part\\_1\\_Facts\\_and\\_figures\\_on\\_human\\_and\\_environmental\\_health\\_issues\\_and\\_regulatory\\_perspectives](http://www.rivm.nl/Documenten_en_publicaties/Wetenschappelijk/Rapporten/2014/september/Bisphenol_A_Part_1_Facts_and_figures_on_human_and_environmental_health_issues_and_regulatory_perspectives).
- National Institute for Public Health and the Environment (2015) Bisphenol A. Part 2. Recommendations for risk management. RIVM Report 2015-0192. Available at: [http://www.rivm.nl/en/Documents\\_and\\_publications/Common\\_and\\_Present/Newsmessages/2016/RIVM\\_recommends\\_more\\_stringent\\_EU\\_standards\\_BPA](http://www.rivm.nl/en/Documents_and_publications/Common_and_Present/Newsmessages/2016/RIVM_recommends_more_stringent_EU_standards_BPA).
- Oehlmann J, Schulte-Oehlmann U, Tillmann M and Markert B (2000) Effects of endocrine disruptors on prosobranch snails (Mollusca: Gastropoda) in the laboratory. Part I: Bisphenol-A and Octylphenol as xenoestrogens. *Ecotoxicology*, 9, 383-397.
- Oehlmann J, Schulte-Oehlmann U, Bachmann J, Oetken M, Lutz I, Kloas W and Ternes TA (2006) Bisphenol A induces super feminization in the ramshorn snail *Marisa cornuarietis* (Gastropoda: Prosobranchia) at environmentally relevant concentrations. *Environmental Health Perspectives*, 114, 127-133.
- Oehlmann J., Oetken M., and Schulte-Oehlmann U. (2008): A critical evaluation of the environmental risk assessment for plasticizers in the freshwater environment in Europe, with special emphasis on bisphenol A and endocrine disruption. *Environ Res* 108 (2), 140-149.
- Pickford D.B., Hetheridge M.J., Caunter J.E., Tilghman Hall A., and Hutchinson T.H. (2003): Assessing chronic toxicity of bisphenol A to larvae of the African clawed frog (*Xenopus laevis*) in a flow-through exposure system. *Chemosphere* 53 (3), 223-235. DOI: 10.1016/s0045-6535(03)00308-4.
- Ratte, H.T. (2009) Statistical Analysis of a Laboratory Study About the Effects of Bisphenol A on the Reproduction of the Ramshorn snail *Marisa cornuarietis* (Mesogastropoda: Ampullariidae) - Draft. Sponsor: German Federal Environmental Agency. FKZ: 363 01 245:1-38.
- Schulte-Oehlmann U., Tillmann M., Casey D., Duft M., Markert B., and Oehlmann J. (2001): Östrogenartige Wirkungen von Bisphenol A auf Vorderkiemenschnecken (Mollusca: Gastropoda: Prosobranchia). *Umweltwissenschaften und Schadstoff-Forschung* 13 (6), 319-333. DOI: 10.1065/uwsf2001.10.070
- SCENIHR (2015) Final opinion on the safety of the use of bisphenol A in medical devices, adopted 18 Feb. 2015. Available at: [http://ec.europa.eu/health/scientific\\_committees/emerging/docs/scenihr\\_o\\_040.pdf](http://ec.europa.eu/health/scientific_committees/emerging/docs/scenihr_o_040.pdf)
- SCOEL (2014) SCOEL/SUM/113, June 2014, Recommendation from the Scientific Committee on Occupational Exposure Limits for Bisphenol-A.
- Segner H, Caroll K, Fenske M, Janssen CR, Maack G, Pascoe D, Schäfers C, Vandenbergh GF, Watts M, and Wenzel A (2003) Identification of endocrine-disrupting effects in aquatic vertebrates and invertebrates: report from the European IDEA project. *Ecotoxicology and Environmental Safety* 54 (3):302-314.
- Staples C., Mihaich E., Ortego L., Caspers N., Klecka G., Woelz J., and Hentges S. (2015): Characterizing the effects of bisphenol A on sediment dwelling benthic organisms. *Environ Toxicol Chem*. DOI: 10.1002/etc.3217
- Tatarazako, N., Takao, K., Kishi, K., Onikura, N., Arizono, K. & Iguchi, T. (2002) Styrene dimmers and trimers affect reproduction of daphnid (*Ceriodaphnia dubia*). *Chemosphere*, 48, 597-601.
- Testing Laboratory (1988) Bisphenol-A: 13 week aerosol toxicity study with Fischer 344 rats.
- Testing Laboratory, (2015) The in vitro Percutaneous Absorption and Metabolism of Radiolabelled Bisphenol A (BPA) Through Fresh human Skin..
- Thayer KA, Doerge DR, Hunt D, Schurman S, Twaddle NC, Churchwell MI, Garantziotis S, Kissling GE, Easterling MR, Bucher JR and Birnbaum LS (2014a) Pharmacokinetics of Bisphenol A in Humans Following Dermal Administration. Preliminary results. Submitted information via public consultation on the restriction proposal to ECHA(Comment reference number 1043 in public comments to BPA restriction proposal available at: <http://echa.europa.eu/restrictions-under-consideration/-/substance-rev/1894/term>
- Tyl, R.W., Myers, C.B., Marr, M.C., Sloan, C.S., Castillo, N.P., Veselica, M.M., Seely, J.C., Dimond, S.S., Van Miller, J.P., Shiotsuka, R.N., Beyer, D., Hentges, S.G. and Waechter, J.M. (2008). Two-generation reproductive toxicity study of dietary bisphenol a in CD-1 (Swiss) mice. *Toxicological Sciences* 104(2): 362-384.
- Watts M, Pascoe D, and Carroll K (2001) Chronic exposure to 17 $\beta$ -ethinylestradiol and Bisphenol A-effects on development and reproduction in the freshwater invertebrate *Chironomus riparius* (Diptera: Chironomidae). *Aquatic Toxicol*. 55 (1-2):113-124.

Yang, X., Doerge, D.R., Fisher J.W. (2013) Prediction and evaluation of route dependent dosimetry of BPA in rats at different life stages using a physiologically based pharmacokinetic model. *Toxicology and Applied Pharmacology* 270(1): 45-59.

## 7.15. Abbreviations

abs.	Absolute
BADGE	Bisphenol A diglycidyl ether (1675-54-3)
BPA	Bisphenol A
bw	body weight
C&L	Classification and Labelling
CMR	Carcinogenic, Mutagenic, Toxic for reproduction
conc.	Concentration
CSR	Chemical Safety Report
d	day(s)
DGEBA	Bisphenol A diglycidyl ether (1675-54-3)
DNEL	Derived No Effect Level
EC <sub>50</sub>	Half maximal effect concentration
ECETOC	European Center for Ecotoxicology and Toxicology of Chemicals
ES	Exposure Scenario
EFSA	European Food Safety Authority
EPA	Environmental Protection Agency
F	Female
GD	Gestational Days
GL	Guideline
GLP	Good laboratory praxis
h	hour(s)
IC <sub>50</sub>	Half maximal inhibitory concentration
IPCS	International Programme on Chemical Safety
LO(A)EL	lowest-observed (adverse) effect level
M	Male
NO(A)EL	no-observed (adverse) effect level
OECD	Organisation for Economic Co-operation and Development
PC	Polycarbonate
PNEC	Predicted no effect concentration
PROC	Process Category
RCR	Risk characterization ratio
rel.	Relative
SCENIHR	Scientific Committee on Emerging and Newly Identified Health Risks
SVHC	Substances of very high concern
TG	Test Guideline
TL	Test Laboratory
w	Week
WHO	World Health Organization