JRC Scientific and Technical Reports

# European Union
# Risk Assessment Report

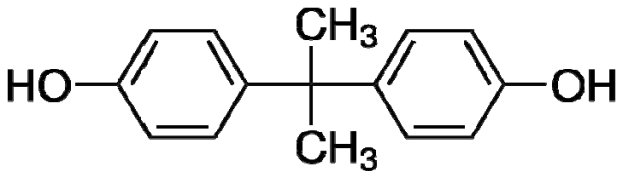
**CAS: 80-05-7** **EINECS No: 201-245-8**

**Environment Addendum of April 2008**

**(to be read in conjunction with published EU RAR of BPA, 2003)**

**4,4'-ISOPROPYLIDENEDIPHENOL**
**(Bisphenol-A)**

**Part 1 Environment**

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The mission of the JRC-IHCP is to protect the interests and health of the consumer in the framework of EU legislation on chemicals, food, and consumer products by providing scientific and technical support including risk-benefit assessment and analysis of traceability.

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# Updated European Risk Assessment Report

# 4,4'-ISOPROPYLIDENEDIPHENOL (BISPHENOL-A)

## CAS Number: 80-05-7

## EINECS Number: 201-245-8

**Environment Addendum of February 2008**

**(to be read in conjunction with published EU RAR of BPA, 2003 for full details)**

Rapporteur for the risk assessment is the United Kingdom.


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The scientific work on the environmental sections was carried out by the Building Research Establishment Ltd (BRE) (with input on the aquatic effects assessment by Watts & Crane Associates), under contract to the rapporteur.


**Date of Last Literature Search :** **2007**
**Review of report by MS Technical Experts finalised:** **2007**
**Final report:** **2008**

# Introduction

A risk assessment of bisphenol-A produced in accordance with Council Regulation (EEC) 793/93 has already been published (EC, 2003). The conclusion was that further information was needed about toxic effects in fish and aquatic snails (and potentially terrestrial organisms), and environmental risks were also identified for certain PVC applications and thermal paper recycling (for the aquatic, sediment and terrestrial compartments). The test requirements were published in two Commission Regulations (EC No. 642/2005[1] and 506/2007[2]) with a delivery deadline of November 2006 and November 2007 respectively.

The UK rapporteur began work on a risk reduction strategy for the environment shortly afterwards, and an interim report was prepared (Defra, 2003). Industry was able to provide more detailed information on use pattern and releases for a number of the applications being considered, including measured emissions data. Based on this evidence, the rapporteur considered that the emissions had been over-estimated in the published report, and revised PECs were agreed at EU Technical Meetings in 2003 and 2005. In addition, bisphenol-A may be formed via the degradation of tetrabromobisphenol-A (CAS no. 79-94-7), which is another ESR priority substance. The relevant information has been summarised in the risk assessment report for that substance (ECB, 2007).

The test programme has now concluded, so this report brings together the revised exposure information and an updated review of ecotoxicity data, as an addendum to the original risk assessment report. The opportunity has been taken to include additional industry information and published data that have become available since the original risk assessment was completed[3]. The opinions of the European Commission's former Scientific Committee for Toxicity, Ecotoxicity and the Environment (CSTEE) on the original report have also been considered (CSTEE, 2002). The assessment uses the latest version of the Technical Guidance Document, which was revised after the original report's publication, so marine scenarios and a PBT assessment are included for the first time.

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1 Official Journal L 107, 28/04/2005 p. 0014 – 0016.

2 Official Journal L 119, 09/05/2007 p. 0024 – 0026.

3 EC (2003) was based on a review of all data published up to 2001. For this report, studies were identified independently by Industry (who provided the rapporteur with an updated reference list) and the rapporteur up to March 2007. The abstracts and, where necessary, main text of these papers were reviewed to establish their relevance. Non-relevant papers are listed in Appendix 1, with a reason for their non-inclusion. Relevant papers have been reviewed in detail and are reported in the main text.

The format of the report is broadly in line with that of the published assessment. A brief summary of the original information is given (*the published report should be consulted for full details*), followed by all significant new data and a comment to indicate how these differ from the original report. An exception is the section on aquatic effects, which has been entirely revised (although the original data have not been re-evaluated) and reformatted (the data had previously been divided into 'toxicity test results' and 'endocrine disrupting effects').

To protect commercial confidentiality, site codes are presented in a separate confidential annex. This can be made available to regulatory authorities on request.

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# TABLES

# 0 OVERALL RESULTS OF THE RISK ASSESSMENT

CAS No: 80-05-7
EINECS No: 201-245-8
IUPAC name: 2,2-bis(4-hydroxyphenyl)propane (also known as 4,4'-isopropylidenediphenol or bisphenol-A)

**Environment**

**Conclusion (i)** There is a need for further information and/or testing.

This conclusion applies to the freshwater and marine aquatic compartments (including sediment, since the equilibrium partitioning approach has been used). Although no risks are indicated using the freshwater and marine PNEC for any scenario, there are still some uncertainties over the potential effects of bisphenol-A on snails, despite the thorough testing undertaken as part of the conclusion (i) programme. Further work being conducted by the UK Government should be taken into account when results are available in 2008.

**Conclusion (ii)** There is at present no need for further information and/or testing and no need for risk reduction measures beyond those which are being applied already.

This conclusion applies to the terrestrial and atmospheric compartments, and to secondary poisoning through the aquatic, terrestrial and marine food chains. It also applies to the risks to wastewater treatment plant micro-organisms. For these end points the conclusion applies to all life cycle steps.[4]

[4] Note that the original risk assessment also drew the same conclusion for the water and sediment compartments for five uses that had negligible emissions (i.e. because the processes are either completely dry or any aqueous effluent produced is disposed of through incineration). These have not been reconsidered in this update, and the conclusion remains valid for these applications.

# 1 GENERAL SUBSTANCE INFORMATION

## 1.1 IDENTIFICATION OF THE SUBSTANCE

No new information is available. 4,4'-Isopropylidenediphenol (CAS no. 80-05-7) is more commonly known as bisphenol-A, and the common name will be used throughout this report.

## 1.2 PURITY/IMPURITIES, ADDITIVES

### 1.2.1 Purity

The purity of bisphenol-A is 99 – 99.8% depending upon the manufacturer (EC, 2003). Impurities typically include phenol (<0.06%), *ortho*- and *para*- isomers of bisphenol-A (<0.2%) and water (<0.2%).

Terasaki *et al.* (2004) reported the results of an analysis of commercial bisphenol-A. This had a purity of 95.3 – 96.8% from the analysis. Fifteen other components were identified, the most abundant of which was the 4,2'-isomer, at 2.95% in one sample. All of the identified components contained phenol groups. [The level of impurity is much higher than is indicated in the risk assessment. The isomer above is indicated as a possible impurity, but at <0.2%.]

## 1.3 PHYSICO-CHEMICAL PROPERTIES

The key physico-chemical property values are presented in Table 1.1 (EC, 2003). No values have been revised as a result of the updated literature search for this addendum. Shareef *et al.* (2006a) reported the determination of the solubility of bisphenol-A in water at a range of pHs and a range of ionic strengths. The solubility of bisphenol-A in pure water was measured as 300±5 mg/l at 25.0±0.5 °C, with no significant variation over the pH range of 4 to 10, and no change with ionic strength (up to 0.1 moles/litre $KNO_3$). This further supports the value used in the published assessment.

Table 1.1 Key physico-chemical properties for bisphenol-A

| Parameter | Value |
|---|---|
| Physical state at normal temperature and pressure | White solid flakes or powder |
| Vapour pressure | 5.3 x$10^{-9}$ kPa at 25°C used in environmental models |
| Solubility in water | 300 mg/l used in environmental models |
| n-Octanol-water partition coefficient (log $K_{ow}$) | 3.4 used in environmental models |
| Flash point | ~ 207°C |
| Autoflammability | ~ 532°C |
| Explosive limits (in air) | Minimum explosive concentration 0.012 g/l with oxygen > 5% |
| Oxidising properties | Not an oxidising agent |

# 2 GENERAL INFORMATION ON EXPOSURE

Table 2.1 summarises the amount of bisphenol-A used within different applications according to the published risk assessment (EC, 2003). This was based upon submissions made by the bisphenol-A manufacturers and end users to CEFIC.

Table 2.1 Bisphenol-A use pattern data

| Use pattern data | Tonnes/year | Percentage of EU consumption |
|---|---|---|
| Polycarbonate production | 486,880 | 71.1 |
| Epoxy resin production | 171,095 | 25.0 |
| Phenoplast cast resin processing | 8,800 | 1.3 |
| Unsaturated polyester resin production | 3,000 | 0.4 |
| Can coating manufacture | 2,460 | 0.4 |
| Use PVC production and processing | 2,250 | 0.3 |
| Alkyloxylated bisphenol-A manufacture | 2,020 | 0.3 |
| Thermal paper manufacture | 1,400 | 0.2 |
| Polyols/Polyurethane manufacture | 950 | 0.1 |
| Modified polyamide production | 150 | <0.1 |
| Tyre manufacture | 110 | <0.1 |
| Brake fluid | 45 | <0.1 |
| Minor uses | 5,990 | 0.9 |
| EU Consumption | 685,000 | |

Figures in the table are approximate and based upon industry submissions for the years 1996-1999.
Minor uses include sales to chemical merchants and minor sales. The uses of these minor sales are not expected to be different from those mentioned above

## 2.1 NEW INFORMATION

### 2.1.1 Tetrabromobisphenol-A

The published risk assessment included consideration of the use of bisphenol-A in the production of tetrabromobisphenol-A (TBBPA). Production of TBBPA no longer takes place in the EU and so this use of bisphenol-A is not included in this addendum. The possible formation of bisphenol-A from the breakdown of TBBPA under certain circumstances is discussed in detail in the risk assessment of that substance (ECB, 2007). The main routes by which this could lead to bisphenol-A in the environment are through degradation in anaerobic sediments and through the application of anaerobically digested sludge to soil. Information on these processes has been used in Sections 3.1.4.6.2 and 3.1.4.7 to estimate possible concentrations of bisphenol-A in sediments and soil.

### 2.1.2 PVC

Further more specific information has been provided on the use of bisphenol-A in PVC-related areas; this is presented in Sections 3.1.2.1, 3.1.2.3 and 3.1.2.4.

### 2.1.3 Thermal paper

Industry has collected additional information on thermal paper recycling and performed monitoring studies at relevant sites. This information is included in Section 3.1.2.5.

### 2.1.4 Revised EU consumption figures

Industry has provided new production and consumption figures for bisphenol-A for 2005/2006. These are included in Table 2.2. These new values have been taken into account in the estimation of emissions in Section 3.1.2.

Table 2.2 Revised production and use tonnages for Western Europe (2005/2006)

| Application | Tonnes/year | % change from published report | Information source |
|---|---|---|---|
| BPA production | 1,150,000 | +64 | PlasticsEurope (1) |
| BPA uses | | | |
| Polycarbonate | 865,000 | +78 | PlasticsEurope (1) |
| Epoxy resins | 191,520 | +12 | PlasticsEurope (2) |
| – can coatings | 2,755 | +12 | PlasticsEurope (2) |
| – ethoxylated BPA | 2,260 | +12 | PlasticsEurope (2) |
| Phenoplast cast resin processing | 8,800 | | |
| Unsaturated polyesters | 3,600 | | Cefic (1) |
| Thermal paper | 1,890 | +35 | ETPA |
| PVC – polymerisation | 0 | | ECVM |
| - stabiliser packages | 450 | -10 | ECVM, Cefic (2), (3), EuPC |
| - phthalate plasticisers | 900 | -10 | ECVM, Cefic (2), (3), EuPC |
| - direct stabilisation | 450 | -10 | ECVM, Cefic (2), (3), EuPC |
| Others | 7,245 | | |
| Net exports | 65,000 | | PlasticsEurope (1) |
| Total consumption | 1,149,870 | +68 | |

Figures for BPA production and polycarbonate use are estimated volumes
Figures for other use categories are calculated from estimated percentage increase/decrease since 2003 figures as provided by relevant industry group.
Information sources:

| | |
|---|---|
| PlasticsEurope (1) | Polycarbonate / Bisphenol A Group |
| PlasticsEurope (2) | Epoxy Resins Committee |
| Cefic (1) | Unsaturated Polyester Resin Committee |
| Cefic (2) | ESPA European Stabiliser Producers Association |
| Cefic (3) | European Council for Plasticisers and Intermediates |
| ETPA | European Thermal Paper Association |
| ECVM | European Council of Vinyl Manufacturers |
| EuPC | European Plastics Converters |

### 2.1.5 Other information

Sidhu *et al.* (2005) measured a wide range of substances in diesel particle extracts and in a sample collected from an uncontrolled domestic waste burn in a steel drum. Bisphenol-A was not reported as detected in the diesel particulate extracts, but was found in the sample from waste burning. The estimated emission rate was 9.66 mg bisphenol-A per kg waste burned. The authors used estimates of waste burned in this way in the United States to estimate an emission of 79 tonnes per year from this source in the US. This is of the same order as the industry emissions reported to the Toxic Release Inventory. There is no equivalent information to allow a similar calculation to be made for the EU, but releases as reported by industry make up only a small fraction of the total estimated emissions and so this source seems unlikely to have a significant impact (if any) on the estimated concentrations. This possible source is not considered further in this assessment.

# 3 ENVIRONMENT

## 3.1 ENVIRONMENTAL EXPOSURE

### 3.1.1 Environmental releases – published information

The emission estimates included in the published risk assessment report were based as far as possible on information specific to the production and use of bisphenol-A. Where this was not possible, default emission factors were used, in combination with information on the likely amounts to be used. The regional and continental emissions estimated in the published risk assessment report are summarised in Table 3.1.

Table 3.1 Summary of regional and continental releases from published risk assessment

| Process | Air (kg/year) | | Emission to wastewater treatment plants (kg/year) | | Emission to receiving waters (kg/year) | |
|---|---|---|---|---|---|---|
| | Regional | Continental | Regional | Continental | Regional | Continental |
| Bisphenol-A production [a)] | 575 | 410 | | | 277 | 215 |
| Polycarbonate bottle washing [b)] | | | 0.10 | 1.0 | 0.05 | 0.4 |
| Epoxy resin production [a)] | | | | | 216 | 187 |
| Phenoplast cast resin processing [b)] | | | 4.2 | 38 | 1.8 | 16 |
| Thermal paper production [a)] | | | | | 36 | 70 |
| Thermal paper recycling [c)] | | | 35,000 | 315,000 | | |
| PVC – Inhibitor during production process [b)] | | | 5,810 | 52,290 | 2,490 | 22,410 |
| PVC – Anti-oxidant during processing [b)] | | | 75 | 674 | 32 | 289 |
| PVC – Preparation of additive packages [b)] | | | 74 | 668 | 32 | 286 |
| PVC –Use of additive package [b)] | | | 75 | 674 | 32 | 289 |
| PVC – Anti-oxidant in plasticiser production | | | 81 | 31 | | |
| PVC – Plasticiser use [b)] | | | 10 | 88 | 4 | 38 |
| Losses from PVC articles in use [a)] | 1,560 | 14,040 | | | 2,250 | 20,450 |
| Total | 2,135 | 14,450 | 41,129 | 369,464 | 5,371 | 44,250 |
| Total in kg/day (averaged over 365 days) | 5.8 | 39.6 | 112.7 | 1,012.2 | 14.7 | 121.2 |

a) Releases to receiving waters calculated in the text (taking into account any WWTP)
b) Releases to wastewater calculated in the text; these are split 70:30 between WWTP and receiving waters in the table
c) ESD indicates all emissions go to WWTP

In addition to the releases in the table, there are also releases to soil of 2,250 kg/year in the regional environment, and 20,450 kg/year in the continental environment.

### 3.1.2 Revised emission estimates

The information presented in this section in some cases goes beyond the estimation of emissions and considers exposure situations. The revised PEC values are however presented later in Section 3.1.4.

#### 3.1.2.1 Production of bisphenol-A

Updated information on emissions from production sites has been provided by industry for 2006 (personal communication from PlasticsEurope, 2007). This information is included in Table 3.2.

Table 3.2 Summary of environmental releases from bisphenol-A production sites

| Site | Air | | Effluent (After wastewater treatment) | | Receiving water type and flow rate |
|---|---|---|---|---|---|
| | Measured levels | Release | Measured levels | Release | |
| BPA1 | <0.2 mg/Nm$^3$ (outlet)<br><0.5 µg/Nm$^3$<br>(50 m from site) | <0.012 kg/day<br><4.4 kg/year | 5.6 µg/l | 0.06 kg/day<br>21 kg/year | Estuary<br>8.64 x 10$^6$ m$^3$/day |
| BPA2 | 2.9 mg/Nm$^3$<br>(outlet discontinuous)<br>0.1 µg/Nm$^3$ (outlet) | 0.00017 kg/day<br>0.0605 kg/year | 3.13 µg/l | 0.07 kg/day<br>27 kg/year | River<br>2.068 x 10$^8$<br>m$^3$/day |
| BPA3 | <1 mg/Nm$^3$ (dust) | <1 kg/day (dust)<br><365 kg/year (dust) | ~0.005 mg/l | 0.31 kg/day<br>113 kg/year | Estuary<br>8.08 x 10$^7$ m$^3$/day |
| BPA4 | | 0.03 kg/day<br>9 kg/year | | 0.096 kg/day<br>35 kg/year | Estuary<br>2.49 x 10$^7$ m$^3$/day |
| BPA5 | | 1.58 kg/day (dust)<br>575 kg/year (dust) | Up to 45 µg/l<br>(average 3.5 µg/l) | 0.019 kg/day<br>*6.8* kg/year | Estuary<br>6.1 x 10$^8$ m$^3$/day |
| BPA 6 | 10 mg/Nm$^3$ (dust) | 0.08 kg/day (dust)<br>31.2 kg/year (dust) | Average 10 µg/l | 0.072 kg/day<br>25.8 kg/year | Sea (dilution factor 100) |

Values changed from the published risk assessment are underlined. The unit of Nm$^3$ refers to air at standard temperature and pressure ( the measurements may have been made originally with hotter air and so are corrected ).

#### 3.1.2.2 Use as an inhibitor in PVC production

The published risk assessment includes the use of bisphenol-A as an inhibitor in PVC production (i.e. the polymerisation of vinyl chloride). This use ceased voluntarily in the EU in 2003 (Defra, 2003), so there are no longer any emissions from this application and it is not considered further.

### 3.1.2.3 PVC additive formulation

#### 3.1.2.3.1 New information

The PVC additive industry (represented by the European Stabiliser Producers Association, ESPA) has carried out two sampling exercises at sites producing PVC additive packages containing bisphenol-A. In addition, information on other sites has been collected relating to cleaning operations, water handling and treatment, water flows, tonnage used, etc.

A total of 13 sites are involved in the production of these packages in the EU. Measurements have been conducted at seven of these, accounting for 82% of the tonnage used in this area. (The tonnage in this area is now estimated at ~1,400 tonnes, which is an increase from the value used in the original risk assessment.) For the remaining sites, some information on the site is available for all but one, and the tonnage used in 2000 is available for all sites.

#### 3.1.2.3.2 Calculation of emission factors

The sampling exercises were timed to coincide with periods of activity at the sites, in particular in relation to cleaning activities where these were relevant. As a result they can be considered to be representative of conditions when the sites are operating normally. The results of the measurements have been used to estimate the amounts of bisphenol-A released, and hence to derive emission factors. The arrangements on the sites have led to three factors being derived:

- emissions from all sources to an off-site treatment plant;
- emissions from all sources after on-site treatment (so release to surface water); and
- release in rainwater run-off.

The factors and the types of release from which they were derived are in Table 3.3.

Table 3.3 Emission factors derived from the data

| Site | Emission factor for water type (kg/tonne) | | | | Notes on combined emissions | External MWWTP |
|---|---|---|---|---|---|---|
| | wash | Rain | process | combined | | |
| 1 | | | | $\underline{5.93 \times 10^{-3}}$ | Flow + process + some rain, after internal treatment | n |
| 2 | | | | | No data | y |
| 3 | | | | $7.2 \times 10^{-3}$ | Flow + process after internal treatment | y |
| 4 | | $4.4 \times 10^{-5}$ | | 0.037 | Process + wash after internal treatment | y |
| 5 | | | | $4.6 \times 10^{-3}$ | Cooling + rain + surface after internal treatment | n |
| 6 | | | | | No data | |
| 7 | | | | | No data | y |
| 8 | | | | $\underline{0.19}$ | Process + wash + rain after internal treatment | y |
| 9 | | | | | No data | n |

Table 3.3 continued overleaf

Table 3.3 continued Emission factors derived from the data

| Site | Emission factor for water type (kg/tonne) | | | | Notes on combined emissions | External MWWTP |
|---|---|---|---|---|---|---|
| | wash | Rain | process | combined | | |
| 10 | | | | $2.8x10^{-5}$ | Process + rain + sewer after internal treatment | n |
| 11 | | $\underline{7x10^{-5}}$ | | | | n |
| 12 | | | | | No data | |
| 13 | | | | | No data | y |

Underlined values are the selected emission factors for further calculations.

MWWTP – municipal wastewater treatment plant

### 3.1.2.4 Anti-oxidant in plasticizer production

Site-specific data for one site were included in the published risk assessment. These were used to estimate the total emissions from this use in the EU. The calculation of the PEC then used the default size for the wastewater treatment plant and the default dilution, resulting in a $C_{local}$ of 1.9 µg/l. It has been pointed out by Industry that a site-specific PEC could be estimated as the size of wastewater treatment plant and river flow for the site were also provided (and in fact included in the original assessment). This calculation has therefore been revised. For the site providing information the actual flows and dilution have been used to estimate the PEC. This site is located on an estuary, and so the concentration relates to marine waters. Further information on the nature of the site, the way in which bisphenol-A is handled and where emissions can arise has also been provided for this site. This indicates that the emission factor used to estimate releases from this site - $1x10^{-4}$ kg/kg - should be applicable to other sites.

Information on the other four sites that use bisphenol-A in this way has also been provided, in the form of the annual quantities used. This has been used to create a generic site to represent the remaining tonnage. The emission factor above has been used to estimate releases from this site, and the TGD default treatment plant and river flows used to estimate the PEC for this generic site. This is used for the freshwater assessment. None of these four sites discharges to marine waters.

### 3.1.2.5 Thermal paper recycling

The published assessment included a number of assumptions related to recycling, based largely on information provided by the European Thermal Paper Association (ETPA). In reaction to risk management activity, ETPA commissioned a number of additional studies to test these assumptions. In particular, measurements were carried out at three sites that use recovered thermal paper. These include two sites receiving waste from the thermal paper production process (known as 'broke'), and a site receiving a general mixed recovered waste paper stream. These sites include examples with and without a de-inking step in the treatment of the recovered paper.

At the same time, better information has been provided on the specific applications for which thermal paper is now used, and also on the likelihood that paper used in these areas will be found in recovered paper streams.

This new information has been used to revise the calculations of PECs for this life cycle step, and hence the risk characterisation.

#### 3.1.2.5.1 Use pattern

The uses of thermal paper have been changing in recent years. Use for industrial fax paper was once a major application, but this is declining. The European Thermal Paper Association (ETPA) has provided more detailed information on the current use pattern of thermal paper (ETPA, personal communication). The major use area is now for point-of-sale (POS) receipts (e.g. supermarket till receipts), followed by self-adhesive labels. Two smaller uses are in lottery tickets and fax paper. The degree to which each of these types of paper is recycled has also been estimated by ETPA (in consultation with the Institute for Paper Science and Technology, Technical University of Darmstadt) and the results are presented in Table 3.4.

Table 3.4 Use and recycling pattern for thermal paper (ETPA, personal communication)

| Use area | Use percentage | Fraction recycled | Percentage of total recycled |
|---|---|---|---|
| Point-of-sale receipts | 50 | 0.3 | 15 |
| Self-adhesive labels | 30 | 0.1 | 3 |
| Lottery | 10 | 0.2 | 2 |
| Fax | 10 | 1 | 10 |

The overall estimate is that around 30% of used thermal paper will enter recycling streams.

The different types of paper are also likely to find their way into different waste paper streams. Based on discussions with ETPA and the Institute for Paper Science and Technology, used fax papers and lottery papers are considered likely to be used in making graphic papers, for which a de-inking step is necessary. In contrast, labels and POS receipts are more likely to enter the mixed waste paper stream, which is used for production of packaging, etc., and where a de-inking step will not be used. Hence both of these types of recycling process need to be considered in the assessment of bisphenol-A.

#### 3.1.2.5.2 Amounts of bisphenol-A used in thermal paper

The amount of bisphenol-A used in thermal paper in the EU is 1,890 tonnes (figure for 2005/6). This is used to make $2.4 \times 10^9$ $m^2$ of thermal paper, an area which is estimated to be equivalent to ~168,000 tonnes of paper. Up to 10% of the paper from the production process is waste (due to trimmings, etc.). This waste material is called ‘broke’. It is sent directly to a small number of recycling plants and so never enters actual commercial use. In other words, 190 tonnes of bisphenol-A will be sent for recycling by the thermal paper production sites each year.

The amount of bisphenol-A actually used in thermal paper in the EU is therefore 1,700 tonnes. Around 30% of this paper is estimated to enter recycling streams (see Section 3.1.2.5.1), which is equivalent to 510 tonnes of bisphenol-A. So, in total, around 700 tonnes of bisphenol-A will find its way to paper recycling sites each year.

#### 3.1.2.5.3 Size of paper recycling sites

As already noted in the original risk assessment, a survey indicated that there were 69 paper recycling sites in Germany in 2000. The original risk assessment divided the amount of thermal paper recycled in the EU over ten sites, which would over-estimate the amount recycled on one site. It is now known that there are around 1,000 paper production sites in the EU, of which around half use recovered paper as a source material (RPA, 2003). The total amount of paper recovered in the EU (all types) is around 42 million tonnes/year (CEPI, 2001). On this basis, an average site would use around 84,000 tonnes of recovered paper[5]. This figure will be used in the generic calculations. The use of an average size of site in this instance is appropriate, as the input of bisphenol-A to a site will in general be proportional to the size of the site (in these calculations it will be based on a representative concentration in the recovered paper used). In addition, the water use at a paper recycling site is (in general) related to the amount of paper used or produced, and so it is appropriate to use an average level of water use (and hence waste water treatment plant or WWTP) with an average size of site. ETPA considered that a WWTP size of 4,000 $m^3$/day was appropriate for this industry. From a study of the UK paper industry (Environment Agency, 2002), typical water consumption rates are in the range 8-16 $m^3$/tonne of paper produced. The average value, 12 $m^3$/tonne, has been used in these calculations; this corresponds to a WWTP with a capacity of 2,880 $m^3$/day for the average site.

There is one area where the available information does not allow a straightforward selection of a representative value to fit the site. This concerns sludge production from the processing of the recovered paper (this does not relate to sludge production in the WWTP). This can vary significantly between plants, and appears to depend much more on the type of paper produced than on the amount of water used. Examples from paper mills in the UK have sludge production rates ranging from 21 kg/tonne to 6.1 tonnes/tonne of paper, although a number are in the range 200-400 kg/tonne (Environment Agency, 2002).

Bisphenol-A measurements have been made at a specific site that takes general waste paper (see Section 3.1.2.5.4). This site has an average sludge production rate of 22.9 kg/tonne paper produced. This is a low figure, related to the lack of a de-inking step in the process, and is consistent with other estimates of losses of 2% of the waste paper used at this stage. This value will be used for the calculations without de-inking. The same value and a value of 200 kg/tonne will be used for calculations with de-inking.

#### 3.1.2.5.4 Information from specific sites

Monitoring studies have been performed at three specific sites (TNO, 2003 & 2004). The information provided consists of:

- flow charts describing the operations carried out,
- quantities handled,
- water flows within the plant, and
- measurements on the levels of bisphenol-A in water within the plant and in the effluent from the final biological treatment.

[5] For comparison, the largest paper recycling site in the UK uses ~400,000 tonnes and the larger of the two thermal paper broke recycling site that provided data uses ~115,000 tonnes.

Details are not included in this report, but the main points relevant for the assessment are presented. An important point common to all of the investigations is that they were carried out at times when the plants were operating under normal conditions.

Sites with de-inking

Two sites were selected as they each receive a high input of bisphenol-A in the form of thermal paper broke from different thermal paper manufacturers. One site is in Germany, the other in Austria. The handling of the thermal paper broke takes place on a batch basis, and the measurements were conducted during the handling of batches of this waste. They can therefore be considered to represent a worst case for each site. The study is reported in TNO (2003).

*De-inking rate*

De-inking takes place as part of the process to reduce the recovered paper down to fibres. Measurements were carried out on the concentration of bisphenol-A in the waste paper fed to the process and on the fibre produced. These showed a removal efficiency for the process of 95%. (The default value used in the original assessment was 100%.)

*Primary treatment*

The water from the de-inking process is treated before it is passed to the biological treatment plant. Here the concentrations of bisphenol-A in the water from the de-inking process were compared to the concentration following the primary treatment. This showed a removal of 95.9% from water. (The default value used in the original assessment was 50%.) The bisphenol-A removed is included in the sludge produced from this process (no specific measurements were made on this sludge at these sites).

*Biological treatment*

The removal rate in the WWTP was estimated by measuring the concentration of bisphenol-A in the influent and in the effluent. The measurements were carried out over a period of time so that any variation in the levels would be observed. The timing of the sampling was arranged so that it covered the expected residence time in the treatment plant where batch paper processes were used. Sampling at regular intervals was employed where the production was continuous. Some variation in the results was seen; as a result the removal rates were calculated from the lowest influent concentrations and the highest effluent[6] concentrations for each site (corrected for recovery). The results indicate a removal level of 99.99% in the WWTP for the two sites.

The results of measurements on mixed samples of effluent (taken over four-hour periods) at both sites showed similar average concentrations of around 20 ng/l. Higher levels were found in a small number of individual spot samples, with maximum concentrations of 170 and 159 ng/l. These higher levels were thought to be due to a release of bisphenol-A when pulping of a batch was completed. These reported levels were not corrected for recovery; this was >95% for the influent samples, but only 33-35% for the effluent samples. Correcting the values for the lower recovery, the maximum effluent concentrations are in fact 500 ng/l and 467 mg/l.

[6] Earlier data reported for these sites in May 2003 were based on a lack of detection in the effluent at a limit of 2 µg/l; further measurements were made with an improved detection limit of 10 ng/l which allowed the actual concentrations in the effluent to be determined.

The process sludges from both sites are incinerated. This is described as standard practice for the countries where the sites are located.

Sites with no de-inking

A site in Germany that uses a representative mixed waste paper stream was chosen for further measurements. It was identified as a representative site by the Institute for Paper Science and Technology, Technical University of Darmstadt. The site produces corrugated packaging materials and does not operate a de-inking process. It operates continuously, and the mixed waste paper stream is checked for consistency. The site also has suitable access to monitoring points, and various internal parameters are routinely monitored. The study is reported in TNO (2004).

*Input*

The average concentration of bisphenol-A in the waste paper input to the plant was 14.7 mg/kg over the period of the study. This is the equivalent of a level of thermal paper in the waste of 0.1%, and gives a daily input of 15 kg of bisphenol-A. The concentration of bisphenol-A in the waste paper fits the expected level based on the estimate of the amount recycled in Section 3.1.2.5.2 (432 tonnes bisphenol-A in 42,000,000 tonnes of paper is ~10 mg/kg.)

*Pulping*

This is the equivalent step to de-inking above, where the recovered paper is reduced to fibres. The concentration of bisphenol-A was measured in the input materials (as indicated above) and in the final paper; the difference indicates that only 10% of the bisphenol-A in the waste paper feed was removed at this stage. This shows that without a de-inking step most of the bisphenol-A is retained in the recovered paper products.

*Primary treatment*

A comparison of the concentrations in water before and after the flotation treatment used as a primary treatment indicates a removal rate from water of 50%. Measurements were also carried out on the sludge produced by this treatment. The concentrations measured in sludge, together with the quantity of sludge produced, indicated that 18% of the input amount was present in the sludge. This leaves 32% of the input amount not accounted for. It is not clear what happens to this. The measurements in water are considered to be reliable, and so a removal rate from water of 50% is assumed for this process. The rest of the substance is assumed to be removed with the solid material for the purposes of this assessment. This leads to a higher concentration in sludge than was actually measured. For comparison, the measured level in the sludge will also be considered in the calculations.

The amount of sludge produced at this stage is 22.68 tonnes per day, which from the pulp production rate is a rate of 22.9 kg/tonne. This is towards the low end of values found for UK mills (Environment Agency, 2002), and reflects the lower sludge production rate for sites with no de-inking.

*Biological treatment*

The concentrations of bisphenol-A in the influent and effluent of the WWTP were measured. The average values were 193 µg/l and 42.7 ng/l respectively, indicating a removal of 99.98%. Measurements on the sludge produced in the WWTP indicate that this contained 0.98% of the

bisphenol-A entering the WWTP. The fate of bisphenol-A in the WWTP is therefore 0.02% to water, 0.98% to sludge with 99% degraded.

All sludges and rejects from the processes are incinerated at the site. This is described as standard practice in Germany.

Summary of the use of data from the three specific sites

Both monitoring studies appear to be well conducted, and the sampling strategy takes account of site operating conditions. The sites are considered to represent the range of situations in which thermal paper may undergo recycling. At one end of the scale there are two sites that receive high loadings of thermal paper (through the inclusion of thermal paper broke in the recovered paper feedstock). At the other end is a site accepting mixed general 'near household' waste paper containing a low level of thermal paper. Therefore the information from these sites will be used to calculate possible PECs for generic paper recycling sites. These calculations will consider sites taking general waste paper, with or without a de-inking step. The number of sites taking thermal paper broke is limited, and the data for the two sites are considered to be representative for this specific scenario (the results of the surveys are consistent despite the different characteristics of the two sites). However, a calculation based on the high level of bisphenol-A input at these sites is also included for information.

*Bisphenol-A input to sites*

The concentration of bisphenol-A measured in the recovered paper input to the site producing corrugated packaging (14.7 mg/kg – see above) is assumed to be typical for general paper waste streams. A concentration of 15 mg/kg is therefore used in the following calculations (this represents a bisphenol-A level of around 0.001%). Considering that broke will contain higher levels, a higher figure will also be used for those sites that use broke as part of their recovered paper feed. The maximum input calculated for the two sites receiving thermal paper broke was 0.074% of bisphenol-A in the paper feed.[7]

*Removal of bisphenol-A from recovered paper*

A removal rate of 95% is assumed for a site with de-inking; a rate of 10% is used for a site with no de-inking.

*Fate during primary treatment*

For a site with no de-inking, removal of 50% from water will be assumed (Section 5.2). A sludge production rate of 22.9 kg/tonne is assumed for this stage (based on data from the site without deinking described above).

For a de-inking plant, removal of 95.9% from water at this step is assumed. As there are no specific data on paper sludge production at de-inking sites, a figure of 22.9 kg/tonne will also be assumed for calculation purposes. However, a higher value of 200 kg/tonne will also be used for comparison based on UK information from paper mills in general (Environment Agency, 2002).

[7] Around 1,600 tonnes of bisphenol-A was used to make ~140,000 tonnes of thermal paper in 2001, giving a bisphenol-A content of 1.1% by weight. The average bisphenol-A content measured in thermal paper at the two 'broke' recycling sites is 0.7% and 0.88%, which are a similar order of magnitude.

*Fate during biological treatment*

The values obtained from the WWTP at the corrugated packaging production site (0.02% to water, 0.98% to sludge, from above) will be used for both processing types. This is assumed to represent a worst case, since the data were obtained with a low rate of substance input, and so WWTP microbial populations are less likely to have become adapted. For comparison, SimpleTreat calculations in the original risk assessment predict an overall emission to water of 12% from this step.

*Use of sludges*

In all three example sites, the sludges from the paper processing steps are incinerated (as are the biological sludges at some sites). This is described as standard practice for the relevant countries (Germany and Austria). It is, however, known that these sludges are applied to land (where they function as a soil improver) in other parts of the EU. Therefore, this route has been considered in the calculations for generic sites. Calculations have been carried out for the application of the paper and biological sludges individually and as a mixture in the proportions in which they are produced.

#### 3.1.2.6 Effect of updated tonnages on local emission estimates

The changes to the tonnages for the various use areas are not considered likely to have a significant impact on the estimates of local emissions, as explained below. The effects on regional and continental emissions are considered later in the addendum.

Bisphenol-A production and polycarbonate production take place together, i.e. there are no polycarbonate production sites at which bisphenol-A is not produced. The emission estimates in the published risk assessment are based on site-specific data. Information from industry is that the emission control measures in place at the sites have been improved such that the emissions are now lower than those reported for the published risk assessment. Some new information is presented in Section 3.1.4.1.

The local emission estimates for epoxy resin use were based on specific information; the relatively small increase in the level of use is considered unlikely to mean significant changes in these values. For can coating and ethoxylated resins, the published risk assessment concludes no emissions to water and so there are no changes.

There is no change to the tonnage used in phenoplast resins. Use in unsaturated polyesters is a dry process according to the published risk assessment and so there are no emissions to change.

The increased tonnage used in thermal paper could mean an increase in the amounts released from paper production sites. There is no specific information on this at the moment. The sites included in the published risk assessment cover a range of sizes (using from 3 to 343 tonnes per year), and these still appear to be realistic within the increased tonnage. Therefore it seems reasonable to continue to use these as representative of this use pattern. For thermal paper recycling, the local estimates are based on a representative paper site using recovered material. The input to the site was based on measured levels in feed. There is no need to change these.

The local estimates for PVC were based on a typical size of site, and this will not change as a result of the reduction in the overall tonnage used in this area, hence the same estimates are retained.

### 3.1.2.7 Revised regional and continental emissions

#### 3.1.2.7.1 Changes due to revised emission estimates and tonnage

Bisphenol-A production

The new information on releases from production sites, which include polycarbonate production as well, has been used to revise the emissions for this part of the life cycle.

Thermal paper recycling

The regional emissions from thermal paper recycling have been recalculated according to the new information presented above. Recovered thermal paper from fax and lottery use is assumed to be de-inked, whereas recovered POS receipts and labels are assumed not to pass through a de-inking step. Thermal paper broke is assumed to be de-inked. The emission factors described above in Section 3.1.2.5.4 have been used to estimate the annual amounts of bisphenol-A released to surface water, to biological sludges and to paper sludges, as in Table 3.5.[8]

Table 3.5 Calculated emissions of bisphenol-A from thermal paper recycling

| | De-inking route | Non-de-inking route | Thermal paper broke |
|---|---|---|---|
| Amount | 204 tonnes | 306 tonnes | 160 tonnes |
| To paper sludge | 187 tonnes | 15.3 tonnes | - |
| To biological sludge | 78 kg | 150 kg | - |
| To surface water | 1.9 kg | 3.5 kg | 1.6 kg |

Sludges from sites processing thermal paper broke assumed to be incinerated

The total amount to sludge (combined) is therefore 202.5 tonnes per year, and the emissions to surface water are 7 kg/year. The emission scenario document for paper (Environment Agency, 2002) suggests that 80% of sludge from paper recycling may be applied to land, hence the emission of bisphenol-A to land from this route is 162 tonnes. Both the surface water and soil emissions are assumed to be distributed as 10% to the region and 90% to the continental scale.

PVC additive formulation

The total releases from this use have been recalculated from those in the published assessment, using the revised information included in Section 3.1.2.3.[9] The total EU emissions to wastewater treatment are estimated as 81 kg/year, and the releases to surface water as 3.45 kg/year. The regional emissions are taken as those of the largest individual source from the published risk assessment; these are 2.76 kg/year for surface water emissions and 37.1 kg/year for emissions to wastewater treatment. The remainder of the totals is allocated to the continental emissions.

[8] Note that the recalculation presented in the risk assessment update of 2005 has been further modified here to take account of the increased quantity used in thermal paper.

[9] The figures presented in the risk assessment update of 2003 have been modified for this addendum to take account of the reduced use of bisphenol-A in PVC.

#### 3.1.2.7.2 Changes due to revised tonnages only

For the other use areas not included in Section 3.1.2.7.1 the basis for the emission estimates has not changed since the published risk assessment. The regional and continental emissions from that assessment have been adjusted to take account of the changes in quantities produced and used, as follows. Only those areas that gave rise to emissions are considered here.

For polycarbonate bottle washing, it has been assumed that the amount of bottles has increased in line with the increased amount of polycarbonate used, and so the emissions have been increased by 78% from those in the published assessment.

The amount of bisphenol-A used in epoxy resins has increased by 12%, so the regional and continental emissions have been increased by the same factor.

There has been no change to the phenoplast resin use so the emissions remain as in the published assessment.

All PVC-related uses are assumed to have had the same reduction of 10% in quantity, and so the emissions from the published assessment have been reduced by 10% (with the exception of additive packages as described in Section 3.1.2.7.1). No adjustment has been made to the releases from PVC in use during its service lifetime. A lifetime of 30 years was assumed in the published assessment, and so it is assumed that any reduction has not had time to have a significant impact on the emissions from this life cycle step.

#### 3.1.2.7.3 Summary of revised emission estimates

The revised estimates of emissions to the regional and continental scales are presented in Table 3.6. Note that the published risk assessment used a split of 70:30 between releases to waste water treatment and to surface water, as specified in the TGD at the time the assessment was being developed. This has been changed in the current addendum to 80:20 in line with the revised TGD. Also note that for some uses the emissions are estimated after any wastewater treatment and so are presented as emissions to surface water.

Table 3.6 Revised regional and continental emissions

| Process | Air (kg/year) | | Emission to wastewater treatment plants (kg/year) | | Emission to receiving waters (kg/year) | |
|---|---|---|---|---|---|---|
| | Regional | Continental | Regional | Continental | Regional | Continental |
| Bisphenol-A production | 575 | 409 | | | 113 | 115.6 |
| Polycarbonate bottle washing | | | 0.23 | 2.05 | 0.05 | 0.52 |
| Epoxy resin production | | | | | 242 | 209 |
| Phenoplast cast resin processing | | | 4.8 | 43 | 1.2 | 11 |
| Thermal paper production | | | | | 49 | 95 |
| Thermal paper recycling | | | | | 0.68 | 6.25 |
| PVC – Anti-oxidant during processing | | | 77 | 693 | 19 | 174 |
| PVC – Preparation of additive packages | | | 37 | 44 | 2.76 | 0.79 |
| PVC –Use of additive package | | | 77 | 693 | 19 | 174 |
| PVC – Anti-oxidant in plasticiser production[a] | | | 73 | 28 | | |
| PVC – Plasticiser use | | | 10 | 91 | 2.7 | 23 |
| Losses from PVC articles in use | 1,560 | 14,040 | | | 2,250 | 20,450 |
| Total | 2,135 | 14,449 | 279 | 1,594 | 2,699 | 21,260 |
| Total in kg/day (Averaged over 365 days) | 5.8 | 39.6 | 0.76 | 4.4 | 7.4 | 58.2 |

a - all emissions via WWTP.

In addition there are emissions to agricultural soil from the application of paper sludge: 16.2 tonnes/year (44 kg/day) to the region and 145.8 tonnes per year (400 kg/day) to the continent.

### 3.1.3 Environmental fate

#### 3.1.3.1 Abiotic degradation

No new information is available. A short atmospheric half-life of 0.2 days is calculated for the reaction of bisphenol-A with hydroxyl radicals (EC, 2003). The physical and chemical properties of bisphenol-A suggest that hydrolysis and photolysis are likely to be negligible.

#### 3.1.3.2 Biodegradation

Results from a number of biodegradation studies were summarised in EC (2003):

- In the OECD 301F manometric respirometry test bisphenol-A meets the criteria for ready biodegradability.
- However in the OECD 301D closed bottle test and OECD 301B modified Sturm test no biodegradation was observed.
- In a modified SCAS procedure bisphenol-A met the criteria for inherently biodegradable substances, although this test can not give any indication of the potential for bisphenol-A to undergo ready biodegradation.

Measured levels of bisphenol-A before and after wastewater treatment at chemical plant and major users of bisphenol-A suggest a high level of removal. It is not possible to say if this is via adsorption to sludge or biodegradation, although based upon its chemical properties biodegradation is likely to be the major removal mechanism.

From the biodegradation studies reported bisphenol-A would appear to be readily biodegradable, possibly with a short period of adaptation. The default rate constant for biodegradation in wastewater treatment plant is k=1 $h^{-1}$ for a readily biodegradable substance meeting the 10-day window. This value will be used in the assessment. The resulting fate in a wastewater treatment plant as estimated by EUSES is 12% to water and 6.2% to sludge, with 81.9% degraded and a negligible fraction to air.

A number of studies on the degradation of bisphenol-A in natural waters were also summarised (EC, 2003). Removal appears to be rapid once the waters have become acclimatised to bisphenol-A. The reported lag-phases before degradation are between 3-8 days. After the lag phase removal was rapid with 50% removal in 1-2 days and 100% removal in 2 to 17 days. These data would appear to indicate that in natural waters bisphenol-A may be classed as readily biodegradable meeting the 10-day test window. The default rate constant for biodegradation of $4.7 \cdot 10^{-2}$ $d^{-1}$ probably under-estimates the removal rate, as it corresponds to a half life of 15 days with 97% removal taking 75 days. However this value has been used in the risk assessment as a conservative approach.

No information was available on the degradation rate of bisphenol-A in soil. Therefore, the degradation rate was estimated from the degradation rate of bisphenol-A in surface water and the soil-water partition coefficient. The half-life for biodegradation of bisphenol-A in soil and the first order rate constant for degradation in soil were calculated by EUSES as 30 days and 0.0231 $d^{-1}$, respectively, based upon bisphenol-A being readily biodegradable in surface waters.

##### 3.1.3.2.1 New information

*Aquatic*

A further ready biodegradability study is available. CERI (2004) performed a manometric respirometry test (OECD 301F) on bisphenol-A. The average percent removal by BOD was 89%, and no parent compound could be detected by HPLC after 28 days. The 10-day window was met in this test.

A CAS (continuous activated sludge) simulation test has been carried out according to the OECD 303A guideline (TNO, 2001). The guideline was adapted to use a completely closed flow

through system, and radiolabelled substance was used in order to test environmentally relevant concentrations and determine a mass balance. The activated sludge system was acclimated to unlabelled bisphenol-A for four weeks, followed by a three week period when $^{14}$C-labelled substance was fed into the system. Bisphenol-A was determined in the influent, effluent, waste sludge and in $CO_2$ traps. Recovery of the dosed radioactivity was 94-99%. Average removal of $^{14}$C-bisphenol-A was 99.1%.

Nakada *et al.* (2006) measured the concentration of bisphenol-A (among a range of substances) in 24-hour composite samples of the influent and effluent from five municipal sewage treatment plants in Tokyo. All five plants used primary and secondary treatment with activated sludge. Bisphenol-A levels in the influent were between 100 and 1000 ng/l; removal of bisphenol-A was >92% on average.

Kang and Kondo (2002) investigated the effect of temperature on the biodegradation of bisphenol-A in river water. Samples of water from fifteen rivers in Japan were spiked with 0.2 mg/l bisphenol-A. At 30°C and 20°C degradation was complete after 10-15 days (half lives from two to seven days depending on the bacterial numbers in the wares samples at the start of the exposures). At 4°C, degradation was slower and had reached 20% after 20 days. Autoclaved water samples showed no removal, demonstrating that the major removal process is biological. The same authors (2002a) isolated specific bacterial strains with a high ability to degrade bisphenol-A. They also demonstrated a lack of degradation of bisphenol A under anaerobic conditions in river water.

Ike *et al.* (2000) studied the degradation of bisphenol-A in three activated sludge microcosms and forty four river water microcosms. The river water microcosms were prepared from water samples from seven rivers, at 15 sites, with conditions ranging from “clean” to “heavily polluted”. Degradation was noted in all of the sludge systems and in forty of the river water systems. Six of the river water systems were able to mineralise the substance completely, and 34 others showed TOC removal of 40-90%. Degradation tended to be greater in microcosms from more polluted waters. In the microcosms with partial removal, common metabolites accumulated, which appeared as two peaks in the HPLC traces. Bacteria isolated from the river water experiments were able to degrade bisphenol-A, and from further work with these the two main metabolites were identified as 2,3-bis(4-hydroxyphenyl)-1,2-propanediol and p-hydroxyphenacyl alcohol.

Suzuki *et al.* (2004a) investigated the biodegradation of bisphenol-A under laboratory conditions, using river water taken from a site on the Tama River in Japan which was influenced by effluent from a sewage treatment plant. After a two or three day lag period, bisphenol-A degraded rapidly, with estimated half lives of 0.4 and 1.1 days at 1 and 10 mg/l respectively. Optical density measurements on the water showed an increase in bacteria after two days of incubation. Metabolites were detected after three days, and correspond to those found in river water at the sampling site. The metabolite in the highest amount was 2,2-bis(4-hydroxyphenyl)propanoic acid (BPA-COOH), at 4.2% of the initial bisphenol-A concentration (1 mg/l). At 10 mg/l bisphenol-A, the metabolite in highest concentration was 2,2-bis(4-hydroxyphenyl)-1-propanol (BPA-OH), which reached a concentration of 679 µg/l after six days, and declined by 14 days. All of the detected metabolites appeared to decrease in concentration over longer exposures.

Kang and Kondo (2005) studied the degradation of bisphenol-A in river water and in seawater. In river water, half-lives of 4 days and 3 days were found at 25°C and 35°C respectively. In autoclaved seawater, no degradation of bisphenol-A was observed over 60 days, indicating no abiotic removal processes. In non-autoclaved seawater samples, no degradation was observed

over the first thirty days of exposure, despite an increase in the number of bacteria over the first three or four days (the numbers of bacteria then declined slowly). Bisphenol-A was degraded after thirty days, with the concentration reducing from 1 mg/l to ~200 µg/l after sixty days at 25-35°C. Some degradation was seen at 4°C, but starting only after 40 days. The concentration had reduced to ~700 µg/l by sixty days.

Ying and Kookana (2003) carried out degradation experiments on seawater and sediments from the coast around Adelaide, South Australia. Seawater samples were spiked with bisphenol-A at a concentration of 5 µg/l. The results showed little or no degradation over the first 35 days of the experiment, followed by rapid degradation over the following seven days. Bisphenol-A was almost completely degraded (>90%) after 56 days. Sediment and water samples (5 g and 5 ml respectively) were spiked with 1 µg/g bisphenol-A and kept under aerobic conditions for seventy days. The half-life of bisphenol-A under these conditions was 14.4 days. Similar sediment and water mixes kept under anaerobic conditions (monitored with resazurin as a redox indicator) showed no degradation of bisphenol-A over 70 days.

Ying *et al.* (2003) carried out biodegradation experiments on aquifer material from South Australia. Limestone sediment samples were taken from a depth of 153-154 m, and native groundwater samples were taken from the same aquifer. The aquifer materials were spiked with bisphenol-A and four other substances (nonylphenol, octylphenol, E2 and EE2), all at 1 µg/g, and incubated at 20°C for 70 days. Aerobic conditions were maintained throughout the experiment. Samples were taken weekly. Autoclaved aquifer materials were used as a control. There was no change in bisphenol-A concentration relative to the controls over the period (there was a slight reduction in concentration in both controls and the exposures).

The same authors carried out similar experiments on the same aquifer materials but under anaerobic conditions. The samples of aquifer material were placed in tubes that were placed in an anaerobic induction chamber under nitrogen for a month, until the redox indicator resazurin indicated that anaerobic conditions had been achieved. Samples were then spiked with the mixed substances. The exposures and sampling were carried out in the anaerobic induction chamber. There were no changes in the bisphenol-A concentration over the exposure period.

Hirooka *et al.* (2005) investigated the ability of green algae *Chlorella fusca* to degrade bisphenol-A. Algae were cultured with bisphenol-A at concentrations from 10 to 160 µM (2.3 to 36 mg/l) over seven days. Removal of bisphenol-A was >95% at concentrations up to 80 µM (18 mg/l), with 70% removal at 180 µM (36 mg/l). Algal growth was promoted over that in the controls at concentrations of 10-20 µM (2.3-4.6 mg/l). The amount of bisphenol-A in the algal cells was measured, and was significantly less than the amount lost from solution; after seven days it was below the limit of detection of the HPLC analysis used. Incubation in the dark resulted in only 27% removal of bisphenol-A. A metabolite, with an additional hydroxy group on one ring, was observed; this increased in concentration up to 72 hours and then decreased. A yeast two-hybrid assay used to assess estrogenic activity showed that this decreased in parallel with the reduction in bisphenol-A concentration.

A *Streptomyces* sp. strain isolated from river water in Japan was able to degrade bisphenol-A. A solution of 1 mg/l of bisphenol-A was degraded by >90% in 10 days at 30°C by a culture of the strain. A half-life of between three and four days was calculated (Kang *et al*, 2004). Zhang *et al.* (2007) isolated a strain of *Achromobacter xylosoxidans* from the compost leachate of municipal solid waste that was able to grow on bisphenol-A. Sasaki *et al.* (2007) isolated a strain (BP-7) of *Sphingomonas* from off-shore seawater samples in Japan which was able to degrade bisphenol-A completely over a period of 40 days alone, or over seven days when combined with a *Pseudomonas* strain.

Impact of new information

The new information supports the conclusion of the published risk assessment that bisphenol-A is readily biodegradable in natural fresh surface waters.

*Terrestrial*

Fent *et al.* (2003) studied the adsorption and degradation of bisphenol-A in soils from Germany: three soils from North-Rhine Westphalia and one from Rhineland Palatinate. The adsorption-desorption studies were carried out according to the OECD Guideline 106, the soil degradation studies according to a SETAC design.

For the degradation study, twelve test systems were set up for each soil type. Bisphenol-A (uniformly labelled with $^{14}C$) was applied at 6 µg/100 g soil. Experiments were continued for 120 days. The test systems were analysed at intervals for the amount of extractable, non-extractable and volatile radioactivity (volatiles captured in soda lime trap for $CO_2$ and oil-wetted quartz wool for VOCs), as well as how much bisphenol-A remained in the system. Bisphenol-A rapidly formed bound residues in soil. After one hour, 19-59% of the applied radioactivity was non-extractable under normal conditions (methanol plus 5% acetic acid). After three days, 84.7 – 88.6% was not extractable. Following hot flux extraction, only a further 2.8% was removed, so that less than 7.4% was extractable using both techniques combined. At the end of the 120 days exposure, less than 2% of the applied radioactivity was extractable.

Depending on the soil, 13.1 – 19.3% of the label was recovered as $CO_2$ after the incubation period. No other volatile radioactive species were found. In one soil, after 1-2 hours, 49.2% of the bisphenol-A applied could be recovered, with 33% as other extractable species (up to five different metabolites). After three days the amount was less than the detection limit (1 µg/kg). No significant metabolites could be found after three days.

The authors comment that forming bound residues is common behaviour for phenols and anilines. Rapid transformation to transient metabolites suggests that most of the bound residues are in fact transformation products.

Ying and Kookana (2005) took samples of a sandy loam soil from a depth of 0-15 cm on a farm in South Australia. Bisphenol-A was added to 5 g of soil to give a concentration of 1 µg/g, and incubated at 20°C for 70 days. Degradation was rapid, with a half-life of seven days calculated from the results. Little or no degradation was seen in sterilised soil samples. When the soil was mixed with an equal amount of river water and allowed to attain anaerobic conditions before addition of the bisphenol-A, no degradation was seen.

Oshiman *et al.* (2007) isolated a bacterial strain, identified as belonging to the *Sphingomonas* genus, from soil from a vegetable-growing field in Japan. The strain was able to utilise bisphenol-A as the sole source of carbon and to use it as an energy source under aerobic conditions. The estrogenic activity of Bisphenol-A in the test medium was ultimately reduced by the strain, although the activity increased initially.

Impact of new information

The new information supports the conclusion of the published assessment that bisphenol-A is readily biodegradable in soil.

#### 3.1.3.3 Distribution

Adsorption coefficients for environmental media were estimated using the TGD methods as implemented in EUSES (EC, 2003). The equation used to predict the $K_{oc}$ value is that for hydrophobic chemicals in general as described in the TGD, using a log $K_{ow}$ value of 3.40. The derived partition coefficients are as follows:

| | | |
|---|---|---|
| $K_{oc}$ | 715 l/kg | Organic carbon-water partition coefficient |
| $Kp_{soil}$ | 14.3 l/kg | Solids-water partition coefficient in soil |
| $Kp_{sed}$ | 35.8 l/kg | Solids-water partition coefficient in sediment |
| $Kp_{susp}$ | 71.5 l/kg | Solids-water partition coefficient in suspended matter |
| $K_{susp\text{-}water}$ | 18.8 $m^3/m^3$ | Suspended matter-water partition coefficient |
| $K_{soil\text{-}water}$ | 21.7 $m^3/m^3$ | Soil-water partition coefficient |
| $K_{sed\text{-}water}$ | 18.7 $m^3/m^3$ | Sediment-water partition coefficient |

These data suggest that bisphenol-A is likely to be moderately adsorbed to solids upon release to the environment.

Volatilisation is not considered to be a significant removal mechanism for bisphenol-A from water. Removal of bisphenol-A in rainwater is also considered to be negligible.

##### 3.1.3.3.1 New information

Höllrigl-Rosta *et al.* (2003) measured the sorption of radiolabelled bisphenol-A to soil on standard batch equilibrium studies according to OECD Test Guideline 106. The soil was a loamy silt soil with an organic carbon content of 1%. A low water:soil ratio of 1.41:1 was used as resembling natural conditions. The substance was analysed in both phases. The $K_{oc}$ value determined was 890±30 l/kg. Dialysis experiments using solutions of humic and fulvic acids as dissolved organic carbon were also carried out. The distribution coefficient $K_{DOC}$ for humic acids was 860±70 l/kg, very similar to the $K_{oc}$ value and considered to indicate that similar binding mechanisms were operating. No formation of adducts with fulvic acids was observed.

As part of a study on bisphenol-A in German soils (see Section 3.1.3.2.2), Fent *et al.* (2003) measured the adsorption of bisphenol-A in four soils using the OECD 106 Guideline. Degradation as well as binding was seen in the adsorption studies (rapid removal was seen in the degradation studies). In studies to measure the $K_{oc}$ values a biocide was employed to reduce the degree of degradation in the experiments. The mean $K_{oc}$ value obtained was 795.9 (mean Kd value 11.01).

Shareef *et al.* (2006b) looked at the sorption of bisphenol-A to mineral surfaces. Little sorption (<20%) was seen to goethite and kaolinite from a 3 µM (0.7 mg/l) solution, with little effect of pH. Sorption to these two minerals was rapid and completely reversible. When montmorillonite was used, sorption was greater and took longer, and only small amounts were desorbed at pH 7. It was proposed that bisphenol-A intercalated into the inter layer spaces of montmorillonite, whereas sorption to the other two minerals was to the surface.

Ying and Kookana (2005) took samples of soils from a depth of 0-15 cm from locations in South Australia. Sorption of bisphenol-A was measured using a batch equilibrium method, shaking for two hours. The organic carbon content of the soils ranged from 0.85 to 2.9%. The resulting $K_{oc}$ values ranged from 251 to 1507, with a mean value of 962.

Loffredo and Senesi (2006) measured the sorption of bisphenol-A to samples of two acid sandy soils using a batch equilibrium method. Surface (0-30 cm) and deep (30-90 cm) horizons of both soils were used. The organic carbon content of the soils ranged from 1.1 to 9.3 g/kg. Bisphenol-A showed linear sorption to all four soils, with no indication of saturation (up to 40 mg/l with 5 g of soil). The $K_{oc}$ values determined ranged from 335 to 703, average value 375. Sorption was almost completely reversible for three of the four soils, the exception being the surface soil with the highest organic carbon content.

The sorption of bisphenol-A to sediments from an aquifer system in South Australia has been studied (Ying *et al*, 2003). Limestone sediment samples were taken from a depth of 153-154 m. Sorption was measured in batch equilibration experiments at room temperature. The samples were shaken over a 16-hour period and then centrifuged. No loss of bisphenol-A (<3%) was found in controls without sediment. The relation between the sorption coefficient and the bisphenol-A concentration was not linear; the data were fitted to the Freundlich equation, and a coefficient of 3.89 with n=0.85 were obtained. The organic carbon sorption coefficient can only be calculated from these data for the concentration range tests, which was 2.5 – 20 µg/l. The value obtained for the coefficient was 778. The organic carbon content of the sediment was 0.5%.

Zeng *et al.* (2006) sampled sediments from five locations on the Xiangjiang River in China. Three samples were taken from each site, mixed and sieved (88 µm). Batch sorption experiments were carried out with six concentrations of bisphenol-A. Equilibrium was reached rapidly, mostly within the first hour. The organic carbon contents of the sediments were from 2.06 to 6.29% by weight. Three functions were fitted to the data – linear, Freundlich and a dual reactive domain model; all gave a reasonably good fit, with the Freundlich model giving the best fit. The linear model gave an average $K_{oc}$ value of 115 l/kg over the five sediments (calculated from the data in the paper); the Freundlich model gave a value of 305 l/kg. Some irreversible sorption was observed in desorption experiments, but not to a great extent. The pH of the solutions had a small effect on the sorption.

Patrolecco *et al.* (2006) sampled surface water, suspended particulate matter and bed sediments in the River Tiber in Italy, in September 2002 (summer sample) and January 2003 (winter sample). The levels of bisphenol-A measured in water and bed sediments are included in Section 3.1.4.6.3. Bisphenol-A was measured in the suspended matter in two of the four samples taken in summer, and in all four taken in the winter. The levels measured in suspended matter and the corresponding water levels were used to calculate $K_{oc}$ values; the range of results was 11,220 to 17,000.

Hu *et al.* (2006) used the partitioning of bisphenol-A between water and solid phase micro-extractant (SPME) fibres to investigate the effect of water parameters on the availability of bisphenol-A. The measured distribution coefficients are not directly relevant to the environment. Increasing salinity of the water increased the availability of bisphenol-A by around 1.2 times (i.e. the sorption to SPME fibres was reduced). An increase in pH from 5.5 to 8.5 decreased the availability by 1-2 to 1.4 times. The technique was also used to look at the effect of humic acids (commercial form) on the free fraction of bisphenol-A. The distribution coefficients on a dissolved organic carbon basis ranged from 4.03 to 5.60 (as log $D_{DOC}$). The values are much higher than those reported by Hollrigl-Rosta *et al.* above. Hu *et al.* note that the concentration of DOC in their study is more lower (1-50 mg/l) than that in the Hollrigl-Rosta study (190 mg/l). If the results are extrapolated to higher DOC values then the results are much closer.

Clara *et al.* (2004) looked at the sorption of bisphenol-A to sewage sludge. Activated sludge from a municipal wastewater treatment plant was used. Sludge from the same plant inactivated

by mercury (II) sulphate was also used, to distinguish between pure absorption and biosorption. In the batch sorption tests, bisphenol-A equilibrated with the sludge in around two hours, although all sorption experiments were carried out over 24 hours. There was no significant difference between the activated and inactivated sludge in terms of the sorption of bisphenol-A. The specific adsorption coefficient $K_D$ (and hence the derived organic matter and organic carbon partition coefficients) was concentration dependent, decreasing with increasing free concentration in water, but no saturation was seen (up to 10 mg/l). From the equation given in the paper, the $K_D$ value at 1 mg/l would be 257 l/kg, a similar value to that used in the published assessment (265 l/kg). The authors also investigated the effect of pH on sorption. Increasing the pH above 9 led to the desorption of bisphenol-A from sludge, and the desorption was complete at pH 12. Such high pHs can occur during sludge dewatering processes where limestone is used.

Impact of new information

The new studies provide slightly different results. Batch equilibrium studies in laboratories on both sediment and soil samples give results that are generally similar to the estimated value used in the published risk assessment. There are some indications from field studies where both water and sediment samples were taken that the degree of sorption may be greater (at least sorption to suspended matter). Comments by the CSTEE prior to publication of the original report (CSTEE, 2002) pointed out that measured sediment levels appeared higher than expected from the water levels from the same locations. There is no explanation at present of what might cause this effect. There are always difficulties when comparing measured levels in different compartments to be sure that the samples can be considered to be in steady state with each other. Although there are some indications of enhanced sorption, the majority of the tests, in particular the standard batch equilibrium studies, give results with similar values to those used in the published risk assessment. The values from the published assessment have therefore been retained in the calculations for this addendum.

### 3.1.3.4 Accumulation and metabolism

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

A bioconcentration factor for earthworms of 7.9 kg/kg was estimated using QSARs (as implemented in EUSES).

#### 3.1.3.4.1 New information

*Bioaccumulation*

Lindholst *et al.* (2003) studied the metabolism of bisphenol-A in zebrafish (*Danio rerio*) and rainbow trout (*Oncorhynchus mykiss*). Adult zebrafish were exposed to 100 µg/l bisphenol-A in a flow through system for 168 hours. Exposures took place in a 100 l aquarium, with a flow rate of eight replacement volumes per day, and 150 fish. The bisphenol-A concentration was measured every two days; the actual concentration found was 97.5±5.2 µg/l. Fish were sampled

at 0, 2, 6, 12, 24, 48, 72, 120 and 168 hours. After this time the remaining fish were transferred to a system to which bisphenol-A was not added and kept for the same length of time, with sampling at the same intervals. Zebrafish tissue samples were analysed for bisphenol-A, bisphenol-A glucuronic acid (BPAGA) and bisphenol-A sulphate (BPAS).

Rainbow trout were exposed under similar conditions for eight days to 100 µg/l bisphenol-A (actual concentration from 2-day samples 107.3±6.3 µg/l). After eight days, gall bladder and blood samples were taken, and the bile fluid and blood plasma analysed for the same three substances (bisphenol-A, BPAGA and BPAS).

Uptake and excretion rates for fish were calculated by fitting data to exponential uptake and decay models (much of the data for rainbow trout came from earlier publications). Uptake was fitted to a first order model, excretion to a first or second order model depending on the goodness of fit. Bisphenol-A was detected in zebrafish after two hours' exposure, and steady sate was reached by 24 hours. Steady state concentrations were 569 ng/g for bisphenol-A, 12.6 µg/g for BPAGA and 39.3 ng/g for BPAS. The whole body uptake rate for zebrafish was calculated as 0.23; tissue specific values from rainbow trout plasma, liver and muscle were 0.73, 0.11 and 0.16, so the rates were similar between the two species despite the different matrices.

Elimination from zebrafish was fitted to a second order model; the first compartment had a half life of <1.1 hours, the second compartment half life was 139 hours. The three trout tissues had elimination half-lives of 3.7, 1.8 and 5.8 hours for plasma, liver and muscle respectively, as first order elimination. The authors suggest that in zebrafish bisphenol-A is rapidly removed from tissues, metabolised by the liver and excreted primarily as BPAGA into the gall bladder (compartment 2). Elimination from the tissues in zebrafish is much more rapid than from trout tissues. Zebrafish have a lower sensitivity to bisphenol-A than does trout when considering vitellogenin synthesis. It is suggested that this may be due to the more rapid metabolism resulting in lower bisphenol-A concentrations and a reduced response. Data on specific tissue concentrations in the liver for bisphenol-A and metabolites was needed to confirm this.

Lee *et al.* (2004) measured the accumulation of bisphenol-A in spotted halibut (*Varaspar variegates*) in a seven-day semi-static exposure, with renewal of solutions every twenty four hours. Nonylphenol was also included in the same exposures at similar concentrations. The bioconcentration factor determined at an exposure level of 70 µg/l was 38±21 l/kg, averaged over the seven days.

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

Koponen *et al.* (2007) studied the uptake of bisphenol-A in larvae of the common frog *Rana temporaria*. Radiolabelled substance was used at a nominal concentration of 1.84 µg/l in water, the solutions were renewed every day for the three day uptake experiment. The results are based on total radioactivity. The effect of UVB exposure was also considered in the experiments, only the results without UVB are considered here. The steady state BCF value obtained was 140±38; the value derived from uptake and depuration rates was 131. Growth correction was applied, and resulted in a small decrease in the elimination rate estimate; the revised BCF values (with growth correction by two methods) were 147 and 144. As a radiolabelled substance was used the results will include any degradation or metabolism products, hence the results have to be interpreted with caution.

Takahashi *et al.* (2003) measured the concentrations of bisphenol-A in water, periphytons and benthos in the Tama River in Japan. The range of concentrations in water was 0.02-0.15 µg/l.

The concentrations in periphytons were 2.0-8.8 µg/kg and in benthos were 0.3-12 µg/kg, giving bioaccumulation factors for periphytons of 18-650 and for benthos of 8-170.

*Metabolism*

Kang *et al.* (2006) have reviewed the metabolism and biodegradation of bisphenol-A in organisms – bacteria, fungi, plankton, plants, invertebrates, fish, birds and mammals. There is evidence of metabolism or biodegradation in all of these. The authors conclude that although the metabolites can enhance estrogenicity or toxicity, in general metabolism leads to detoxification of bisphenol-A. This does not mean that the substance does not show effects in organisms.

Metabolism of bisphenol-A by plant tissues has been demonstrated (Nakajima *et al.* 2002). Tobacco BY-2 cells in suspension culture reduced the concentration of added bisphenol-A rapidly after addition, with no bisphenol-A detected 2.5 hours after application. Use of radiolabelled substance allowed four metabolites to be observed, the most abundant being a glucopyranoside derivative (BPAG). When labelled bisphenol-A was administered to the roots of tobacco seedlings, radioactivity was incorporated in BPAG and three other unidentified metabolites that were accumulated in the leaves.

Schmidt and Schupan (2002) demonstrated the metabolism of bisphenol-A in plant cell suspension cultures. The products found were glycosides of bisphenol-A, non-extractable residues and highly polar, presumed polymeric, products. The proportion of each product type varied with plant species. It is possible that bisphenol-A could be liberated from the glycosides, for example under acid conditions, but the other products appeared stable for the most part.

[Note: uptake into plants is not a major route for bisphenol-A. The assumptions in the assessment are that any substance taken up into the plant is available, so metabolism is likely to reduce the level in plants.]

Spivack *et al.* (1994) carried out further work on the metabolic pathways of bisphenol-A in bacterial strain MV1 (details included in EC, 2003). The major pathway was found to account for 85% of the metabolised bisphenol-A, the minor route for the other 15%. Both routes lead to mineralisation, in whole or in part. Similar metabolic pathways with similar degrees of importance were found in a bacterial isolate *Pseudomonas paucimobilis* (Jin *et al*, 1996).

Sasaki *et al.* (2005) purified components of the cytochrome P450 monooxygenase system from a *Sphingomonas* sp. strain A01 (see also soil degradation in Section 3.1.3.2.1), which was able to degrade bisphenol-A. Two degradation products were detected by HPLC analysis and were thought to be 1,2-bis(4-hydroxyphenyl)-2-propanol and 2,2-bis(4-hydroxyphenyl)-1-propanol.

Yim *et al.* (2003) screened 26 species of micro-organisms for ability to degrade bisphenol-A. The species *Aspergillus fumigatus* KCTC 6145 was found to be able to metabolize bisphenol-A. The main product from the metabolism was bisphenol-A-*O*-β-D-glucopyranoside (BPAG). It is not clear from the report whether this was the only species to metabolize bisphenol-A, or whether it was the most successful. The process to obtain sufficient metabolite to allow identification is described as preparative scale biotransformation. Kang *et al.* (2004) isolated a strain of *Streptomyces sp*. from river water in Japan that was able to degrade bisphenol-A, with a half life of three to four days.

Impact of new information

The new BCF values for fish are generally similar to that used in the published risk assessment and so no change is necessary.

### 3.1.4 Predicted Environmental Concentrations (PECs)

This section presents the PEC values derived from a combination of the new data and that in the published risk assessment. The next four sections present the calculation of Clocal values for uses where the local emissions have been revised based on new information. The calculation of the regional and continental concentration follows. The PEC values for all current uses are then presented for each compartment in turn, together with the results of a survey of monitoring data. PEC values for STP ($PEC_{microorganisms}$) and for air are not included, as there were no risks for either of these compartments in the published risk assessment and the emissions have either reduced or remained the same.

#### 3.1.4.1 Bisphenol-A production

The revised information on releases from production and polycarbonate sites has been used to calculate revised PEC values for the sites. These new values are included in Table 3.9.

#### 3.1.4.2 PVC additive formulation

The factors presented in Table 3.3 were used to estimate emissions from the other sites, using whatever site information was provided for these. Emissions were also estimated for routes of release not covered by the measurements at the seven sites (usually rainwater run-off). Rainwater run-off estimates were only made where it was clear that the rainwater from the site was channelled into a receiving water. The resulting concentrations are presented in Table 3.6.

Table 3.7 $C_{local}$ values for PVC additive sites

| Site | $C_{local}$ | Notes |
|---|---|---|
| 1 | 0.02 µg/l | Marine. |
| 2 | 4.2 ng/l | |
| 3 | 0.074 µg/l | |
| 4 | 0.012 µg/l | |
| 5 | 0.013 µg/l | |
| 6 | 0.01 µg/l | Marine |
| 7 | 8 ng/l | Marine |
| 8 | <0.022 µg/l | |
| 9 | 0.2 µg/l | |
| 10 | <0.32 ng/l | |
| 11 | 1.1 ng/l | |
| 12 | 0.065 µg/l | No information on presence of MWWTP – calculations performed for scenarios with and without MWWTP, and higher concentrations included here |
| 13 | 0.48 ng/l | Marine |

MWWTP Municipal wastewater treatment plant

#### 3.1.4.3 Anti-oxidant use in plasticiser formulation

For the specific site, the actual wastewater treatment plant and river flows at the site have been used to calculate a Clocal value of 2 ng/l. For the generic site, the default wastewater treatment plant and dilution have been used to give a Clocal of 0.36 µg/l.

#### 3.1.4.4 Thermal paper recycling

##### 3.1.4.4.1 Site with de-inking

The concentration of bisphenol-A in the waste paper feed is 15 mg/kg. An average site will use of 84,000 tonnes of waste paper per year, over 350 days (ETPA, personal communication). This is equivalent to 240 tonnes of paper/day. The bisphenol-A input to the site is therefore 3.6 kg/day.

De-inking removes 95% from the paper, hence 3.42 kg/day is emitted to water.

At primary treatment, 95.9% is removed to the paper sludge, i.e. 3.28 kg/day. The remainder stays in the water, so 0.14 kg/day is emitted to a WWTP.

In the WWTP: 0.98% to biological sludge, so 1.4 g/day.

0.02% to effluent, so 28 mg/day.

The WWTP flow is 2,880 $m^3$/day, hence the effluent concentration is 9.7 ng/l. Dilution by 10 (the default factor) gives a Clocal of 0.97 ng/l.

*Sites receiving thermal paper broke*

An estimated maximum input of 0.074% of bisphenol-A in the paper feed corresponds to an input of 178 kg/day for the generic site. Following the same calculations as above, but using a removal rate in the WWTP of 99.99% (the value obtained from the two specific sites based on corrected concentrations, reflecting the higher level of removal at sites receiving a higher rate of input of bisphenol-A), gives a Clocal of 24 ng/l.

For comparison, the maximum concentration measured in the effluents for these sites (after correction for recovery) was 500 ng/l, giving a Clocal of 50 ng/l based on the default dilution factor. The maximum Clocal estimated from actual receiving water flow rates is 55 ng/l. Since these are maximum values, only the value for the generic site given in the preceding paragraph will be taken through to the risk characterisation section.

Sludges from the thermal paper broke recycling sites are assumed to be incinerated. There are no data on levels in sludge from these sites at the moment.

##### 3.1.4.4.2 Site without de-inking

As above the bisphenol-A input to the site is estimated to be 3.6 kg/day.

Pulping removes 10% from the paper, hence 0.36 kg/day is emitted to water.

At primary treatment, 50% is removed to paper sludge (i.e. 0.18 kg/day). The remainder is emitted to water, so 0.18 kg/day is emitted to a WWTP.

In WWTP: 0.98% to biological sludge, so 1.76 g/day.

0.02% to effluent, so 36 mg/day.

The WWTP flow rate is 2,880 $m^3$/day, so the effluent concentration is 12.5 ng/l. Dilution by 10 (default factor) gives a Clocal of 1.25 ng/l. The average concentration in the effluent from the actual site measurements was 43 ng/l; assuming a ten-fold dilution gives a Clocal of 4.3 ng/l, which is in good agreement with this generic estimate. Again, only the generic estimate will be taken forward to the risk characterisation section.

#### 3.1.4.5 Regional and continental concentrations

The regional and continental concentrations have been calculated using EUSES 2.0.3. The emissions used are summarised in Table 3.1. The resulting regional PEC values are:

$PECregional_{water}$ = 32 ng/l

$PECregional_{sediment}$ = 0.52 µg/kg wwt

$PECregional_{soil}$ = 0.07 µg/kg wwt

$PECregional_{marine\ water}$ = 2.7 ng/l

$PECregional_{marine\ sed}$ = 0.034 µg/kg wwt

The estimated regional concentration in water is comparable to the concentration of bisphenol-A found in the feed water to the general paper recycling site described in Section 3.1.2.5.4, which was 32 ng/l (average of three samples).

#### 3.1.4.6 PEC values – water (fresh and marine)

##### 3.1.4.6.1 Calculated PEC values

The PEC values calculated using EUSES 2.0.3 are presented in Table 3.8 (for uses where Clocal has not changed from the published assessment) and Table 3.9 (for uses where new Clocal values were calculated in the preceding sections). Values for marine waters and sediments have been added for the generic scenarios, and for specific sites where these discharge to marine or estuarine waters (for these specific sites the marine values replace the freshwater values). For the generic marine scenarios it is assumed that the effluent is not treated in a wastewater treatment plant, and a default dilution of 100 for marine waters has been used. Specific dilution rates have been used for individual sites where this information is available, otherwise the default value of 100 is used with the site-specific information.

##### 3.1.4.6.2 Bisphenol-A from tetrabromobisphenol-A (TBBPA) in sediment

The risk assessment for TBBPA (ECB, 2007) concludes that there is strong evidence that TBBPA can degrade to give bisphenol-A under certain anaerobic conditions. This has been demonstrated conclusively for marine or saline sediments, freshwater sediments and anaerobic sewage sludge, and it is possible that it could also occur in other anaerobic systems. From Section 3.1.3.2 of this addendum, bisphenol-A is expected to be stable under anaerobic

conditions. It is therefore possible that the degradation of TBBPA in sediment could lead to the production of bisphenol-A.

An initial estimation of possible levels can be obtained by assuming that all of the TBBPA present in anaerobic sediment degrades to bisphenol-A. The results of such calculations are presented in Tables 3.10 and 3.11; the concentrations of TBBPA in sediment are taken from the TBBPA risk assessment report (ECB, 2007) and the calculation assumes that 90% of the total sediment concentration is converted (i.e. 100% conversion of TBBPA in the anaerobic part of the sediment which makes up 90% of the total sediment) . Note that only those activities taking place within the EU are included in the table (the risk assessment also has example calculations for other processes but these are not relevant to the EU).

Table 3.8 PEC values for water and sediment (fresh and marine) for uses where Clocal is unchanged from the published risk assessment[a]

| | Freshwater | | Marine | |
|---|---|---|---|---|
| | $PEC_{water}$ (µg/l) | $PEC_{sed}$ (µg/kg) | $PEC_{marine\_water}$ (µg/l) | $PEC_{marine\_sed}$ (µg/kg) |
| Site specific | | | | |
| ER 1 | 0.033 | 0.53 | | |
| ER 2, ER 3, ER 6 | 0.032 | 0.52 | | |
| ER 4 | 0.99 | 16 | | |
| ER 5 | 0.062 | 1.0 | | |
| PAPER 1 | 0.31 | 5.1 | | |
| PAPER 2 | 0.14 | 2.3 | | |
| PAPER 3 | 0.10 | 1.6 | | |
| PAPER 4 | 1.03 | 17 | | |
| PAPER 5 | 1.03 | 17 | | |
| PAPER 6 | 0.97 | 16 | | |
| PAPER 7 | 0.07 | 1.1 | | |
| Generic scenarios | | | | |
| Polycarbonate bottle washing | 0.032 | 0.53 | 0.003 | 0.046 |
| Phenoplast cast resin processing | 1.47 | 24 | *1.2*[a] | *20*[a] |
| PVC – Anti-oxidant during processing | 0.19 | 3.0 | 0.13 | 2.1 |
| PVC – Plasticiser use | 0.14 | 2.3 | 0.09 | 1.5 |

a This scenario is included for completeness, although no relevant sites discharging to marine waters have been identified (see Section 3.3.1.2)

Table 3.9 PEC values for water (fresh and marine) for thermal paper, PVC additives and anti-oxidant use in plasticiser production

| | Freshwater | | Marine | |
|---|---|---|---|---|
| | $PEC_{water}$ (µg/l) | $PEC_{sed}$ (µg/kg) | $PEC_{marine\_water}$ (µg/l) | $PEC_{marine\_sed}$ (µg/kg) |
| *Production* | | | | |
| BPA 1 | | | 0.01 | 0.16 |
| BPA 2 | 0.032 | 0.53 | | |
| BPA 3 | | | 0.008 | 0.13 |
| BPA 4 | | | 0.006 | 0.11 |
| BPA 5 | | | 0.003 | 0.05 |
| BPA 6 | | | 0.10 | 1.7 |
| *PVC additive package* | | | | |
| Site A1 | | | 0.023 | 0.38 |
| Site A2 | 0.036 | 0.58 | | |
| Site A3 | 0.11 | 1.8 | | |
| Site A4 | 0.044 | 0.71 | | |
| Site A5 | 0.045 | 0.73 | | |
| Site A6 | | | 0.013 | 0.21 |
| Site A7 | | | 0.011 | 0.18 |
| Site A8 | 0.054 | 0.88 | | |
| Site A9 | 0.27 | 4.4 | | |
| Site A10 | 0.032 | 0.52 | | |
| Site A11 | 0.033 | 0.54 | | |
| Site A12 | 0.097 | 1.6 | | |
| Site A13 | | | 0.009 | 0.15 |
| *Anti-oxidant use in plasticiser production* | | | | |
| Specific site | | | 0.005 | 0.08 |
| Generic site | 0.39 | 6.4 | | |
| *Thermal paper recycling* | | | | |
| With deinking | 0.033 | 0.54 | 0.003 | 0.045 |
| Without deinking | 0.033 | 0.54 | 0.003 | 0.046 |

Table 3.10 Estimated maximum concentrations of bisphenol-A from anaerobic degradation of TBBPA in sediment

| Scenario | | | Estimated concentration of tetrabromobisphenol-A in sediment (mg/kg wet wt.) | Estimated maximum concentration of bisphenol-A in sediment (mg/kg wet wt.) |
|---|---|---|---|---|
| Reactive flame retardant use | Manufacture of epoxy and/or polycarbonate resins | | 0.36-0.44 | 0.13-0.16 |
| | Processing of epoxy resins | | $2.7\times10^{-3}$-$4.9\times10^{-3}$ | $1.0\times10^{-3}$-$1.9\times10^{-3}$ |
| Additive flame retardant use | ABS | Compounding | 14.6-17.8 | 5.5-6.7 |
| | | Conversion | 0.66-0.81 | 0.25-0.31 |

The calculations given above make a number of worst case assumptions: all of the TBBPA in aerobic sediment is degraded; the only product is bisphenol-A; there is no degradation or removal of the bisphenol-A formed; degradation of TBBPA is instantaneous. In reality the formation of TBBPA will take place over time and other processes will act on the bisphenol-A formed. A more realistic analysis of the situation has been carried out by EURAS (2006). This approach considers the adsorption/desorption of bisphenol-A and its degradation in water and aerobic sediment, as well as the similar processes for TBBPA. This approach assumes that the bisphenol-A produced is able to desorb to water and be degraded or removed; this would also be necessary for bisphenol-A to be available to have effects. A degradation rate for TBBPA (for conversion to bisphenol-A) equivalent to ready biodegradability was assumed as a worst case (this is four orders of magnitude greater than the degradation rate for TBBPA used in the risk assessment). The concentrations of TBBPA and bisphenol-A estimated using this approach are in Table 3.11. These are considered to be more realistic than the initial estimates and so will be used in the risk characterisation.

Table 3.11 Estimated concentrations of bisphenol-A from anaerobic degradation of TBBPA in sediment (more realistic approach)

| Scenario | | | Estimated concentration of tetrabromobisphenol-A in sediment (mg/kg wet wt.) | Estimated maximum concentration of bisphenol-A in sediment (mg/kg wet wt.) |
|---|---|---|---|---|
| Reactive flame retardant use | Manufacture of epoxy and/or polycarbonate resins | | 0.36-0.44 | $(1.42\text{-}1.95)\times10^{-4}$ |
| | Processing of epoxy resins | | $2.7\times10^{-3}$-$4.9\times10^{-3}$ | $(1.23\text{-}1.7)\times10^{-6}$ |
| Additive flame retardant use | ABS | Compounding | 14.6-17.8 | $(5.75\text{-}7.9)\times10^{-3}$ |
| | | Conversion | 0.66-0.81 | $(2.6\text{-}3.6)\times10^{-4}$ |

The calculations were only performed for the freshwater environment. The estimated concentrations of TBBPA in marine sediments are approximately one order of magnitude below those in freshwater (with one exception). The marine sediment concentrations of bisphenol-A resulting from TBBPA breakdown are therefore expected to be around one order of magnitude lower than those in Table 3.11.

#### 3.1.4.6.3 Measured concentrations

Industry (PlasticsEurope, 2007) have reviewed the available monitoring studies for bisphenol-A. The studies were reviewed for their quality in two ways. Firstly, the completeness of the information reported in the studied was considered (on methods, locations, quality assurance (QA) procedures, etc.). Secondly the quality of the analytical methods and QA, etc., were assessed. Only studies that were considered as reliable or very reliable in both assessments were included in the further analysis. A total of 99 papers were reviewed initially, with 79 retained for the further analysis. The majority of the samples came from 1998 – 2003.

A number of issues arose in combining the data from different studies to categorise different regions, including high numbers of not detected results and different detection limits. A non–parametric method (Kaplan-Meier) was adopted to address these issues. The results of the evaluation are in Table 3.13 (freshwater), Table 3.14 (freshwater sediments), Table 3.15 (marine waters) and Table 3.16 (marine sediments). A summary of the data is presented in Table 3.12.

Table 3.12 Summary of measured levels data for water and sediment

| | Freshwater | Freshwater sediment | Marine water | Marine sediment |
|---|---|---|---|---|
| Observations: | | | | |
| Total number of weighted observations | 848 | 249 | 115 | 67 |
| Number of weighted observations below detection limit | 415 | 75 | 58 | 44 |
| Number of imputed observations[a] | 10 | 65 | 0 | 0 |
| Concentrations: | *(µg/l)* | *(ng/g dw)* | *(µg/l)* | *(ng/g dw)* |
| Median | 0.01 | 16 | 0.0016 | 8.5 |
| Mean | 0.13 | 60 | 0.017 | 75 |
| SD | 1.5 | 134 | 0.052 | 209 |
| 5th percentile | 0.0005 | 0.5 | 0.00005 | 1.1 |
| 95th percentile | 0.35 | 256 | 0.088 | 566 |

a Where individual data points were not available, representative points were imputed from the summary statistics where possible.

Table 3.13 Bisphenol-A concentrations in freshwaters in the EU (all units are µg/l)

| Country | Author | Sample dates(s) | Sample Description | No. of Samples | Minimum Detection Limit | Frequency Detection (%) | Summary Statistics |
|---|---|---|---|---|---|---|---|
| Austria | Sattelberger and Scharf, 1999 | 1998 | 34 locations in 15 rivers | 34 | 0.01 | 9/34 (26%) | Min = <0.01<br>Median = <0.01<br>95th % = 0.0559<br>Max = 0.075 |
| | Paumann and Vetter, 2003; Bursch *et al*., 2004; Hohenblum *et al*., 2004 | 2001-2002 | Monthly samples collected from 24 rivers | 272 | 0.01 | 72/272 (26%) | Min = <0.005<br>Median = <0.005<br>95th % = 0.16<br>Max = 0.6 |
| Belgium | Loos *et al*., 2007 | 2003 | 3 rivers, south of Ghent (Schelde, Molenbeek, Gaverbeek) each sampled upstream and downstream of wastewater discharge | 18 | NA | 16/18 (89%) | Mean of 3 samples at each location, range: 0.003 to 0.055 |
| Czech Republic | Stachel *et al*., 2002; Wiegel *et al*., 2004 | 1999 & 2000 | Elbe River and mouths of its tributaries | 17 | 0.001 | 15/17 (88) | Min = <0.001<br>Median = 0.019<br>95th % = 0.089<br>Max = 0.114 |
| | Umweltbundesamt, 1999 and 2000; secondary reference to Gandrass, 1999 | 1998 | 4 locations (Bilina, Dolni Berkovice, Synthesia, Horenice) | 4 | 0.0003 | 4/4 (100%) | Min = 0.0015<br>Median = 0.0278<br>95th % = 1.10<br>Max = 1.29 |
| Denmark | Umweltbundesamt, 1999 and 2000; secondary reference to Boutrup, *et al*, 1998 | 1998 | 2 locations in Aarhus County | 2 | 0.1 | 0/2 (0%) | < 0.1 |
| | Christiansen *et al*., 2002; secondary reference for Danish reports by Christiansen and Plesner, 2001 and Boutrup and Plesner, 2001 | NA | 2 lakes and 3 streams | NA | 0.001 | NA | Min = < 0.001<br>Max = 0.44 |
| France | Jeannot *et al*., 2002 | NA | Orleans, downstream of wastewater effluent | 1 | 0.0005 | 0/1 (0%) | < 0.0005 |

| Country | Author | Sample dates(s) | Sample Description | No. of Samples | Minimum Detection Limit | Frequency Detection (%) | Summary Statistics |
|---|---|---|---|---|---|---|---|
| Germany | Umweltbundesamt, 1999 and 2000; secondary reference for Gandrass, 1999; Voigt, 1999; Koerner, 1998 | 1998 | River Elbe | 11 | 0.0003 | 11/11 (100%) | Min = 0.0047<br>Median = 0.0127<br>95th % = 0.0369<br>Max = 0.0406 |
| | | 1999 | River Rhine - 7 locations, sampled monthly for 6 months | NA | 0.01 | NA | Mean ranges from <0.01 to 0.08 |
| | Fries and Puettmann, 2002 | 2000-2001 | | NA | 0.020 | NA | Min = < 0.020<br>Mean ranges from 0.051 to 0.084 |
| | Bolz *et al*., 2001 | 1998-1999 | Baden-Wurttemberg - streams and rivers; evaluated the influence of STP discharges on water quality | 23 | 0.050 | NA | Min = <0.050<br>Max = 0.272<br>Median = 0.0721 for water receiving STP discharge; <0.050 with no STP discharge |
| | Kuch and Ballschmiter, 2001 | 2000 | Southern Germany - Danube River, Blau River, Nau River (upstream and downstream of STP effluent discharge), Iller River, Schussen Creek, Laiblach Creek, Argen Creek | 31 | 0.00004 | 31/31 (100%) | Min = 0.0005<br>Median = 0.0038<br>95th % = NA<br>Max = 0.014 |
| | Heemken *et al*., 2000 | 1998 | River Elbe (10 locations) and 4 of its tributaries | 18 | 0.00005 | 18/18 (100) | Min = 0.0089<br>Median = 0.0585<br>95th % = 0.223<br>Max = 0.776 |
| | Stachel *et al*., 2002; Wiegel *et al*., 2004 | 1999-2000 | River Elbe and mouths of its tributaries | 35 | 0.001 | 35/35 (100) | Min = 0.003<br>Median = 0.023<br>95th % = 0.093<br>Max = 0.100 |
| | Wenzel *et al*., 1998; Fromme *et al*., 2002 | 1997 | North Rhine-Westphalia, Rheinland-Pfalz, Brandenburg & Berlin: rivers, lakes and channels. Used 2 methods of analysis: GC-MS and HPLC. | 116 | 0.0001 (GC-MS); 0.002 (HPLC) | 116/116 (100%) (GC--MS); 73/116 (63%) (HPLC) | Min = 0.0005 (GC-MS); <0.002 (HPLC)<br>Max = 0.229 (GC-MS); 0.410 (HPLC) |
| | Fleig, 2000 | NA | River Rhine - 3 locations (Karlsruhe, Mainz, Duesseldorf) | NA | NA | NA | Mean at each site: 0.027, 0.028, 0.033<br>90th % at each site: 0.052, 0.044, 0.050 |
| Italy | Vigano *et al*., 2006 | 2005 | River Po, upstream and 2 locations downstream of confluence of River Lambro; samples collected every other day for 3 weeks | 27 | 0.00333 | 27/27 (100%) | Mean of samples at each location: 0.270, 0.302, 0.494 |

| Country | Author | Sample dates(s) | Sample Description | No. of Samples | Minimum Detection Limit | Frequency Detection (%) | Summary Statistics |
|---|---|---|---|---|---|---|---|
| | Lagana *et al*., 2004 | 2002 | Rome; Tiber River - downstream of wastewater effluent discharge | 7 | 0.0002 | 7/7 (100%) | Min = 0.015 |
| | | | | | | | Median = 0.022 |
| | | | | | | | 95th % = NA |
| | | | | | | | Max = 0.029 |
| | Loos *et al*., 2003 | 2002 | 8 locations in River Seveso and upstream and downstream of 3 STPs near Como | 15 | 0.002 | 3/15 (20%) | Min = <0.002 |
| | | | | | | | Median = <0.002 |
| | | | | | | | 95th % = 0.040 |
| | | | | | | | Max = 0.043 |
| | Loos *et al*., 2007 | 2003 | 2 rivers (Seveso, Lambro) upstream and downstream of wastewater discharge; located in textile industry region | 6 | 0.002 | 5/6 (83%) | Min = <0.002 |
| | | | | | | | Median = 0.053 |
| | | | | | | | 95th % = 0.150 |
| | | | | | | | Max = 0.175 |
| | Patrolecco *et al*., 2004 and 2006 | 2002 & 2003 | Tiber River - upstream and downstream of urban sources, including wastewater from Rome | 5 locations, sampled twice | 0.030 | 9/10 (90) | Min = < 0.030 |
| | | | | | | | Median = 0.080 |
| | | | | | | | 95th% = 0.122 |
| | | | | | | | Max = 0.140 |
| Netherlands | Umweltbundesamt, 1999 and 2000; secondary reference for Belfroid *et al*., 1999 | 1997 | 6 locations (Rhine at Lobith; Maas at Eijsden; Nieuwe Waterweg at Maassluis and Benelux Tunnel; Haringvliet at Haringvlietsluizen; Noordzeekanaal at Ijmuiden) | 12 | NA | 10/12 (83%) | Min = 0.0099 |
| | | | | | | | Median = 0.0355 |
| | | | | | | | 95th % = 0.108 |
| | | | | | | | Max = 0.16 |
| | Belfroid *et al*., 2002 | 1999 | River Dommel, River Meuse (Eysden), Bergermeer Lake | 7 | 0.011l | 2/7 (29%) | Min = <0.011 |
| | | | | | | | Median = < 0.018 |
| | | | | | | | 95th % = 0.16 |
| | | | | | | | Max = 0.17 |
| | Vethaak *et al*., 2002 and 2005 | 1999 | Nationwide monitoring program | 97 | NA | 50/97 (52%) | Min = <0.0088 |
| | | | | | | | Median = 0.018 |
| | | | | | | | 95th % = 0.322 |
| | | | | | | | Max = 1.0 |
| Norway | Pettersen and Fjeld, 2005 | 2005 | Drammen waterway | 2 | 0.010 | 1/2 (50) | Min = <0.010 |
| | | | | | | | Max = 43.0 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Portugal | Azevedo *et al*., 2001 | 1999 | National monitoring program; samples collected monthly for three months at 8 locations - rivers and coastal locations | 24 | 0.002 | 13/24 (54%) | Min = < 0.002 |
| | | | | | | | Median = 0.35 |
| | | | | | | | 95th % = 2.0 |
| | | | | | | | Max = 4.0 |
| | Quiros *et al*., 2005 | 2001-2002 | 10 rivers (from Ponte Nova Barcelos to Esteiro Seixal), sampled monthly from April 2001 to Dec. 2002; summary statistics calculated using the averages for each location | 183 | 0.09 | 132/183 (72%) | Min = <0.01 |
| | | | | | | | Median = 0.10 |
| | | | | | | | 95th % = 0.88 |
| | | | | | | | Max = 0.92 (individual sample max = 5.03) |
| Spain | Brossa *et al*., 2005 | 2001-2002 | Catalonia: Ebre River and irrigation canal of Ebre Delta | 36 | 0.002 | 2/36 (6%) | Min = < 0.002 |
| | | | | | | | Median = < 0.002 |
| | | | | | | | 95th % = 0.004 |
| | | | | | | | Max = 0.02 |
| | del Olmo *et al*., 1997 | NA | Granada: Santa Maria farm spring water | NA | 0.6 | NA | < 0.6 |
| | Gonzalez-Casado *et al*., 1998 | NA | Granada: Loja - river water | 3 | 0.0012 | 0/3 (0%) | <0.0012 |
| | Brossa *et al*., 2002 | NA | Catalonia: Ebro River | NA | 0.01 | NA | < 0.01 |
| | Cespedes *et al*., 2006 | 2001 | Ter River and 2 of its tributaries (9 locations) - receive discharge from STPs | 9 | 0.05 | 0/9 (0%) | < 0.05 |
| | Cespedes *et al*., 2005 | 2001 | Llobregat River Basin - 10 locations, including Anoia and Cardener tributaries | 11 | 0.09 | 7/11 (64%) | Min = < 0.09 |
| | | | | | | | Median = 0.09 |
| | | | | | | | 95th % = 1.91 |
| | | | | | | | Max = 2.97 |
| | Penalver *et al*., 2002 | NA | Ebro River | NA | 0.06 | 0% | < 0.06 |
| | Brossa *et al*., 2004 | NA | Catalonia: river water | 1 | 0.002 | 0/1 (0%) | <0.002 |
| | Petrovic and Barcelo, 2001 | 2000 | Anoia and Cardener rivers - 6 sites, upstream and downstream of STPs | 6 | 0.1 | 0/6 (0%) | <0.1 |
| | Rodriguez-Mozaz, *et al*., 2004 and 2005 | 2002 | Llobregat River - monthly samples tested for 6 months | 6 | 0.0063 | 6/6 (100%) | Min = 0.065 |
| | | | | | | | Median = 0.138 |
| | | | | | | | 95th % = 0.279 |
| | | | | | | | Max = 0.295 |

| Country | Author | Sample dates(s) | Sample Description | No. of Samples | Minimum Detection Limit | Frequency Detection (%) | Summary Statistics |
|---|---|---|---|---|---|---|---|
| Switzerland | Voutsa *et al*., 2006 | 2004 | Glatt River (10 locations; each sampled 3 times) | 30 | 0.007 | 30/30 (100%) | Min = 0.009 |
| | | | | | | | Median = 0.026 |
| | | | | | | | 95th % = 0.058 |
| | | | | | | | Max = 0.076 |
| | Fleig, 2000 | NA | River Rhine at Basel | NA | NA | NA | Mean = 0.010 |
| | | | | | | | 90th % = 0.024 |
| UK | Fawell *et al*., 2001 | 1998 | Severn Trent water: Trent, Severn, and Derwent rivers; Tame/Trent confluence | 8 | 5.1 | 0/8 (0%) | <5.1 |
| | Liu *et al*., 2004b | 2003 | England, river water - East and West Sussex. Upstream, downstream and near sewage outfall (3 locations) | NA | 0.0053 | NA | Min = < 0.0053 |
| | | | | | | | Max = 0.024 |
| | Readman *et al*., 2006 | 2006 | Swindon: River Ray upstream of Rodbourne STP | 1 | 0.0104 | 0/1 (0%) | < 0.0104 |
| | | | Swindon: River Ray downstream of Rodbourne STP (3 locations; max. 8 km downstream) | 3 | 0.0104 | 3/3 (100%) | Min = 0.338 |
| | | | | | | | Median = 0.436 |
| | | | | | | | Max = 0.449 |
| | | | River Ock (reference site) | 1 | 0.0104 | 0/1 (0%) | < 0.0104 |
| | Environment Agency, 2003 | 2003 | 12 locations (each sampled 2 to 5 times); includes Boveney Ditch above Thames; River Aire; River Don; Manchester Ship Canal; River Douglas; River Tame; Sowe River | 42 | 0.013 | 33/42 (79%) | Min = < 0.01 |
| | | | | | | | Median = 0.092 |
| | | | | | | | 95th % = 0.526 |
| | | | | | | | Max = 0.899 |

NOTE:

NA - Not available

STP - Sewage treatment plant

Table 3.14 Bisphenol-A concentrations in freshwater sediments in the EU (all units are ng/g dw unless otherwise stated)

| Country | Author | Sample dates(s) | Sample Description | No. of Samples | Minimum Detection Limit | Frequency Detection (%) | Summary Statistics |
|---|---|---|---|---|---|---|---|
| Czech Republic | Stachel *et al*., 2005 | 2002 | 37 locations along Elbe River and mouths of tributaries after a flood | 37 | 5 | NA | Min = < 5<br>Median = 30<br>Max = 1630 |
| Denmark | Umweltbundesamt, 1999 and 2000; secondary reference to Boutrup, *et al*, 1998 | 1998 | 5 locations in Aarhus County, including residential and agricultural areas | 36 | 2 | NA | Mean of samples at each location, range: < 10 to 150 |
| Germany | Bolz *et al*., 1999 | NA | Baden-Wurttemberg (South Germany): Lake Constance and 2 small streams (Korsch and Sulzbach) | 3 | 10 | 0/3 (0) | < 10 |
| | Bolz *et al*., 2001 | 1996-1999 | Baden-Wurttemberg – streams and rivers; evaluated the influence of STP discharges on water quality | 11 | 0.5 | 9/11 (82) | Min = <0.5<br>Median = 5<br>95th % = 13<br>Max = 15 |
| | Heemken *et al*., 2000 | 1998 | Elbe River (8 locations) and 3 of its tributaries | 11 | 0.5 | 11/11 (100) | Min = 66<br>Median = 132<br>95th % = 311<br>Max = 343 |
| | | 1998-99 | Elbe River – monthly sampling at one location (Schnackenburg) | 12 | 0.5 | 12/12 (100) | Min = 127<br>Median = 211<br>95th% = 288<br>Max = 322 |
| | Stachel *et al*., 2002; Wiegel *et al*., 2004 | 2000 | Elbe River and mouths of its tributaries | 12 | NA | 12/12 (100) | Min = 10<br>Median = 55<br>95th % = 300<br>Max = 379 |
| | | 1998 | Alster River | 2 | NA | 2/2 (100) | Min = 143<br>Max = 192 |
| | | 1996 | Berlin/Brandenburg surface waters | 12 | 0.2 | NA | Min = <0.2<br>Max = 190 |
| | Wenzel *et al*., 1998; Fromme *et al*., 2002 | 1997 | Brandenburg and Berlin – 35 waterways (rivers, lakes, and channels). Used 2 methods of analysis: GC-MS and HPLC. | 35 | 1 (GC-MS); 5 (HPLC) | 30/35 (86%) | Min = 18 (GC-MS); 10 (HPLC)<br>Max = 190 (GC-MS); 150 (HPLC) |

| Country | Author | Sample dates(s) | Sample Description | No. of Samples | Minimum Detection Limit | Frequency Detection (%) | Summary Statistics |
|---|---|---|---|---|---|---|---|
| Italy | Vigano *et al*., 2006 | 2005 | River Po, upstream and 2 locations downstream of confluence of River Lambro | 3 | 3 | 0/3 (0%) | < 3 |
| | Patrolecco *et al*., 2004 and 2006 | 2002 & 2003 | Tiber River - upstream and downstream of urban sources, including wastewater from Rome | 4 locations, sampled twice | 30 | 0/8 (0%) | < 30 |
| Netherlands | Vethaak *et al*., 2002 and 2005 | 1999 | Nationwide monitoring program | 18 | NA | 14/18 (78%) | Min = 0.5 |
| | | | | | | | Median = 2.35 |
| | | | | | | | 95th % = 27 |
| | | | | | | | Max = 43 |
| Norway | Fjeld *et al*., 2004a | 2003 | Landfills or industrially contaminated sites: leachate ponds | 6 | NA | 6/6 (100) | Min = 7.06 |
| | | | | | | | Median = 108.68 |
| | | | | | | | 95th % = 346.33 |
| | | | | | | | Max = 371.16 |
| | | | Lake Mjosa and Lake Losna | 4 | NA | 4/4 (100) | Min = 10.64 |
| | | | | | | | Median = 37.10 |
| | | | | | | | 95th % = 47.88 |
| | | | | | | | Max = 48.04 |
| | | | Drammens River (industrialized area). | 7 | NA | 7/7 (100) | Min = 6.07 |
| | | | | | | | Median = 25.48 |
| | | | | | | | 95th % = 227.65 |
| | | | | | | | Max = 279.8 |
| | Fjeld *et al*., 2004b | 2004 | Lagen and Vorma Rivers (inlet and outlet of Lake Mjosa) | 6 | NA | 6/6 (100) | Min = 9.27 |
| | | | | | | | Median = 27.79 |
| | | | | | | | 95th % = 50.14 |
| | | | | | | | Max = 50.53 |
| | | 2003 | Drammens River (industrialized area) | 1 | NA | 1/1 (100) | 53.14 |
| | Pettersen and Fjeld, 2005 | 2005 | Drammen waterway | 17 | 1 to 5 | 6/17 (35) | Min = <1 |
| | | | | | | | Median = <1 |
| | | | | | | | 95th % = 26 |
| | | | | | | | Max = 62 |
| Spain | Petrovic and Barcelo, 2001 | 2000 | Anoia and Cardener rivers - 6 sites, upstream and downstream of STPs | 6 | 10 | 2/6 (33%) | Min = < 10 |
| | | | | | | | Median = < 10 |
| | | | | | | | 95th % = 34 |
| | | | | | | | Max = 40 |
| Sweden | Hedlund *et al*., 2006 | 2003-2004 | Nationwide monitoring program | 35 | 50 | 3/35 (9%) | Min = <50 |
| | | | | | | | Median = < 50 |
| | | | | | | | 95th % = 83 |

| Country | Author | Sample dates(s) | Sample Description | No. of Samples | Minimum Detection Limit | Frequency Detection (%) | Summary Statistics |
|---|---|---|---|---|---|---|---|
| | | | | | | | Max = 320 |
| UK | Liu *et al*., 2004a | 2003 | England, Sussex Rivers: River Uck, River Ouse; upstream and downstream of sewage outfall (7 locations) | 15 | 3.4 | 8/15 (53%) | Min = <3.4 |
| | | | | | | | Max. not reported; max. ave. = 9; std dev = 2.7 |
| | Centre for Environment, Fisheries and Aquaculture Science (CEFAS) | 1999-2000 | England - national monitoring program (50 locations, upstream and downstream of STP outfalls) | 50 | 1.07 ng/g wet weight | 2/50 (4%) | Min = <1.07 ng/g wet wt |
| | | | | | | | Median = <1.07 ng/g wet wt |
| | | | | | | | 95th % = <1.07 ng/g wet wt |
| | | | | | | | Max = 56.8 ng/g wet wt |

NOTE:

NA - Not available

STP - Sewage treatment plant

Table 3.15 Bisphenol-A concentrations in marine waters in the EU (all units are µg/l)

| Country | Author | Sample dates(s) | Sample Description | No. of Samples | Minimum Detection Limit | Frequency Detection (%) | Summary Statistics |
|---|---|---|---|---|---|---|---|
| Germany | Heemken *et al*. 2000 | 1998-1999 | North Sea (11 locations, sampled twice) | 20 | 0.00005 | 10/20 (50%) | Min = <0.00005<br>Median = 0.00083<br>95th % = 0.0514<br>Max = 0.249 |
| | Beck *et al*., 2005 | 2003-2004 | Baltic Sea (5 locations, sampled twice) | 29 | 0.00004 | 28/29 (97%) | Min = <0.00004<br>Max = 0.0057<br>Mean at each location: 0.00022 to 0.0054 |
| | Stachel *et al*., 2002; Wiegel *et al*., 2004 | 2000 | Elbe River (mouth) | 1 | 0.001 | 1/1 (100%) | 0.0038 |
| Italy | Famiglini *et al*., 2005 | NA | Adriatic Coast (middle-western) - near shore and mouths of rivers and canals | 20 | 0.0032 | 2/20 (10%) | Min = < 0.0032<br>Median = < 0.0032<br>95th % = 0.074<br>Max = 0.0845 |
| | Pojana *et al*., 2004a | 2001-2002 | Venice Lagoon - 2 locations near the historical centre and 1 location near the industrial area; bimonthly samples collected for 10 months | 15 | 0.001 | 14/15 (93%) | Min = <0.001<br>Mean at each location: 0.010, 0.0045, 0.0044<br>Max = 0.030 |
| | Pojana *et al*., 2004b | 2001-2002 | Venice Lagoon - 25 locations sampled 4 times | NA | 0.001 | NA | Min = <0.001<br>Max = 0.066 |
| Netherlands | Umweltbundesamt, 1999 and 2000; secondary reference for Belfroid *et al*., 1999 | 1997 | 5 locations (Zeehavenkanaal at Delfzijl; Westerschelde at Hansweert and Terneuzen; Kanaal Gent-Terneuzen; Oosterschelde Oesterput) | 5 | NA | 5/5 (100%) | Min = 0.0035<br>Median = 0.0038<br>95th % = 0.019<br>Max = 0.023 |
| | Belfroid *et al*., 2002 | 1999 | Wadden Sea (Bocht van Wattum, Dantziggat, and Den Oever) | 10 | 0.01 | 5/10 (50%) | Min = <0.01<br>Median = 0.016<br>95th % = 0.33<br>Max = 0.33 |

| Country | Author | Sample dates(s) | Sample Description | No. of Samples | Minimum Detection Limit | Frequency Detection (%) | Summary Statistics |
|---|---|---|---|---|---|---|---|
| Spain | del Olmo *et al*., 1997 | NA | Malaga - sea water | NA | 0.6 | 0% | < 0.6 |
| | Brossa *et al*., 2005 | 2001-2002 | Catalonia: industrial port of Tarragona | 12 | 0.002 | 2/12 (17%) | Min = < 0.002 |
| | | | | | | | Median = < 0.002 |
| | | | | | | | 95th % = 0.015 |
| | | | | | | | Max = 0.02 |
| | Gonzalez-Casado *et al*., 1998 | NA | Granada: Motril - sea water | 3 | 0.0012 | 0/3 (0%) | <0.0012 |
| | Brossa *et al*., 2004 | NA | Catalonia: industrial port of Tarragona | 1 | 0.002 | 0/1 (0%) | <0.002 |
| | Petrovic and Barcelo, 2001 | NA | Barcelona, Almeria, Tarragona - 14 sites near outfalls of industrial plants and municipal wastewater discharges | 10 | 0.1 | 0/10 (0%) | <0.1 |

NOTE:

NA - Not available

STP - Sewage treatment plant

Table 3.16 Bisphenol-A concentrations in marine sediments in the EU (all units are ng/g dw)

| Country | Author | Sample dates(s) | Sample Description | No. of Samples | Minimum Detection Limit | Frequency Detection (%) | Summary Statistics |
|---|---|---|---|---|---|---|---|
| Denmark | Umweltbundesamt, 1999 and 2000; secondary reference to Boutrup, *et al*, 1998 | 1998 | Aarhus County; 2 locations | 10 | 2 | NA | Mean at each location: < 2 and 13 ng/g |
| Norway | Fjeld *et al*. 2004a | 2003 | Norwegian coast from near Russian border to the outer Oslofjord | 12 | NA | 12/12 (100%) | Min = 0.01 |
| | | | | | | | Median = 89.13 |
| | | | | | | | 95th % = 448.0 |
| | | | | | | | Max = 623.38 |
| | Fjeld *et al*., 2004b | 2003 | Drammersfjord | 1 | NA | 1/1 (100%) | 51.05 |
| Spain | Petrovic and Barcelo, 2001 | NA | Barcelona, Almeria, Tarragona - 14 sites near outfalls of industrial plants and municipal wastewater discharges | 14 | 10 | 0/14 (0%) | < 10 |
| | Morales-Munoz *et al*., 2005a and 2005b | NA | Aguadulce (near Almeria) - composite sample collected near outfall of an urban STP; used 2 different extraction methods | 1 | 0.2 | 1/1 (100%) | Mean = 19.6 |
| Sweden | Hedlund *et al*., 2006 | 2003-2004 | Nationwide monitoring program; 10 locations | 14 | 50 | 0/14 (0%) | <50 |
| UK | Kelly *et al*., 2006 | NA | National monitoring program; 22 locations near urban or industrial areas (includes Tees River, Tyne River, Belfast Lough, Burbo Bight, River Dee) | 22 | 10 | 6/22 (27%) | Min = < 10 |
| | | | | | | | Median = < 10 |
| | | | | | | | 95th % = 1030 |
| | | | | | | | Max = 1140 |

NOTE:

NA - Not available

STP - Sewage treatment plant

#### 3.1.4.6.4 Comparison of measured and calculated levels

In general it is not possible to assign the measured values to a corresponding calculated value, either by specific use or by scale. The measured values are considered to provide a good picture of the bisphenol-A levels in industrial/urban areas and can be considered as a mixture of local and regional concentrations. Hence only a general comparison is possible.

For freshwater, the calculated values fall within the range of the 95%ile or maximum values from the measurements. The calculated regional concentration falls toward the lower end of the range of 95%ile values. The calculated regional PEC value of 34 ng/l is higher than the median value from the whole freshwater data set, 10 ng/l, but is just below the 75%ile value from the data set, 42 ng/l.

For freshwater sediment, the measured values are reported as dry weight, so need to be reduced by a factor of 2.6 to be on the same wet weight basis as the calculated values (using the standard water content of sediment in the TGD). The highest of the 95%iles from the measured values are above the range of calculated values. The higher calculated values are similar to the middle of the range of measured levels, 10-20 µg/kg wwt (25-50 ng/g dwt).

The amount of measured data for marine waters is more limited, but covers a similar range to the calculated values, the highest calculated values being a little above the highest measured levels reported. Measured and calculated levels for marine sediment also cover largely similar ranges (after adjusting to the same basis as above). The highest measured values are somewhat above the highest calculated levels, and the lowest calculated level (the regional background) is below the range of measurements.

Overall the calculated and measured values are comparable. There are some exceptions, but these cannot be related to specific situations. Therefore the risk assessment will be based on the calculated values.

### 3.1.4.7 PEC values - terrestrial

PEC values for the terrestrial compartment have been calculated using EUSES 2.0.3. The only significant route to the terrestrial environment is through the application of sewage sludge. As in the published assessment, values have not been calculated for most of the site-specific scenarios, as the information obtained indicates that disposal of the sludge from many of these is either by incineration or as controlled waste to landfill[10]. Where there is no specific information then a calculation has been performed, but this does not necessarily mean that sludge from the site is actually applied to land. Sites with no on-site biological treatment that do not release to an off-site treatment plant are also excluded.

The resulting PEC values are in Table 3.17.

[10] A calculation for one epoxy resin site (ER4) with sludge application was included in the published assessment. Information provided for this update shows that sludge from this site is no longer applied to land. There is therefore no sludge application related to epoxy resin production and this scenario has been deleted from the terrestrial assessment.

Table 3.17 PEC values for the terrestrial compartment (agricultural soil at 30 days)

| | PEC (µg/kg wwt) |
|---|---|
| *Site specific* | |
| PVC additive package: A2 | 1.43 |
| A3 | 0.86 |
| A4 | 1.38 |
| A6 | 3.46 |
| A8 | 0.77 |
| A13 | 0.07 |
| *Generic scenarios* | |
| Phenoplast cast resin processing | 20 |
| PVC – anti-oxidant during processing | 2.2 |
| PVC – plasticiser use | 1.6 |
| Anti-oxidant in plasticiser production | 5.0 |
| Thermal paper recycling with deinking | 633 (p); 1.4 (b); 534 (c) |
| Thermal paper recycling without deinking | 35 (p); 1.7 (b); 29 (c) |

p Paper sludge;

b Biological sludge;

c Combined paper and biological sludges (in ratio produced)

Note that these PECs are calculated using the usual TGD method, i.e. sludge is assumed to be applied once per year for 10 years, and the PEC represents the situation 30 days after the final application. In this case, the bisphenol-A concentration is effectively zero after one year, so the PEC is equivalent to the concentration 30 days after an initial application of sludge. However, the $PNEC_{soil}$ is derived from toxicity data based on the initial concentrations of bisphenol-A applied to soil (see Section 3.2.3.1). The concentrations in soil for the risk characterisation must therefore also be expressed on the same basis. This is considered further in Section 3.3.2.

#### 3.1.4.7.1 Thermal paper recycling

Some specific considerations in relation to thermal paper recycling are included here.

*Concentrations in sludges from sites with de-inking*

From paper treatment, 5.5 tonnes of sludge are produced per day. A total bisphenol-A content of 3.28 kg gives a sludge concentration of 597 mg/kg dry weight (dwt).

From biological treatment, 1,022 kg of sludge are produced per day. A total bisphenol-A content of 1.4 g gives a sludge concentration of 1.4 mg/kg dwt.

If sludges are mixed in the proportions in which they are produced, then the mixed sludge concentration is 504 mg/kg dwt.

The bisphenol-A concentrations in soil at 30 days after application of these sludges[11] (using the TGD method, with input from air neglected) is as follows:

- paper sludge: 633 µg/kg wet weight (wwt)
- biological sludge: 1.5 µg/kg wwt
- combined: 534 µg/kg wwt.

For comparison, if the paper sludge production rate at the site were 200 kg/tonne, then the combined sludge concentration would be 66 mg/kg, and the resulting soil concentration would be 70 mg/kg wwt.

Sludges from the thermal paper broke recycling sites are assumed to be incinerated. There are no data on levels in sludge from these sites at the moment.

*Concentrations in sludges from non-deinking sites*

From paper treatment, 5.5 tonnes of sludge are produced per day. A total bisphenol-A content of 0.18 kg gives a sludge concentration of 33 mg/kg dwt.

From biological treatment, 1,022 kg of sludge are produced per day. A total bisphenol-A content of 1.76 g gives a sludge concentration of 1.7 mg/kg dwt.

If sludges are mixed in the proportions in which they are produced, then the mixed sludge concentration is 28 mg/kg dwt.

The bisphenol-A concentrations in soil at 30 days after application of these sludges[11] (using the TGD method, with input from air neglected) is as follows:

- paper sludge: 35 µg/kg wwt
- biological sludge: 1.8 µg/kg wwt
- combined: 29 µg/kg wwt.

For comparison the measured concentrations in the paper sludge and biological sludge from the actual site producing corrugated packaging were 12 mg/kg and 5.5 mg/kg respectively. Combining the two sludges gives a calculated concentration of 8.1 mg/kg. The resulting soil concentrations would be 13 µg/kg wwt (paper sludge), 5.9 µg/kg (biological sludge) and 8.6 µg/kg (combined). These figures are broadly in line with the generic calculation, but note that in reality these sludges are incinerated at the site.

#### 3.1.4.7.2 Bisphenol-A in sludge from the degradation of TBBPA

A further possible exposure route for the soil compartment is the degradation of TBBPA during anaerobic wastewater treatment processes, in particular anaerobic sludge digestion[12]. If this did occur, then it is possible that the bisphenol-A formed would be applied to agricultural land with

[11] As bisphenol-A is readily biodegradable there is no residual substance in soil from previous applications.

[12] Anaerobic digestion of sewage sludge is carried out at elevated temperatures (e.g. 35-37°C (mesophilic digestors) or 55°C (thermophilic digesters)) and the residence time of sludge within the system is usually in the range 10-20 days but can be longer).

the digested sludge. The available experimental evidence on this is discussed in the TBBPA risk assessment (ECB, 2007) and is conflicting. A recent study has shown that TBBPA can be degraded to bisphenol-A by anaerobic sewage sludge when incubated at 35°C, but the rate of degradation was relatively slow, for example the half-life for the initial loss of TBBPA from the system was around 19 days, and total yield of bisphenol-A was around 48% after 120 days. However much more rapid disappearance of TBBPA has been demonstrated in a test system using digested sewage sludge (the half-life for degradation of tetrabromobisphenol-A was reported to be 0.59 days) but this study has not yet been fully validated. In contrast to this, a further (unpublished) study has reported little or no degradation of TBBPA in bench-scale reactor systems based on the contact anaerobic process and the conventional aerobic activated sludge process.

A rough estimate has been made of the maximum possible concentration of bisphenol-A that would be present in soil if it was formed from TBBPA during sludge digestion. The concentrations of TBBPA in sludge are taken from the TBBPA risk assessment. The calculation assumes that all the TBBPA present in sludge is converted to bisphenol-A on a molar basis, and that when the sludge is applied to agricultural soil, bisphenol-A will be susceptible to biodegradation in the aerobic conditions present. The resulting concentrations in soil have been estimated with EUSES and are shown in Table 3.18. These figures are speculative, as it is not certain that this reaction occurs during anaerobic sludge digestion, and the calculations do not take into account the rate of the reaction.

#### 3.1.4.7.3 Measured levels

No information on measured levels in soil was available for the published risk assessment and no new information has been located. Limited data on measured levels in sewage sludge were included in the published assessment and showed values which were around three orders of magnitude lower than those calculated; the values calculated for this addendum are similar to those calculated for the published assessment and so are also higher than the available measurements.

### 3.1.4.8 PEC values - Secondary poisoning

EUSES 2.0.3 has been used to calculate concentrations of bisphenol-A in freshwater fish and earthworms. For the site specific calculations, the site with the highest emission to the appropriate compartment (water or soil) has been used as the basis for the calculations. Concentrations in worms are only calculated for those uses with releases to soil via sludge, as in Section 3.1.4.7. The results are in Table 3.19.

Table 3.18 Estimated maximum concentrations of bisphenol-A in soil that could potentially result from application of sewage sludge from TBBPA processes

| Scenario | | | Estimated concentration of TBBPA in sewage sludge (mg/kg dry weight) | Estimated maximum concentration of bisphenol-A | |
|---|---|---|---|---|---|
| | | | | in sewage sludge (mg/kg dry wt.) | in agricultural soil (30-day average) (mg/kg wet wt.) |
| Reactive flame retardant use | Manufacture of epoxy and/or polycarbonate resins | | 28-30 (sludge from the eight major brominated epoxy resin companies in the EU is not applied to agricultural land) | 12.6 | 0.013 |
| | Processing of epoxy resins | | 0.052-0.056 | 0.024 | $2.5\times10^{-5}$ |
| Additive flame retardant use | ABS | Compounding | $1.13\times10^{3}$-$1.22\times10^{3}$ | 512 | 0.54 |
| | | Conversion | 51.6-55.5 | 23.3 | 0.025 |

Table 3.19 PECs for secondary poisoning

| | PEC in freshwater fish for predators (µg/kg) | PEC in worms for predators (µg/kg) |
|---|---|---|
| *Site specific* | | |
| Bisphenol-A production (BPA 2) | 2.2 | - |
| Epoxy resin (ER 4) | 29 | - |
| Thermal paper production (PAPER 6) | 28 | - |
| PVC additive package (A6) | 8.9 | 1.6 |
| *Generic scenarios* | | |
| Polycarbonate bottle washing | 2.2 | - |
| Phenoplast cast resin processing | 35 | 7.8 |
| PVC – anti-oxidant during processing | 5.7 | 1.2 |
| PVC – plasticiser use | 4.7 | 0.92 |
| Anti-oxidant use in plasticiser production | 11 | 2.2 |
| Thermal paper recycling with deinking | 2.2 | 237 (p); 0.84 (b); 200 (c) |
| Thermal paper recycling without deinking | 2.2 | 13 (p); 0.98 (b); 12 (c) |

p Paper sludge;

b Biological sludge;

c Combined paper and biological sludges (in ratio produced)

For those scenarios with possible releases to the marine environment, concentrations for exposure of predators and top predators have also been calculated, and are included in Table 3.20. For production, only the highest PEC is presented.

Table 3.20 PECs for secondary poisoning for marine predators

| | PEC in food for marine predators (µg/kg) | PEC in food for marine top predators (µg/kg) |
|---|---|---|
| *Site specific* | | |
| Bisphenol-A production (BPA 6) | 3.5 | 0.85 |
| PVC additive package (A1) | 0.72 | 0.29 |
| *Generic scenarios* | | |
| Polycarbonate bottle washing | 0.2 | 0.2 |
| Phenoplast cast resin processing | *28*[a] | *5.8*[a] |
| PVC – anti-oxidant during processing | 3.2 | 0.77 |
| PVC – plasticiser use | 2.3 | 0.6 |
| Anti-oxidant use in plasticiser production | 7.1 | 1.6 |
| Thermal paper recycling with deinking | 0.2 | 0.2 |
| Thermal paper recycling without deinking | 0.2 | 0.2 |

a This scenario is included for completeness, although no relevant sites discharging to marine waters have been identified (see Section 3.3.1.2)

#### 3.1.4.8.1 Measured levels in biota

There is a limited amount of data on levels of bisphenol-A in biota. Belfroid *et al.* (2002) reported levels of bisphenol-A in fish from the Netherlands. Fish were taken from seven locations, both freshwater and marine. The fish species sampled were bream (*Abramis brama*) and flounder (*Platichthys flesus*). The range of concentrations measured was 2 to 75 ng/g dry weight in liver samples, and 1 to 11 ng/g dry weight in muscle samples. These are based on pooled fish samples.

In addition to the fish data reported by Belfroid *et al.* (2002), Vethaak *et al.* (2002) included data on levels in freshwater mussels (*Dreissena polymorpha*) and saltwater mussels (*Mytilus edulis*). These were sampled at locations where higher concentrations of bisphenol-A had been found in the water. In freshwater mussels the concentrations (at two sites) were 0.22 and 0.36 ng/g wet weight; in saltwater mussels (three sites) levels were 0.26 – 1.8 ng/g.

Fjeld *et al.* (2004a) report the results of a screening study in Norway for a range of substances, including bisphenol-A. Sampling for the study took place largely in 2003. Samples were taken from a variety of locations, including lakes and associated rivers, a fjord and its associated river and coastal marine sites (harbours, a contaminated site and open waters). Biota was sampled at a subset of these sampling sites. The bisphenol-A concentration measured in freshwater fish are summarised in Table 3.21.

Table 3.21 Concentrations of bisphenol-A in freshwater fish in Norway

| Location | n | Concentration (ng/g) | | | |
|---|---|---|---|---|---|
| | | wet weight | | Lipid | |
| | | min | max | min | max |
| Lake Mjøsa (whole fish) | 5 | 1.4 | 13.7 | 58 | 466 |
| Lake Vorma (muscle) | 2 | 6.1 | 10.4 | 201 | 1,350 |
| Lake Øyeren (whole fish) | 2 | 1.0 | 1.2 | 32.9 | 74.5 |
| Inner Drammensfjord (brackish water, muscle) | 4 | 1.9 | 14.1 | 24.6 | 407.8 |

n Number of samples

In the marine samples (cod liver), bisphenol-A was not detected (at 2-4 ng/g wet weight) in four samples, and was measured at 7 and 62 ng/g wwt in two other samples.

Fjeld *et al.* (2004b) reported further measurements on concentrations in fish from the Drammensfjord, Norway. The levels of bisphenol-A in the fish samples varied between 0.61–13,73 ng/g wwt, lowest in the muscle sample from ide (*Leuciscus idus*) from 1998 and highest in the liver sample from flounder (*Platichthys flesus*) from 2004.

Levels of bisphenol-A in biota from Germany have also been reported (Fraunhofer, 1999). The majority of the samples were collected between 1990 and 1996. The values found in freshwater organisms were: bream (*Abramis brama*) muscle <1-3.3 µg/kg; and zebra mussel (*Dreissena polymorpha*) 1-5.3 µg/kg; and for marine samples: eel pout (*Zoarces viviparus*) muscle <1-3.3 µg/kg; blue mussels (*Mytilus edulis*) <1-1.3 µg/kg; and brown algae (*Fucus vesiculosus*) <1-2.8 µg/kg.

#### 3.1.4.8.2 Comparison with calculated values

The measured values are of the same order of magnitude as the calculated concentrations in fish for the secondary poisoning scenario, and cover a similar range when considering the whole fish values (the calculated values are for whole fish). Individual values are higher, in particular for specific tissues. The data are not extensive, and it is not possible to allocate the measured data directly to either a local or a regional situation. The calculated values are therefore used in the risk characterisation, supported by the measured values.

## 3.2 ENVIRONMENTAL EFFECTS

### 3.2.1 Aquatic compartment

This section is a complete reformat and update of the aquatic effects sections presented in EC (2003). Given the rapid biodegradability of bisphenol-A in aquatic systems, studies that do not involve confirmation of exposure concentrations are of limited usefulness for PNEC derivation, especially over longer durations (since the concentration that causes any observed effect cannot be established; this is particularly the case for static tests). Nevertheless, such studies may still be considered qualitatively.

#### 3.2.1.1 Micro-organisms

##### 3.2.1.1.1 Toxicity data

Experiments have been performed with two *Pseudomonas* species, and these are summarised below.

1. Dow (1988) report the determination of an acute bacterial toxicity test carried out using bisphenol-A. The test was performed to good laboratory practice guidelines. Cultures of *Pseudomonas putida* from an agar-solidified medium were added to culture vessels and incubated at 25°C for 18 hours with bisphenol-A. The growth rate of the bacteria was measured by turbidimetry. The highest concentration tested was 320 mg/l, and at this concentration no inhibition of cell growth was observed. (Note that this concentration is slightly above the water solubility of 300 mg/l.)
2. Stone and Watkinson (1983) conducted a growth inhibition test on *P. fluorescens* as part of their studies on bisphenol-A biodegradation. They reported an $IC_{50}$ of 54.5 mg/l for the inhibition of the growth of *P. fluorescens* by bisphenol-A.

Data on micro-organisms are not usually included in a species sensitivity distribution to protect the freshwater compartment. No data were found on the effects of bisphenol-A on saltwater micro-organisms.

##### 3.2.1.1.2 PNEC derivation for WWTP microorganisms

The TGD indicates that tests with *P. fluorescens* should not be used to determine the $PNEC_{WWTP}$ because it uses glucose as a substrate. Results of a cell multiplication test with *Pseudomonas putida* may be used with care. For *P. putida* a NOEC based on cell growth of ≥320 mg/l is reported. This is not a true NOEC since it is the highest concentration used in the test and no effects were observed at this concentration. However, in the absence of any other data this value will be used as the NOEC for the derivation of a PNEC for microorganisms. For a NOEC from a specific population the $PNEC_{WWTP}$ is set equal to the NOEC value. Therefore the $PNEC_{WWTP}$ for bisphenol-A is taken as 320 mg/l.

#### 3.2.1.2 Primary producers

##### 3.2.1.2.1 Freshwater primary producers

Experiments have been performed with one algal and one higher plant species, and these are summarised below.

1. Alexander *et al*. (1985b, 1988) report 96-hour $EC_{50}$ values, based upon cell count and total cell volume of 2.73 mg/l and 3.10 mg/l respectively for the green alga *Pseudokirchneriella subcapitata* (previously known as *Selenastrum capricornutum*). Both of the test results are based upon changes in biomass. In addition to the $EC_{50}$ values reported, the percentage inhibition of cell count and cell volume is reported for the concentrations tested. From these data it is possible to derive an $EC_{10}$ using probit analysis. The calculated 96-hour $EC_{10}$ values

are 1.36 mg/l based upon cell count and 1.68 mg/l based upon cell volume. The test report describes the test methods and test concentrations were measured.

Stephenson (1983) reports a 96-hour $EC_{50}$ of 2.5 mg/l, based upon cell count, for *Ps. subcapitata*. The test report describes the test method used, but does not give details of the test conditions. The test concentration is based upon nominal concentrations. This result supports the data reported by Alexander *et al*. (1985b).

For algae studies it is generally accepted that a 72-hour (or longer) NOEC value can be considered as a chronic result. The TGD indicates that if a long-term NOEC is not available then an $EC_{10}$ obtained by extrapolation using appropriate statistics, such as probit analysis, can be considered as if it were a NOEC.

| |
|---|
| In summary, the 96-h $EC_{10}$ of 1.36 mg/l for *Ps. subcapitata* is considered valid for use in the PNEC derivation and SSD. |

1. Putt (2003) reports a 7-d frond density, biomass and growth rate NOEC of 7.8 mg/l for the duckweed *Lemna gibba*. The static-renewal study was performed to GLP according to OECD Guideline 221 and analytical measurement of bisphenol-A showed that test concentrations remained between 79-100% of nominal. The test report describes the test methods and test concentrations.

| |
|---|
| The 7-d NOEC of 7.8 mg/l for *L. gibba* is considered valid for use in the PNEC derivation and SSD. |

#### 3.2.1.2.2 Saltwater primary producers

Experiments have been performed for two algal species, and these are summarised below.

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

| |
|---|
| The 96-h $EC_{10}$ of 0.40 mg/l for *S. costatum* is considered valid for use in the derivation of a saltwater PNEC if required. |

1. Ishii *et al*. (2003) report a study in which the marine microalga *Nannochloropsis oculata* (ST-3 strain) was exposed to bisphenol-A for more than 15 days. The paper is in Japanese and a translation is currently unavailable, so experimental details could not be determined (and its suitability for PNEC derivation is unknown). However, the abstract, figures and tables are in English and show that there were no effects over 12 days at concentrations up to 3 mg/l, but substantial effects occurred after 1-3 days at concentrations at 6 mg/l and above. Figures in the paper show that exponential growth occurred over a period of about seven days in this study, so the effects occurred during the exponential growth phase.

#### 3.2.1.3 Invertebrates

Many species have been studied, and these are grouped below in taxonomic sequence.

##### 3.2.1.3.1 Freshwater invertebrates

Sponges (Poriferans)

Hill *et al*. (2002) exposed individual gemmules of the freshwater sponges *Heteromyenia* sp. and *Eunapius* sp. to bisphenol-A for nine days in 24-well tissue culture plates with renewal of test medium every 2-3 days. The highest test concentration (160 mg/l) was chemically analysed. The growth of *Heteromyenia* was significantly reduced at 16 mg/l, with no significant effects at 1.6 mg/l. The authors report that there was a similar response in *Eunapius*, but no statistical tests were performed due to small sample sizes. The precise amount of bisphenol-A to which the sponges were exposed for three days between renewals is unknown. However, due to the general robustness of the design (five replicates per treatment, frequent renewal of test solutions), this study is classed as "valid with restriction".

| |
|---|
| The 9-d growth NOEC of 1.6 mg/l for *Heteromyenia* sp. is considered valid for use in the PNEC derivation and SSD. |

Hydra

Experiments have been performed for two *Hydra* species, and these are summarised below.

1. The effects of bisphenol-A on the cnidarian *Hydra vulgaris* have been studied by Pascoe *et al*. (2002). Chemical analysis of test concentrations was performed, and polyp survival, structure, regeneration and mortality were monitored over 96 hours. The 96-h $LC_{50}$ was 6.9 mg/l. The structure and physiology of polyps (considered to be a growth-related end point for the purposes of this assessment) was adversely affected at concentrations greater than 42 µg/l over 6 weeks, and a concentration-dependent inhibition of regeneration was seen above 460 µg/l. The effect levels for 17α-ethinylestradiol were similar to those of bisphenol-A. The authors concluded that the signalling processes responsible for control and regulation of cell movement and differentiation during normal development, regeneration and sexual reproduction were not disrupted by either of the chemicals at low concentrations.

| |
|---|
| The 6-week polyp structure NOEC of 42 µg/l for *H. vulgaris* is considered valid for use in the PNEC derivation and SSD. |

1. The reproductive effects of bisphenol-A on another cnidarian, *H. oligactis*, were studied by Fukuhori *et al*. (2005). Mature polyps were exposed individually in 5 ml of medium for 35 days (males) or 50 days (females) to study effects on sexual reproduction, with renewal of test medium on the 12$^{th}$, 24$^{th}$ and 36$^{th}$ days. The incidence and number of gonads (testes or eggs) in each polyp were counted at the end of the experiment. Male polyps were also exposed in a separate treatment to examine asexual reproduction, with medium renewal three times a week. The number of buds detached from each parent polyp was recorded at the end of the 35-day asexual study. Concentrations of bisphenol-A were analysed in stock solutions at the start of both experiments only. Testis formation was unaffected at 0.5 mg/l but declined significantly and dose-dependently at 1-4 mg/l in unfed males exposed at 10$^{o}$C. However, males that were fed during the study showed significant effects (25-30% reduction) on the number of testes at the lowest test concentrations of 0.5 and 1 mg/l, with no differences at higher test concentrations of 2 and 3 mg/l, but complete inhibition at 4 mg/l. In

starved females, a significant decline in egg production began at 2 mg/l, with a substantial albeit non-significant reduction at 1 mg/l, and no effects at 0.5 mg/l. Results for fed females were not reported in this study. In the group of male polyps used to examine asexual budding, there were no effects at 0.5 mg/l, stimulation of budding occurred at 1 mg/l and a suppression of budding occurred at 2-4 mg/l when animals were exposed at 20°C. When exposure was at 10°C, there was stimulation of budding at both 0.5 and 1 mg/l. These effects at different temperatures could be explained by greater uptake of bisphenol-A at 10°C, which analysis of radiolabelled bisphenol-A showed was 1.4 times higher than at 20°C. The lowest test concentration of 0.5 mg/l elicited a response in some endpoints. Since this response was between 20-30% of the control, a NOEC could be derived by dividing this value by a factor of 3 (i.e., 0.5/3 = 0.17 mg/l), as has been done in some ESR assessments, e.g. for zinc. This study is not used for estimating a PNEC because test solutions were not analysed as frequently, the level of replication was lower, and the final result was less sensitive than in the Pascoe *et al*. (2002) study.

Nematodes

Kohra *et al*. (2002a) exposed young nematode worms *Caenorhabditis elegans* to bisphenol-A in agar plates. On transfer to clean plates the movement of worms to a food source was monitored. Both levels of exposure (10 µM and 0.1 µM) resulted in a reduction in the number of worms reaching the food source after time periods of up to 24 hours. A similar level of effect was seen in both exposures. Kohra *et al*. (2002b) also reported that the respiration of *C. elegans* declined when exposed to 0.1 and 10 µM bisphenol-A in agar. The results cannot be used to derive a no-effect level, and the exposure conditions cannot be easily related to the environment.

Several similar studies with *C. elegans* have been reported in which nematodes were exposed to bisphenol-A incorporated into agar. Ji *et al*. (2004) exposed different strains to 70, 80 and 90 mM of bisphenol-A in agar plates to investigate resistant mutants, and Watanabe *et al*. (2005) reports on studies with a mutant *C. elegans* strain that is particularly sensitive to bisphenol-A and could be used as a sensitive screening assay. Hoshi *et al*. (2003) found a significant increase in the relative percentage of *C. elegans* germ cells when they were exposed to $\geq 10^{-9}$ M bisphenol-A in agar for six days, with no effects at $10^{-10}$ M. Tominaga *et al*. (2003) exposed *C. elegans* to bisphenol-A on agar plates over four generations and found sublethal effects on fourth generation abundance at 1 nM. Once again, none of these results can be used to derive a no-effect level because the exposure conditions cannot be related to environmental concentrations. However, the results do show that multigenerational effects may occur at concentrations much lower than the $LC_{50}$ from a short-term test.

Rotifers

A 48-hour test was performed with the rotifer *Brachionus calyciflorus* to determine the effects of bisphenol-A on the intrinsic rate of population increase (Springborn Smithers, 2006a). Chemical concentrations were analysed in replicates at the start and end of the exposure period and were in close agreement (95-97%) with nominal concentrations. The NOEC was 1.8 mg/l based on measured concentrations. This study was performed to GLP and is fully reported.

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| The 48-h reproduction NOEC of 1.8 mg/l for *B. calyciflorus* is considered valid for use in the PNEC derivation and SSD. |

Molluscs

Experiments have been performed with two species, and these are summarised below.

1 *Marisa cornuarietis*

Three groups of experiments have been performed on the ramshorn snail *Marisa cornuarietis* (a tropical species of prosobranch snail, not found in Europe).

a) Studies of Oehlmann and co-workers

*First test series*: Oehlmann *et al*. (2000), Schulte-Oehlmann *et al*. (2001) and Oehlmann *et al*. (2001) report the effect of bisphenol-A on *M. cornuarietis*. Adults were exposed to nominal concentrations of bisphenol-A (1, 5, 25, and 100 µg/l) under semi-static laboratory conditions (with renewal every 24 hours) for five months and in a complete life-cycle test for 12 months. Both experiments included a solvent control, and were carried out at 22ºC. No analysis of the exposure solutions was carried out in these experiments. In both experiments a complex number of alterations referred to as "superfeminisation" occurred. Effects included the enlargement of the accessory pallial sex glands, gross malformations of the pallial oviduct section resulting in an increased female mortality, and a massive stimulation of oocyte and spawning mass production. These effects were statistically significant at each test concentration when compared to the control, and were concentration dependent with the exception of mortality, which was virtually the same in all four bisphenol-A exposure groups (13.3-15.7% compared to control mortality of 3.8%). The cumulative numbers of eggs and the cumulative number of egg masses increased with increasing bisphenol-A concentrations. The hatching success of eggs from the organisms in the five-month experiment (used to start the life cycle test) was not affected by exposure to bisphenol-A.

*Second test series*: Schulte-Oehlmann *et al*. (2001) and Oehlmann (2001) also report a further experiment using lower bisphenol-A concentrations. The same semi-static exposure system was used, and the duration of exposure was 180 days. The nominal exposure concentrations were 0.05-1.0 µg/l, and the concentrations were checked by analysis following sampling on three occasions. The initial concentrations in the exposures were close to the nominal values. Observations over the 24-hour period between the changes of solution showed that the concentration of bisphenol-A decreased with time. After two months of the experiment, the half-life of bisphenol-A in the exposure solutions was around six hours. After four months the half-life had decreased to two hours and a similar value was found after six months. The concentrations were measured at 2-hour intervals; these were used to calculate average exposure concentrations over a 24-hour period as a time-weighted average. The detection limit was 30 ng/l.

The phenomenon of superfeminisation was again observed in all of the treated groups (with the exception of the 0.05 µg/l (nominal) group). The incidence was at a lower level than in the high concentration experiment (although the level of incidence in the one concentration common to both studies, 1 µg/l, was the same). Mortality was not significantly enhanced in any of the bisphenol-A groups in comparison to the controls. Egg production was also stimulated as in the previous experiment, although the results over the whole 180-day exposure period showed a significant increase only at the two highest concentrations. The authors observe that the exposure period in this second experiment included the season of the year (October to February) when spawning activity in this population of *M. cornuarietis* increases naturally. It was therefore considered that the effect of bisphenol-A might be masked to some degree by the natural increase. (The first experiment took place completely outside this active season.) The experimental results were therefore split into three periods of 60 days, with the middle period containing the season of greatest natural spawning activity. The initial 60-day period showed an increase in the cumulative numbers of eggs and spawning masses in the exposed organisms, with a significant increase over the control for

all but the lowest exposure level. Over the middle period, the animals exposed to bisphenol-A showed a reduction in the cumulative number of spawning masses in all treated groups when compared to the control; in the final 60-day period the pattern was similar to that in the first period. Based on the cumulative egg production over the first 60 days of exposure, the following effect concentrations were obtained: LOEC 48.3 ng/l; NOEC 7.9 ng/l; $EC_{10}$ 13.9 ng/l (all based on the average exposure levels calculated from the measured concentrations).

*Third test series*: Follow-up studies with *M. cornuarietis* are reported by Oehlmann *et al*. (2006) with the stated objective of resolving identified shortcomings in their earlier studies (see discussion below). Exposures were semi-static, with medium renewal every one or two days. The first of the two experiments reported in this paper is identical to that reported in Oehlmann *et al*. (2000) and Schulte-Oehlmann *et al*. (2001) (i.e., these data are not new).

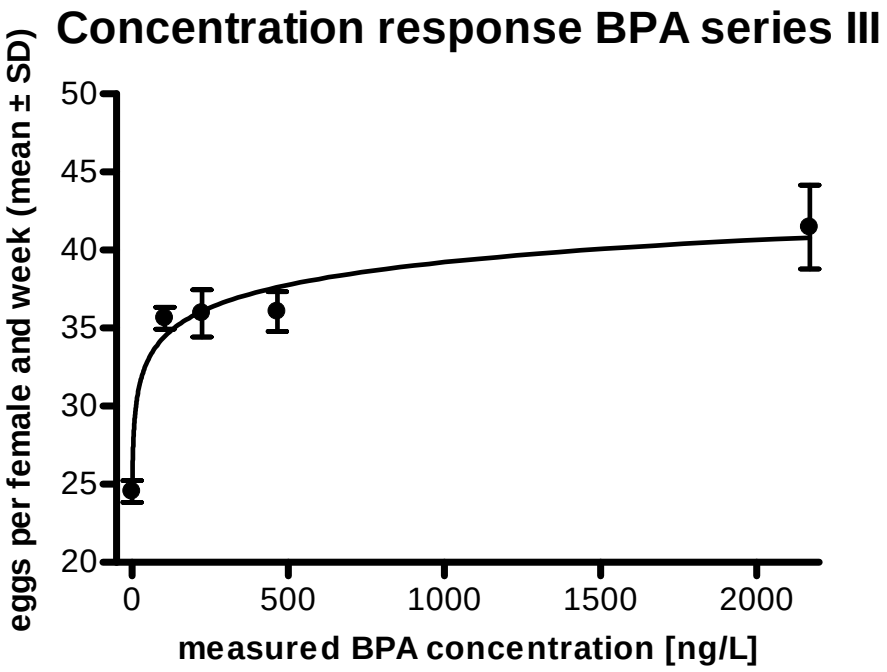
The results of the second experiment have not been published previously. In that study, two replicates, each of 30 sexually mature snails, were exposed to five concentrations of bisphenol-A (0, 0.25, 0.5, 1, and 5 µg/l). Two further treatments of 5 µg/l bisphenol-A with either 3 µg/l of the anti-estrogen ICI 182 780 or 10 µg/l of the anti-estrogen tamoxifen were also used. Exposure was for five months (February-July, which is outside the main spawning period for this population of snails) at two different temperatures (20°C or 27°C) with analysis of all surviving animals at the end of the study. Survival, numbers of eggs and clutches, and numbers of eggs per clutch were recorded daily. Analytical determinations of exposure concentrations over a 24-h period were undertaken in month 1. Measured initial concentrations were very close to nominals, but concentrations declined between renewals. Results were therefore expressed in terms of median (rather than time-weighted) measured concentrations, which were between 39.0% and 48.3% of nominal levels. Bisphenol-A half-lives were slightly lower at 27°C when compared with those at 20°C.

Snails exposed to bisphenol-A at 20°C produced significantly more clutches and eggs compared to controls. A NOEC could not be calculated because there were significant effects (compared to the control) at the lowest test concentration of 106 ng/l. $EC_{10}$ values were estimated to be 14.8 ng/l (95% confidence interval 6.07 – 36.2 ng/l) and 18.0 ng/l (95% confidence interval 6.2-52.5 ng/l) for egg and clutch production, respectively. The dose-response curve derived by Oehlmann *et al*. (2006) is provided in Figure 3.1 (this is a replot of Figure 2C in the original paper provided by the lead author, but the y-axis is the estimate of eggs laid per female per week, rather than the overall egg numbers as in the paper). The curve shown is a fitted Weibull distribution as used by the authors.

At 27°C, none of the treatment groups produced significantly more clutches, or eggs on a per female basis, than the control. A significant increase in egg production could only be detected if measured in terms of cumulative egg number, for the nominal 1 and 5 µg/l exposure groups. Based on measured concentrations, the NOEC for egg production was 205 ng/l ($EC_{10}$ = 998 ng/l; 95% confidence interval 161-6,200 ng/l) and the NOEC for clutch production rose to ≥1,990 ng/l ($EC_{10}$ = 2,090 ng/l; 95% confidence interval 796-5,460 ng/l).

There were no significant differences in egg numbers per female for any of the exposed groups when comparing the output at both temperatures (around 700-800 over the study period), i.e. no dose-response relationship was evident. The temperature-related differences in NOECs are a direct consequence of the lower egg production in controls observed at 20°C (~500 eggs/female over the 5-month period).

Figure 3.1 Dose-response curve for snails exposed to bisphenol-A at 20°C (from Oehlmann *et al*., 2006)




Females with oviduct malformations were only found at 20°C, with an incidence of 4.8%, 8.0%, 14.8% and 11.5% in the groups receiving 0.25, 0.5, 1, and 5 µg/l bisphenol-A respectively. Increased mortality was observed in those groups experiencing oviduct malformation (numbers are not cited, but from Figure 2E in the paper, around 10 deaths were observed in each treatment group at 20°C, compared to 3 in the control – like egg production, there was no clear dose-response).

Some anti-androgenic effects (e.g., a significant concentration-dependent decrease in penis length of males at 20°C) were also observed (neither the magnitude of this change nor a NOEC/$EC_{10}$ for the effect are indicated in the paper).

When snails were simultaneously exposed to bisphenol-A and an anti-estrogen, the stimulatory effect of bisphenol-A on egg production was completely antagonised. Competitive receptor displacement experiments with cytostolic preparations showed the existence of androgen- and estrogen-specific binding sites. Bisphenol-A appeared to have a higher binding affinity for the *M. cornuarietis* estrogen receptor than for fish estrogen receptors.

The first and second test series above were included in the published risk assessment (ECB, 2003). At that time it was concluded that these were not suitable for use in deriving a PNEC for the assessment, and that further work on this species was necessary. A method development and testing programme has been carried out, and the results from this are presented below.

*b) Conclusion (i) programme*

The conclusion (i) programme was made up of three phases. In the first phase, *Marisa cornuarietis* were obtained from a pristine habitat in the wild[13], and colonies established in three laboratories. The effects of temperature, photoperiod, population density, food, etc., on reproduction, fecundity and juvenile growth were investigated to establish husbandry conditions. It was found in this work that external characteristics of the snails could be used to reliably sex the animals, which allowed a test design based on breeding pairs (Oehlmann *et al*. have reported that reliable sexing based on external characteristics is not possible with the *Marisa* in their laboratory). Partial life cycle tests without chemical exposure were conducted at each of the three laboratories to investigate inter and intra-laboratory variability in endpoints. The main finding was that the primary source of variability was at the level of the breeding pairs. Following the fecundity of adult snails over a 12-month period showed a decrease over the first few months and a plateau thereafter (but no evidence of seasonal variation). This phase of the work is reported in Aufderheide *et al.* (2006) and Selck *et al.* (2006).

The second phase of the work was a preliminary toxicity test to define the range of bisphenol-A concentrations to be used in the definitive test. This was carried out at one laboratory in flow-through apparatus using breeding pairs of snails, with the adult pairs exposed over three months at 25°C. An analytical method to determine bisphenol-A concentrations was developed. This phase investigated the degree of replication and the statistical power needed to identify substance-induced effects. The exposure concentrations used were 0.1, 1, 16, 160 and 640 µg/l. No effects were seen on any of the endpoints studied – reproduction (eggs/female/month), egg hatchability (percent hatch, time to first hatch, time to 50% hatch) and growth rate. There was no increase in fecundity on exposure to bisphenol-A in this phase. This phase of the work is reported in Forbes *et al.* (2007a and 2007b).

The third phase of the work was the definitive toxicity study based on the methodology and results of the earlier phases (Warbritton *et al.*, 2007a). For the adult fecundity trial, replicate exposure aquaria were divided into ten equal size chambers using perforated glass partitioning. Each chamber randomly received a breeding pair of snails. Six replicate exposure aquaria were used for each bisphenol-A exposure concentration, with twelve replicate aquaria for the control. The test temperature was 25°C. Four bisphenol-A concentrations were used: 0.1, 1, 25 and 640 µg/l (nominal), with an intermittent flow-through dosing system, and exposure was for six months. The number of egg masses and the number of eggs per egg mass were counted.

An egg hatchability trial was also conducted. Five females in each of three of the replicate exposure aquaria (and in six of the control aquaria) were randomly selected, and five consecutive egg masses were collected starting at two months after the beginning of the fecundity trial. The egg masses were placed individually in the appropriate test solutions in glass-nylon mesh baskets. The percent hatch, the time to first hatch and the time to 50% hatch were recorded.

A juvenile growth trial was also conducted. One egg clutch was selected randomly from each of five females in each replicate vessel (three replicates per bisphenol-A treatment and six from the controls). The eggs were exposed as in the hatchability trial. At 32 days post hatch five juvenile snails were selected from each female's offspring, giving 25 young per

[13] The snails were taken from a reservoir in Puerto Rico, to which they had been introduced in 1960 (Aufderheide *et al*, 2006).

replicate, and were placed in aquaria (one aquarium for each of the three replicates at each concentration). Snails were individually marked, and were weighed weekly over the three-month exposures. Animal gender was determined for each individual based upon internal examination of the gonads at the termination of the exposure.

An additional fecundity trial was carried out at a lower temperature of 22°C over a twelve-week period, at a single bisphenol-A concentration of 25 µg/l (Warbritton *et al*., 2007b). Four replicates were used for the exposure, along with four controls. The other conditions were the same as those for the main fecundity trial.

The concentrations of bisphenol-A in the exposures were measured on a weekly basis throughout the adult fecundity trials and the juvenile growth trial, and more frequently during the hatchability trials. The mean measured concentrations were 74-135% of the nominal concentrations. No bisphenol-A was detected in the control exposures at a detection limit of 0.06 µg/l. The results are expressed in terms of the nominal concentrations.

There was no significant effect of bisphenol-A exposure on adult egg production at any of the tested concentrations. Statistical tests were carried out on the number of eggs per female per month. Comparisons with the controls were carried out by calculating the mean value for each replicate vessel and then testing the means of the replicates using a two-sided Dunnett's test (looking for either increases or decreases compared to the control). Differences in bisphenol-A concentration explained only 1.6% of the total variation in egg production.

There was no significant effect of bisphenol-A on the percentage of eggs hatching, and no significant difference between the controls and any of the bisphenol-A treatments (based on the mean percentage hatch per treatment). ANOVA suggested a significant effect of bisphenol-A on the time to first hatching, but the two-sided Dunnett's test showed no significant difference between any of the treatments and the control. First hatch occurred over a narrow period of time, generally not much more than 24 hours. The timing of the observations in the lab could have meant just including or just excluding snails from a time period, and so could have affected the result quite strongly. No significant effects on the time to 50% hatch were found.

In the juvenile growth trial, bisphenol-A had a significant effect on female growth rate, female wet weight and male growth rate. Growth rates were calculated by fitting a third degree polynomial curve to the data, and taking the slope of the function at 60 days post hatch as the growth rate. The point on the curve at 60 days was noted as the wet weight at this time. Comparison with the control values (using the mean growth rate or wet weight for each replicate) found a significant reduction in female growth at the highest exposure level. There was also a marginal effect (reduction) on female weight at the same level. A significant increase in male growth rate, and a marginal increase in wet weight, was found for the 1 µg/l treatment group. However, a much greater proportion of the variability in the data was explained by variation between pairs, and between siblings from the same pair, than by bisphenol-A treatment (for example, for male growth rate 42% of the variation was between siblings from the same breeding pair, 24% between breeding pairs, 21% related to bisphenol-A). The effect was not seen in the Phase 2 data when these were re-examined with separated data for males and females. The growth endpoint had a high level of variability, showing the highest difference for an endpoint between the three laboratories in the Phase 1 study. The test facility also noted variation between the growth rates in Phases 2 and 3. The difference in growth rates between Phases 2 and 3 at the test facility was greater than the difference between the growth rates at the BPA exposure levels in Phase 3. Different ages of

the adult snails used to produce the egg masses may account for some of this (between laboratories and/or phases).

There were no significant differences between the fecundity (as eggs/female/month) of the controls and snails exposed to 25 µg/l at 22°C and 25°C. The increase in temperature increased the number of eggs/female/month by 5.1% in the controls and by 11.6% in the exposed snails. Exposure to bisphenol-A increased egg production by 6.6% at 22°C and by 13.2% at 25°C. These differences were not statistically significant.

The overall NOEC from the study was concluded to be 25 µg/l, related to the growth of juvenile female snails. It should be noted that this is a conservative value since the LOEC is significantly higher (i.e. the true NOEC lies somewhere between 25 and 640 µg/l).

c) Studies of Schirling *et al*.

Schirling *et al*. (2006a) reported the development of a test method using eggs of *Marisa cornuarietis* to assess the effects of potential developmental and endocrine disruptors. Eggs were exposed to bisphenol-A in Petri dishes, with 15-20 eggs per dish. Two exposure concentrations were used, 50 and 100 µg/l, with nine replicates for each concentration and the control. Exposure solutions were renewed at least every third day, as was the stock solution. Eggs were observed under a microscope from the day of laying until the hatching of the snail. Endpoints monitored were mortality, formation of eyes, formation of tentacles, hatching (all as percentages of the exposed organisms) and heart rate. The weight of the snails on hatching was also recorded (hatching took place from 9-14 days after laying in the controls.

Bisphenol-A had no effect on the development of eyes or tentacles compared to the controls. There was a significant reduction in the heart rate in the 100 µg/l exposure at nine days. Slightly more animals hatched in the exposed than the control groups at 11 days, but this was reversed at 12 and 13 days, and none of the differences from the controls were statistically significant. The weight of newly hatched snails was significantly higher at 100 µg/l than in the controls. Similar results to those at 100 µg/l bisphenol-A were seen with 17α-ethinylestradiol at 10 µg/l. The study was intended as a development of the method and not for the determination of dose-responses, but a NOEC of 50 µg/l could be tentatively drawn.

2) *Potamopyrgus antipodarum*

As part of studies to investigate the relative sensitivities of fish and molluscs, Jobling *et al*. (2003; corrected version published 2004) exposed *Potamopyrgus antipodarum* (a temperate species of prosobranch snail, common in Europe) to bisphenol-A in water. The exposures lasted up to 90 days, in a semi-static system with 50% of the dosed water being replaced every four days. The exposure levels were nominally 1, 5, 25 and 100 µg/l. No analysis of the exposure solutions was performed. The endpoints monitored were growth and embryo production. Growth was measured by the length of the shell and the width of the shell opening. For embryo production, the number of embryos in the brood pouch was counted, distinguishing between shelled and unshelled embryos. The former are at a much later stage of development, and so the latter gave a measure of new embryo production.

No effects were seen on survival at any concentration of bisphenol-A (or for octylphenol at the same concentrations, or for 17α-ethinylestradiol ($EE_2$) at concentrations three orders of magnitude lower). Shell height and operculum width were also little affected for the most part, but at nine weeks the shell height in the 5 µg/l exposure were significantly increased over the six week value. There were no significant effects at higher doses. Embryo

production was significantly increased over that in the controls after three weeks at 5 µg/l. At 63 days, the 5 and 25 µg/l exposures had significantly more embryos than the controls, the 1 µg/l exposure had higher numbers but not significantly so, and the numbers at 100 µg/l were lower than in the controls. This indicates an inverted U-shaped response, similar to that seen with $EE_2$ (at ng/l levels). From the studies reported here and from other studies, the authors concluded that fish appear to be more sensitive to disruption in reproductive output caused by $EE_2$, but that snails may be more responsive to low concentrations of some xenoestrogens than fish.

This study cannot be used directly for the PNEC derivation or SSD because of the lack of confirmation of exposure concentrations. However, it does suggest that the NOEC for this species might be below that for fish (see Section 3.2.1.4.1), providing additional evidence that snails could be more sensitive than other groups of freshwater organisms. It may be noted that this study was performed in the same German laboratory that has performed a number of tests with *M. cornuarietis* reported above (S Jobling, personal communication to the Environment Agency).

The toxicity of bisphenol-A in sediments to *Po. antipodarum* has also been reported by Duft *et al*. (2003), and this study is discussed in section 3.2.2.1 of this report. In summary, stimulation of embryo production occurred at all test concentrations (i.e., the NOEC was below 1 µg/kg nominal dry weight) after eight weeks' exposure.

Discussion of the mollusc studies

Studies on three species of prosobranch snails (*Po. antipodarum*, *M. cornuarietis* and *Nucella lapillus* - see Section 3.2.1.3.2) – mostly performed in a single laboratory – indicate effects of bisphenol-A on reproductive parameters. The main underlying effect seems to be a stimulation of production of embryos, eggs and/or spawning masses[14]. In the case of *M. cornuarietis,* which appears to be particularly sensitive based on the work of Oehlmann and co-workers, this can lead to a rupture of internal organs and death in a proportion of the snails (this appears to depend on the morphology of the pallial oviduct, and the observation is so far restricted to this one species). Changes to other organs in the animals were also observed. These types of effects were not observed in the extensive conclusion (i) study, which had much greater statistical power (the most sensitive endpoint identified was growth of juvenile females; tissues were not examined for histopathological changes).

There are a number of drawbacks in the experimental methodology of some of the tests performed by Oehlmann and co-workers that makes it difficult to interpret the results with confidence. For example:

- The source of the snails is not well documented. The breeding population was originally established using snails obtained from Dusseldorf Zoo, with occasional inputs of snails from an unnamed source in Florida (J Oehlmann, personal communication).

- In the initial experiments with *M. cornuarietis* (Oehlmann *et al*., 2000; Schulte-Oehlmann *et al*., 2001; Oehlmann *et al*., 2001) two concentration ranges were used, i.e. high (1-100 µg/l) and low (0.05-1 µg/l). Concentrations were not measured in the first (high concentration) experiment. Measurements in the second (low concentration) experiment showed that the

[14] It may be noted that bisphenol-A has also been found to increase egg production in the copepod *Acartia tonsa* – see main text under Section 3.2.1.3.2 (saltwater *Crustacea*).

concentrations of bisphenol-A decreased rapidly over the 24-hour period between renewals of solution. The rate of disappearance was more rapid at later times in the test, despite the renewal of the solutions each day. Bisphenol-A is not susceptible to rapid abiotic degradation in solution, so it would appear that biodegradation or metabolism occurred in the solutions, with some indication of adaptation over the course of the experiment. In view of the rapid disappearance of the substance, the nature of the chemical species present in the exposures is unclear, particularly in the later parts of the experiment. For example, for a half-life of six hours only 6% of the substance would remain after 24 hours; for a half-life of two hours there would be effectively none of the substance left after twelve hours.

- The report of the second (low concentration) experiment also indicates that the control exposure solutions initially contained 30-40 ng/l of bisphenol-A at the first time of sampling for analysis. This was found to be due to leaching of the test compound from the plastic tubes used in the filter systems of the exposure tanks. Following replacement of these tubes with glassware, bisphenol-A could not be detected in the control group in the subsequent sampling.

- As noted in the description of the studies above, the period of the second (low concentration) experiment included the natural spawning season of the snails. This makes it difficult to compare the two studies. Both experiments included a nominal exposure concentration of 1 µg/l. The cumulative egg production over the first 60 days of the second experiment (taken as a period less affected by the natural spawning) was much higher than that seen over the 180 days of the high concentration experiment at the same exposure level, but the incidence of females with malformed oviducts was identical in both 1 µg/l exposure groups. The cumulative egg production in the control of the low concentration experiment was similarly higher than that for the high concentration experiment. These observations presumably relate to the difference in the natural spawning rate, and make it difficult to distinguish the effects due to the substance. The conclusion (i) study found no indications of seasonality in spawning in the *Marisa* used in that study.

- Snail density and volume per snail can both affect the growth, natality rates and calcium uptake rates of aquatic snails. This is due for example to competition for nutrients and food, ammonia formation, and the removal or dilution of beneficial growth factors secreted by the snails (JD Thomas, personal communication). In this case, snail densities were as high as 3.5 snails/litre, and this changed as snails were removed for analysis. Densities above about 1 snail/litre have been shown to have a negative effect on reproductive output of this species even under flow-through conditions (Aufderheide *et al*., 2006). Density-dependent effects may therefore have confounded the results.

- The level of replication should be as high as possible because aquatic snail reproductive traits are generally highly variable (JD Thomas, personal communication). However, only one replicate test chamber was used per exposure concentration. The absence of replication means that inferential statistics cannot be applied, i.e., trends can be observed but they cannot be extrapolated to the 'population' of interest (Leidi, 2005). Further detailed criticisms of the statistical methods are presented in van der Hoeven (2005). In summary, statistical experts consider it invalid to calculate a NOEC from the data or to test the effect of concentration on snail mortality. The main point is that there could be many other factors causing mortality in a given test vessel that have nothing to do with exposure concentration, which is why replicates are needed.

In view of the apparent instability of the substance under the exposure conditions used, statistical uncertainties, issues over snail density and other test conditions, and the possible overlap with natural changes, the effect concentrations from the initial *Marisa* studies are not considered suitable for use in the PNEC derivation.

This led the research group to conduct further studies, which have been reported recently (Oehlmann *et al*., 2006). Despite the criticisms of the original studies, the new study appears to indicate very similar effects, with a 5-month egg production $EC_{10}$ of 14.8 ng/l at 20°C. (This value was inferred since significant effects occurred at the lowest median measured test concentration of 106 ng/l, equivalent to an increase in egg production of ~40% compared to control females.) At 27°C, depending on how the data are interpreted, there are either no effects on egg production (in terms of eggs per female), or a NOEC of 205 ng/l can be derived based on cumulative egg numbers (with an estimated $EC_{10}$ of 998 ng/l or 0.998 µg/l). This paper and the underlying dataset were reviewed by members of an expert group that was set up to guide the conclusion (i) testing programme for snails (as reported above). This review identified a number of issues, as follows:

- Snails were exposed in duplicate tanks at each treatment level. This level of replication permits better statistical analysis than the earlier experiments. However, interpretation of the results from work with groups of snails (rather than paired individuals) remains difficult because it is known from the conclusion (i) test programme that there can be considerable animal-to-animal variability in egg production. By presenting the cumulative egg production per tank and not per female, intra- and inter-female variability is ignored, i.e. apparent differences in egg production among treatments and controls may in fact be related to natural intra- and inter-female variability. The test design still does not allow separation of breeding pairs and analysis of the intra- and inter-female variability in reproductive output. The conclusion (i) study required a very high degree of replication to overcome this problem.

- There are still significant criticisms about the application of the statistical techniques that were used in the paper (van der Hoeven, 2005 and Leidi, 2005 & 2006). For example:
  - The analysis assumed that identical sex ratios were employed in the replicates and exposures, and that mortality did not affect these ratios, nor the fecundity. This influences calculations of egg production per female, and adds uncertainty to the reported results that is not addressed.
  - Van der Hoeven (2005) and Leidi (2005 & 2006) were unable to replicate the derivation of the $EC_{10}$ value from the raw data provided by the authors for this purpose. Whilst the Weibull distribution appears to fit the data very well ($r^2 = 0.936$), the small number of data points means that this could simply be the result of overfitting (van der Hoeven, 2005). Unfortunately there are no details in the paper about how this curve was calculated to permit independent validation.
  - Several alternative statistical models could have been used. For example, simple linear correlation has been found to be significant ($p=0.02$), although the fit is not as good ($r^2 = 0.718$) (van der Hoeven, 2005). This is not necessarily the correct distribution for the data, but it is the simplest. A quadratic relationship was also used, but did not provide a better fit compared with the linear model.

- The authors used the control group repeatedly in their tests of significance, making the results of the individual comparisons dependent on each other. The p-values should have been adjusted accordingly.

- The variability in the data set is surprisingly small. The mean coefficient of variation (CV) for reproductive output is ~3% for all treatment groups. In comparison, van der Hoeven (1998) found that the median CV in a ring test of a highly standardised method with clonal *Daphnia magna* was 14.4%; the median CV in less-standardised tests with *Folsomia candida* and *Eisenia fetida* was about 50%. Leidi (2006) has also pointed out that the observed variability was much lower than expected. This suggests that the dataset is unusual in that the tanks can not be considered to be truly independent replicates: no variability was observed between a few tanks at the same dose. One explanation might be that each individual snail is negatively correlated with the rest (Collett, 2002).

- Some of the experimental issues identified for the original studies still remain, for example:
  - the varying snail density (although this did not vary as much as in the earlier experiments, with an initial density of 1.11 snails/l, dropping to 0.72-1.00 snails/l at the end, depending on the mortality in the different treatment groups); and
  - the very rapid loss of bisphenol-A in the test system, which is a major additional complication. The only analytical measurement of test solution stability occurred after one month, over one test media renewal cycle. The test substance half-life is reported as 3.0-3.9 hours, and in all but the highest dose group, no bisphenol-A was detectable in the media at the end of the renewal period. It is therefore not clear what substance concentration actually caused the apparent effects in each treatment. The authors used the median measured concentrations to derive an $EC_{10}$ value. For example, the lowest nominal concentration of 0.25 µg/l had a median measured concentration of 0.106 µg/l, but the standard deviation for this value is 0.113 µg/l, demonstrating the wide variation observed. Given the lack of information to derive proper time-weighted average concentrations over the whole course of the experiment, the rapporteur considers that this approach is unreliable.

- The paper suggests a possible mode of action in which bisphenol-A binds more strongly to *M. cornuarietis* receptors than to the vertebrate estrogen receptor, which helps to explain why this species is so sensitive. However, some experts have identified experimental drawbacks about this part of the study, which raises some doubt about its reliability (e.g. Dietrich *et al*, 2006). Despite this, the elimination of effects when snails were exposed to a mixture of bisphenol-A and an anti-estrogen lend some support to the hypothesis. In any case, this mechanistic information does not directly affect the interpretation of the bisphenol-A toxicity data themselves.

The Oehlmann *et al*. (2006) study clearly suggests that there are temperature-driven differences in the observed effects[15], and this is linked to an apparently natural increase in egg production at higher temperatures. It should be noted that reproductive traits are more variable in this species at lower temperatures, which could have some influence on the findings due to the test design and method of statistical analysis. Oviduct malformations and associated mortality are not seen

[15] It has been suggested that the lower temperature might not be relevant for this species. However, although mainly tropical in distribution, *M. cornuarietis* is tolerant of a wide range of temperatures, and can exist in Florida (at the edge of its range) at an average temperature of 20-22°C. The snail population used for this experiment was a mixture of laboratory-derived stock and snails obtained from Florida. Control mortality at 20°C was very low during the experiment (5% over a period of 5 months) and even slightly lower than in controls at 27°C of the same experiment (J Oehlmann, personal communication). The lower temperature therefore seems to be appropriate.

at the higher temperature of 27°C (the study authors state that the oviduct becomes widened during natural periods of higher egg production).

Comparison of the studies performed by Oehlmann and co-workers with the conclusion (i) study is not straightforward because the latter was not intended to be an exact replica of the original work. Rather, it was developed to specifically take account of the influence of key husbandry parameters such as water quality, food type, snail density and temperature on snail responses. The findings of the initial phases were used to develop a statistically robust test based on breeding pairs of snails which allowed the intra- and inter-female variability to be investigated, with sufficient replication to detect an increase in fecundity of ~20% under the conditions of the test.

An obvious difference between the two groups of studies is temperature. A temperature of 25°C was chosen for the main test of the conclusion (i) study because:

- of practical considerations such as timing and the laboratory space available to house the required number of aquaria (the snails showed a higher degree of variability (i.e. more control tanks are needed) and grow more slowly at lower temperatures); and
- this is closer to the temperatures that this population of *Marisa* normally encounters in the wild (the original stock of snails was collected from a tropical lake).

There was no increase in egg production at any of the tested concentrations at this temperature. The most sensitive endpoint was growth of female juveniles, which had a NOEC of 25 µg/l.

A trial at 22°C at the same concentration also showed no significant difference in fecundity compared to controls (and only slightly lower egg production than at 25°C). This test concentration and temperature is the same as one in the first test series by Oehlmann and co-workers, when effects on both egg production and mortality were seen.

Another obvious difference is the exposure regime. Bisphenol-A is readily biodegradable, and a flow-through test system is usually preferred for such substances. This was the regime chosen for the conclusion (i) study. The studies of Oehlmann and co-workers used semi-static exposures, and there was rapid disappearance of the parent compound. It is therefore possible that metabolites could have been present at higher concentrations in the semi-static studies. The same metabolites may have been present in the conclusion (i) study, but the actual levels of any metabolites, and their role in the observed effect, is unknown.

Clearly there is a significant difference in the responses of the *Marisa* used in the two major groups of studies. This does not appear to be simply due to temperature differences, because the lower temperature trial in the conclusion (i) study did not result in any effect. Whilst differences in experimental design will obviously have influenced the results, it may be noted that the snails in the studies by Oehlmann and co-workers showed seasonal spawning behaviour, which was not present in the animals used for the conclusion (i) study (no stimulation of egg production was seen in the Oehlmann's snails during their active spawning phase). The fact that these two groups of snails come from different geographical sources has been suggested as a possible contributory factor to this difference, and this demonstrates the difficulties in working with species that have not been properly ring-tested.

In summary, the studies performed by Oehlmann and co-workers have major limitations, which make the numerical results derived from them of questionable reliability. However, whilst preference would normally be given to the fully valid conclusion (i) study, the findings of mortality and morphological changes cannot easily be discounted. This is also supported by the

observation of similar types of effects (in relation to stimulation of aspects of reproduction) in other species such as *Potamopyrgus* and *Nucella*, although none of these other studies provides a value that is suitable for use in the risk assessment (and the tests were performed in the same laboratory and so could be subject to similar drawbacks). In addition, the snails used by Oehlmann and co-workers have a seasonal breeding cycle. It is therefore possible that an effect was missed by using a strain of snails that did not have a seasonal breeding cycle in the conclusion (i) study.

The calculated $EC_{10}$ reported by Oehlmann *et al*. (2006) may be an artefact of the statistical approach and the choice of values used to represent the exposure concentrations. For example, van der Hoeven (2005) calculated an alternative $EC_{10}$ of 2.1 µg/l at 20°C (with a 95% confidence interval from 1.0 to 11 µg/l), based on a simple linear two-parameter model and nominal test concentrations[16]. If the mean measured concentrations were used, the values would be approximately halved, but the rapporteur believes that the lack of proper chemical analysis makes these too unreliable.

One approach to overcome the problem of which value to use for *M. cornuarietis* would be to derive a geometric mean of the available NOECs to take some account of both studies (which would be consistent with the approach used for the *Xenopus* studies reported below). This is not preferred since if seasonality were a key factor in snail sensitivity, the importance of the 'low dose' findings would be diluted. Both studies will therefore be taken into account in the PNEC derivation.

In summary, the 5-month egg production $EC_{10}$ of 0.0148 µg/l at 20°C from Oehlmann *et al.* (2006), the recalculated $EC_{10}$ value of 2.1 µg/l for the same endpoint by van der Hoeven (2005), and the NOEC of 25 µg/l at 25°C for juvenile female growth from the conclusion (i) programme for *M. cornuarietis* are considered in the PNEC derivation and SSD.

Crustacea

Experiments have been performed with three species, and these are summarised below.

1) Four 48-hour $EC_{50}$ values based upon immobilisation of *Daphnia magna* are reported. Stephenson (1983) reports a value of 3.9 mg/l, Chen *et al*. (2002) report a value of 10 mg/l, and Hirano *et al*. (2004) report a value of 12.8 mg/l, all based upon nominal concentrations. Alexander *et al*. (1985c) report a 48-h $EC_{50}$ of 10.2 mg/l based upon measured concentrations. The methods used are documented in all of these studies, but the latter test result based upon measured concentrations is considered to be the most reliable, and is supported by two of the other studies.

   A 21-day $NOEC_{reproduction}$ of ≥3.146 mg/l for *Daphnia magna* is reported by Bayer AG (1996). The method used is fully documented in the test report and the test concentration is measured. At the highest concentration tested (nominal concentration of 3.2 mg/l) no effect on reproduction was observed. The $NOEC_{reproduction}$ is therefore given as ≥3.146 mg/l (measured concentration).

   Caspers (1998) studied the moulting behaviour of parthenogenetic *D. magna* females in what is likely to be the same study as Bayer AG (1996). The author did not observe any change in

16 Other relationships could be used to fit the data. For example, the $EC_{10}$ estimate is 0.38 µg/l using a quadratic relationship. This does not provide a significantly better fit than the linear one (the *p*-value was 5.6%).

moulting behaviour at exposure concentrations of 0.316 and 3.16 mg/l. Moulting behaviour has been claimed to be a toxicological endpoint that is able to reflect effects of endocrine disruption.

Mu *et al*. (2005) report both acute and chronic effects of bisphenol-A on *D. magna* in semi-static test systems with daily renewal. The $EC_{50}$ for juveniles less than 24 hours old was 16 mg/l (95% confidence interval of 15.9-16.4 mg/l). The authors report a chronic toxicity threshold of 1.3 mg/l for effects on female fecundity after a 21-day exposure period. However, this threshold is based upon a second order regression model fitted to the data. Figure 6 in the paper shows that a plausible model could be fitted that would lead to a higher threshold (i.e., a NOEC) of approximately 5 mg/l. At concentrations >5 mg/l there was evidence of an increase in the intermoult period for neonates, and at 10 mg/l there was an increase in neonatal abnormalities. The authors propose that bisphenol-A effects on daphnid reproduction are due to anti-ecdysteroidal activity. There was no chemical analysis of exposure concentrations in this study, so these results are not themselves suitable for inclusion in an SSD but can be used to support the Bayer AG (1996) study.

Brennan *et al.* (2006) carried out acute and chronic tests on *Daphnia magna*. The acute test were carried out over 48 hours, measuring immobilisation at 24 and 48 hours, and the number of discarded carapaces as a measure of the moulting frequency, also at 24 and 48 hours. Three replicates were used at each concentration, with five *Daphnia* in each. The results were $EC_{50}$ (24 hours) 8.57 mg/l (95% confidence limits 8.28 – 8.86 mg/l), and $EC_{50}$ (24 hours) 7.75 (7.65 – 7.85) mg/l. Results are based on nominal concentrations. There were no effects on the moulting frequency from bisphenol-A exposure, up to the highest tested concentration of 10.5 mg/l. This contrasts with the results reported by Mu *et al*. (2005), where a longer time between birth and first moult was found at concentrations above 5 mg/l. The organisms in the Mu *et al.* study were <1 hour old at the start of the exposures; those in the current study were <24 hours old in line with the ISO guideline.

In the chronic studies, single *Daphnia* were exposed to bisphenol-A over 21-day exposures, with ten replicates for each concentration. The test solutions were renewed three times per week. The endpoints monitored were survival, moulting frequency and the number of offspring produced. Again results are based on nominal concentrations. There were no effects on the cumulative number of moults or the cumulative number of offspring per female at concentrations up to 1.0 mg/l, the highest used, in either the first or second generations. The $LC_{50}$ for mortality in the first generation was 0.806 mg/l over the 21 days. (The second generation value is not given, but the exposure at 0.6 mg/l had 50% mortality in the second generation. Probit analysis of the second generation data carried out for this assessment gives an $EC_{10}$ value of 0.2 mg/l.)

Wang *et al.* (2005) developed a short-term assay with Daphnia to screen for endocrine effects. Specifically, the screen was for the ability to stimulate the production of male offspring under conditions when the offspring would normally be all female. This is promoted by juvenoid hormones in crustaceans. Bisphenol-A had no agonistic effect in Daphnia, and no males were produced. When a low level of methyl farnesoate, a potent agonist, was used together with bisphenol-A, the effect was potentiated compared to that of methyl farnesoate alone. The bisphenol-A level used was 10 mg/l. A possible mechanism was suggested in which bisphenol-A inhibits the enzyme that degrades methyl farnesoate. As only a single concentration was used and the endpoints are indicators, the study is not suitable for use in the risk assessment.

In summary, the 21-d reproduction NOEC of 3.146 mg/l (as a limit value) for *D. magna* is considered valid for use in the PNEC derivation and SSD.

2) Watts *et al*. (2001a) exposed the freshwater amphipod *Gammarus pulex* to bisphenol-A and examined toxicity over a 10-day period and precopulatory behaviour over a 24-hour period. Chemical analysis of test concentrations showed good agreement with nominal concentrations. The $LC_{50}$ was 12.8 mg/l after 24 hours, 5.6 mg/l after 48 hours, and plateaued at around 1.5 mg/L after 120 hours. Precopulatory guarding behaviour was only affected at concentrations close to these lethal levels (0.83 mg/l).

   Johnson *et al*. (2005) exposed *G. pulex* to 0, 1, 10, 100 and 1,000 µg/l bisphenol-A for 14 days in a semi-static exposure system. Ten pairs of animals were exposed to each concentration in the form of precopula pairs (i.e., males clasping the females during the pre-mating period) and observed daily to determine whether they had moulted or died, and to count any juveniles produced. There was reduced survival at the highest test concentration (1,000 µg/l), but there were no significant effects on female moulting rate or juvenile production at any concentration. However, the results were variable, so there would have been little statistical power to detect differences. In addition, although the authors state that samples were taken for analysis at the start of the study, no analytical results are reported, so true exposure concentrations are uncertain. Short-term data reported by Johnson *et al*. (2005) also suggest effects on *G. pulex* survival only at higher concentrations, with mortality over 96 hours of 6.7% in controls, 10% in solvent controls and at 1,000 µg/l, 30% at 3,200 µg/l and complete lethality at concentrations above 10,000 µg/l.

   Both of these studies provide information on short-term or lethal effects of bisphenol-A on *G. pulex*, so are unsuitable for inclusion in an SSD.

3) Springborn Smithers (2006b) report the results of a 42-day reproduction test with the amphipod *Hyalella azteca* (known as the scud) during aqueous exposures. Mean measured concentrations during the test were 0.12, 0.22, 0.49, 1 and 2.2 mg/l, which were 63%, 58%, 65%, 67%, and 73% respectively of nominal concentrations. The NOEC for cumulative number of offspring per female was 0.49 mg/l. There were no effects on body length or dry weight up to the highest concentration tested. This study was performed to GLP using US EPA guidelines and a full study report is available.

   The 42-d reproduction NOEC of 0.49 mg/l for *H. azteca* is considered valid for use in the PNEC derivation and SSD.

Insects

Experiments have been performed with two *Chironomus* species, and these are summarised below.

1) Sayers (2005) reports a 96-h $LC_{50}$ of 2.7 mg/l (95% confidence interval of 2.1 - 3.2 mg/l) and a 96-h NOEC for survival of 1.4 mg/l for the midge *Chironomus tentans* exposed to bisphenol-A under flow-through conditions. The test was performed according to US EPA guidelines and was GLP compliant, and mean measured concentrations ranged between 84% and 110% of nominal. The test report describes the test methods and test concentrations, but this is only a short-term study.

2) Hahn *et al*. (2002) examined the effect of bisphenol-A on the yolk protein content of *Ch. riparius* and found a significant reduction in vitellogenin in males at all test concentrations of 1, 100 and 3,000 µg/l, and in females at 3,000 µg/l. Test concentrations were not chemically

analysed. These results, which the authors found surprising, may have been influenced by cross-reactivity in the immunoassay that was used, although the authors regarded this as unlikely. This study is not suitable for PNEC derivation because the method is in development and it also lacked confirmation of exposure concentrations.

Watts *et al.* (2003) report the effects of bisphenol-A on larval moulting and mouthpart structure in *Ch. riparius*. Midges were exposed throughout their entire life-cycle, first in repli-dishes when exposed as eggs, and then in glass vials containing 10 ml of test solution when the eggs hatched into larvae. Chironomids require a substrate for normal development and this was provided in the form of a minimal amount of filter paper, previously soaked for 24 hours in the relevant test solution. Test solutions were renewed daily and chemical analysis of the 1 mg/l concentration confirmed that it was within 20% (830 µg/l) of the nominal concentration. Time to first moult and mean wet weights of first instar larvae were only affected at the highest test concentration of 1 mg/l, with no effects at the next lowest concentration of 100 µg/l. There is a substantial difference between the two concentrations, and clearly the actual NOEC could be significantly higher than 100 µg/l. The incidence of mouthpart mentum deformities was significantly higher than controls at lower and intermediate exposure concentrations (10 ng/l and 1 µg/l). There were no significant differences at higher exposure concentrations (or at the intermediate concentration of 100 ng/l), and there were no significant effects on other mouthparts.

Exposure of chironomids in this study could have been via both overlying water and pre-soaked filter paper, but equilibrium partitioning theory suggests that the fugacity of bisphenol-A should be similar from both sources, and the amount of filter paper used in the test was small. In addition to this, analytical confirmation of one exposure concentration plus daily renewal is not an ideal experimental design, but would have been adequate to characterise exposure concentrations sufficiently for use in risk assessment. The ecological consequences of the deformities observed in the study remain unclear, and the lack of a clear linear or U-shaped dose-response makes these data unsuitable for PNEC derivation. However, the data on time to first moult and first instar larval weight are valid.

| In summary, the growth NOEC of 100 µg/l (as a limit) for *Ch. riparius* is considered valid for use in the PNEC derivation and SSD. |
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#### 3.2.1.3.2 Saltwater invertebrates

Annelids

Biggers and Laufer (2004) used a rapid settlement and metamorphosis assay with the polychaete *Capitella* sp. to assess the juvenile hormone activity of bisphenol-A and other phenolic compounds. Two-day old metatrochophore larvae were exposed in 10 ml of artificial seawater (salinity 30 ppt) and the number of larvae that settled and metamorphosed was assessed after 1 hour. The authors reported an $EC_{50}$ of 0.05 µM, equivalent to 11.5 µg/l. There was no chemical analysis of exposure concentrations, and coupled with the short study duration, this means that the study is unsuitable for PNEC derivation.

Molluscs

Experiments have been performed with three species, and these are summarised below.

1) Adult Dogwhelks *Nucella lapillus* (a prosobranch gastropod) from the field were exposed for three months in the laboratory to concentrations of 1, 25 and 100 µg/l, with renewal every 24

hours (Oehlmann *et al*., 2000). Superfeminisation with enlarged pallial sex glands and an enhancement of oocyte production was observed. No oviduct malformations were found (it was noted that there are differences in gross anatomical structure of the pallial oviduct between this species and *M. cornuarietis*). A lower percentage of exposed specimens had ripe sperm stored in their vesicula seminalis and males exhibited a reduced length of penis and prostate gland when compared to the control. Statistically significant effects were observed at all the test concentrations. The authors concluded that the results show that prosobranchs are sensitive to endocrine disruption at the lowest concentrations of bisphenol-A tested (1 µg/l nominal).

The lack of confirmation of exposure concentrations means that these results cannot be used directly for PNEC derivation. However, the study does provide additional evidence of toxicity to prosobranch molluscs in support of the findings for freshwater species.

2) Canesi *et al*. (2005) injected 0.1 and 0.5 µM of bisphenol-A into the mussel *Mytilus galloprovincialis* and examined effects on lysosomal stability and kinase-mediated cell signalling in haemocytes after 6, 12 and 24 hours. Canesi *et al*. (2004) also exposed haematocyte monolayers from the same species to 25 µM of bisphenol-A. These data cannot be used for this assessment because the method of exposure cannot be related to environmental concentrations, and the end points cannot be related to demographically important factors.

3) Blue mussels *Mytilus edulis* were exposed to bisphenol-A, diallylphthalate (DAP) and tetrabromodiphenyl ether (congener 47) for three weeks in filtered seawater at 10-12°C (Ortiz-Zarrogoitia and Cajaraville, 2006). The exposure level for bisphenol-A was 50 ppb. At the end of the exposures 20 animals were sampled. Bisphenol-A exposure did not significantly induce Acyl-CoA oxidase activity in comparison with the controls, and there were no significant changes in the peroxisomal volume density. These two endpoints were used as a measure of exposure to general pollution. Resorption of gametes was observed in 35% of the female and male animals in the bisphenol-A exposure group. Alkali-labile phosphate levels (considered as a measure of vitellogenin-like proteins) were not affected by exposure to bisphenol-A. There were no changes in oocyte athresia after exposure to bisphenol-A. The authors note that the mussels used in this experiment were at the mature gonad stage, and that they may be more sensitive at earlier stages of gonad development. The study appears to have exposed all of the animals in one vessel, hence there were no true replicate exposures. Only one concentration was used, and so no NOEC value can be determined for the one examined endpoint that showed effects. The study is not suitable for use in the risk assessment.

   Aarab *et al.* (2006) exposed blue mussels *Mytilus edulis* to one concentration of bisphenol-A (50 µg/l) for three weeks in a flow through system. Mussels were obtained from a pristine site in Norway. After exposure, mussels were dissected and the gonadal tissue in the mantle was sampled. Histological examination revealed that the control female animals were in a late pre-spawning stage. Mussels exposed to bisphenol-A exhibited two different patterns; half were considered to be in a post-spawning stage, while the other half had atreitic ovocytes, interpreted as relating to spawning delay. Male control mussels showed no evidence of spawning, while mussels exposed to bisphenol-A showed evidence of spawning having taken place. An alkali-labile phosphate assay to determine total phosphate protein was used as an indicator of vitellogenin-like protein levels. Bisphenol-A exposed female mussels had slightly increased levels over the controls, males had similar levels to the controls. The authors comment that this method may not be suitable for assaying VTG levels in mussels. With only one concentration tested the result cannot be used in the risk assessment.

Crustacea

Experiments have been performed with three species, and these are summarised below.

1) Andersen *et al*. (1999) report a 72-hour immobilisation $EC_{50}$ of 0.96 mg/l for the saltwater copepod *Acartia tonsa*. Kusk and Wollenberger (1999) report 24 and 48-hour $EC_{50}$ values of 5.1-6.3 and 3.4-5.0 mg/l, respectively, for the same species.

   Andersen *et al*. (1999, 2001) studied the effects of a range of substances on the development of nauplii of *A. tonsa*. In Andersen *et al*. (1999) semi-static exposures of copepod eggs were performed with nominal bisphenol-A concentrations of 0.2, 2 and 20 µg/l and medium renewal on days 2, 4 and 6. On day 8 hatched juveniles were divided into groups and placed in vessels with new test medium, and egg production was monitored every day for the next three days. Exposure to 20 µg/l bisphenol-A caused a significant increase in egg production on day 10 of the study, but not on days 9 or 11. In Andersen *et al*. (2001) semi-static exposures were also used, with solution renewal after three days; there was no monitoring of test concentration. The exposures were carried out for five days or until at least 50% of the organisms had undergone metamorphosis from the nauplius to copepodite stage, whichever was the longer. The larval development rate was expressed as the ratio of copepodites to the sum of nauplii and copepodites. The $EC_{50}$ value established for this effect was 0.55 mg/l, and the $EC_{10}$ value was 0.10 mg/l. Although this test is of relatively short duration, it assesses what is considered to be a sensitive endpoint.

   None of these studies is considered suitable for the PNEC derivation or SSD, because of the lack of confirmation of exposure concentrations.

2) The effects of bisphenol-A on the harpacticoid copepod *Tigriopus japonicus* have been studied (Marcial *et al*., 2003). This is an intertidal organism, which thrives at a wide range of temperatures and salinities. It has six naupliar and six copepodid stages, of which the last is the adult. Tests were conducted at 2.5% salinity. Stock solutions of bisphenol-A were changed every week. Acute toxicity was determined in 48-hour exposures, the result being an $LC_{50}$ of 4.32 mg/l (95% confidence limits 4.25 – 4.39 mg/l).

   Longer-term exposures were carried out at four concentrations: 0.01, 0.1, 1.0 and 10 µg/l, with three replicates at each concentration. Nominal concentrations are reported, and the test solutions were renewed daily by replacing around 50% of the working volume each time. Twenty nauplii less than 24 hours old were used at each exposure level. The survival and developmental stage of the organisms was assessed at the renewal of the solutions, at which time they were also fed. For the first eight days the exposures were in 24-well plates; after this time the surviving copepodids were transferred to the chambers of 6-well plates, with food and fresh solution, to initiate copulation. After two to three days, six mature females (bearing ovisacs) were randomly selected from the population and transferred individually to new plates. The number of nauplii produced up to the third brood was monitored for each organism. After 21 days, the sex ratio of the copepodids and the percentage survival were determined. The first brood of nauplii were cultured in the same conditions and the same parameters were monitored for 21 days.

   Survival rates were not affected by bisphenol-A exposure in either the parent or the F1 generation. A significant delay in completion of the naupliar stages (compared to the controls) was seen at concentrations of 0.1 µg/l and above in the parent generation, and at all concentrations for the F1 generation. The time to sexual maturity was increased at 1 µg/l in the parent generation, and at all concentrations for the F1 generation. The sex ratios of copepodids were not significantly different from the controls at any concentration, for either

of the generations. There were also no effects on fecundity (as measured by the average number of nauplii per female) at any concentration. The authors concluded that bisphenol-A (and the other chemicals tested, alkylphenols and 17β-estradiol) had no extensive effect on reproductive parameters, and would have little impact on the demographic profile of the copepod. However, the effects on development could be a potential indicator of exposure to estrogens for crustacean species.

This study is not considered to be suitable for the PNEC derivation or SSD because of the lack of confirmation of exposure concentrations.

3) The most sensitive acute result reported for the mysid shrimp *Americamysis bahia* is a 96-hour $LC_{50}$ of 1.1 mg/l (NOEC = 0.51 mg/l) (Springborn Bionomics, 1985b; Alexander *et al*., 1988). The test conditions and methods are fully described in the test report, concentrations were measured and the test is considered to be valid. This value is supported by a 96-hour $LC_{50}$ of 1.03 mg/l reported by Hirano *et al*. (2004) in a study without analytical confirmation of test concentrations. Both of these studies report short-term lethality results, which are not suitable for inclusion in an SSD (but the 96-h $LC_{50}$ of 1.1 mg/l could be used in the derivation of a saltwater PNEC).

Echinoderms

1) Roepke *et al*. (2005) exposed sea urchin *Strongylocentrotus purpuratus* embryos to bisphenol-A for 96 hours post-fertilisation and measured the percentage achieving the pluteus stage when compared to controls. The $EC_{50}$ was 0.227 mg/l (95% confidence interval 0.122 – 0.324 mg/l). The concentration of bisphenol-A in the 20 ml glass vials used to run these tests was not measured. Addition of tamoxifen, an estrogen receptor agonist, substantially reduced these teratogenic effects, while addition of ICI 182 780, a complete estrogen receptor antagonist in mammals, increased developmental abnormalities by 10-20%.

2) Kiyomoto *et al.* (2006) investigated the effect of ethynylestradiol and bisphenol-A on the development of sea urchin embryos and juveniles. Two species of sea urchin were used, *Hemicentrotus pulcherrimus* and *Strongylocentrotus nudus*; both were collected from the wild in Japan. Eggs and sperm were obtained from the collected animals in the laboratory. Exposures were started either with newly fertilised eggs, or with embryos following hatching at 12 hours post fertilisation. In both cases 500 organisms (eggs or embryos) were used. Exposures took place over different durations, up to 48 hours post fertilisation. The exposure levels ranged from 1.25 to 10 µM (0.29 to 2.3 mg/l). The development of the embryos was observed and categorised in five stages.

   The control eggs hatched at 12 hours after fertilisation, and reached stage 5 (pluteus larvae) after 48 hours. In the bisphenol-A exposed animals, this normal development was only affected at the higher concentrations 1.1 and 2.3 mg/l, and only when the exposure began with the eggs. Embryos exposed from 12 hours after fertilisation showed no effects. Ethynylestradiol produced effects at much lower concentrations and in exposures beginning with embryos as well as with eggs. Although the concentrations were not measured the exposures were relatively short (in particular those over 12 hours from fertilisation), and this part of the study indicates a NOEC of 0.71 mg/l for effects on eggs.

   The authors also exposed juvenile sea urchins (*H. pulcherrimus*) following metamorphosis (~45 days after fertilisation) to bisphenol-A at 0.5 µM (0.11 mg/l) for 80 days. The exposure solutions were renewed every week. After 80 days the test diameters of the juveniles were measured. Animals exposed to bisphenol-A had an average test diameter only half that in the

controls. Ethynylestradiol exposure produced animals with a larger diameter than the controls. As only one concentration was tested no NOEC can be derived and so the result cannot be used in the assessment. This part of the study showed effects at lower concentrations than the egg and embryo exposures.

These studies are not considered to be suitable for the PNEC derivation or SSD because of the lack of confirmation of exposure concentration.

#### 3.2.1.4 Vertebrates

##### 3.2.1.4.1 Fish

Given the widespread interest in the effects of endocrine disrupting substances on organisms, it is not surprising that many studies have been performed using fish, including both whole organisms and isolated tissues. For example, Smeets *et al*. (1999) determined the *in vitro* estrogenic potential of bisphenol-A using cultured hepatocytes from the male carp (*Cyprinus carpio*). Estrogenicity was measured as induction of vitellogenin. Bisphenol-A was found to induce vitellogenin production with a relative potency of $1.10^{-4}$ to 17β-estradiol and a LOEC of 50 µM (11 mg/l). Bisphenol-A was also found to exhibit cytotoxic effects at 100 µM (22 mg/l) the highest concentration of bisphenol-A tested. Pawlowski *et al*. (2000) studied the estrogenic response of bisphenol-A in cells from rainbow trout (*Oncorhynchus mykiss*) and the variation of the response with temperature. Estrogenic response was measured *in vitro* using cultured hepatocytes from male rainbow trout using a non-radioactive dot blot/RNAse protection assay and by RT-PCR. They found that bisphenol-A was estrogenic with a relative potency of $10^{-4}$ to $10^{-5}$ of that of 17β-estradiol. They also found that a higher response rate was measured at 18°C than 14°C with a LOEC of 10 µM (2.3 mg/l) after 48 hours exposure at 14°C and a LOEC of 1 µM (0.23 mg/l) after 48 hours exposure at 18°C. The lowest LOEC measured for vitellogenin induction was 0.1 µM (23 µg/l) after 96 hours exposure at 18°C. Jurgella *et al*. (2006) incubated fragments of liver and kidney tissue from immature lake trout (*Salvelinus namaycush*) with bisphenol-A, and found that 100 µM (23 mg/l) inhibited the production of water soluble (conjugated) metabolites of 17β-estradoil. Several other recent papers have also investigated the effects of bisphenol-A on fish hepatocytes or other cells (e.g., Gushiken, 2002; Hassanin *et al*., 2003; Letcher *et al*., 2005; Rouhani Rankouhi *et al*., 2004; Suzuki and Hattori, 2003), or have investigated bisphenol-A binding affinities and interactions with ligands in fish (e.g., Alo' *et al*., 2005; Ohkimoto *et al*., 2003; Tollefsen *et al*., 2004).

Whilst such *in vitro* studies are useful for elucidating mechanisms of action or for developing environmental screening tools, they are not useful for deriving a PNEC for protecting populations of organisms. However, a similar type of study that may be of greater environmental relevance is reported by Thomas and Doughty (2004). They collected sperm from Atlantic croaker (*Micropogonius undulatus*) and treated it with a progestin in the presence or absence of several potential endocrine disrupting chemicals. The lowest concentration of bisphenol-A that significantly reduced upregulation of sperm motility by the progestin was 0.1 µM, which is equivalent to 23 µg/l. This result may be significant for the functioning of fish reproduction, but the authors acknowledge that the environmental relevance of their findings remain unclear. In this case, the lack of confirmation of exposure concentrations also makes the study unsuitable for the PNEC derivation.

The following sections discuss the available *in vivo* studies, grouping the data for individual species together (freshwater first, followed by saltwater).

Freshwater species

1) Carp *Cyprinus carpio*

Bowmer and Gimeno (2001) have studied the effects of bisphenol-A on the development of the male carp reproductive tract when exposed during sexual differentiation (only an extended abstract of this study was available at the time of writing and no published paper has been found subsequently). Males were exposed to nominal concentrations of 10, 32, 100, 320 and 1,000 µg/l bisphenol-A under flow through conditions, during the period of sexual differentiation (from 45 to 55 days post hatch onwards). Two experiments were performed, the first conforming to the OECD principles of GLP. In both experiments nominal concentrations were confirmed by analysis. In the first experiment 28- and 49-day NOECs for growth (wet weight) were >600 and 100 µg/l bisphenol-A; in the second experiment 28- and 56-day NOECs were both 226 µg/l. In the first experiment 28- and 49-day NOECs for oviduct formation were 100 and 16 µg/l bisphenol-A while in the second experiment they were 60 and 17 µg/l. These results should be considered as "valid with restriction" because a full report is not available. The effects on oviduct formation cannot be related directly to demographic parameters such as survival, growth or reproduction, and so are not used in the PNEC derivation directly.

The 49-d growth NOEC of 100 µg/l for *Cy. carpio* is considered suitable for use in the PNEC derivation and SSD.

2) Goldfish *Carassius auratus*

Suzuki *et al*. (2003) exposed immature fish to a single concentration of $10^{-6}$ M (~230 µg/l) bisphenol-A for 8 days and measured effects on plasma vitellogenin, calcium and calcitonin levels. Vitellogenin was detected in the exposed fish. Calcium concentrations were significantly higher than controls on day 4 and significantly lower on day 8. Plasma calcitonin concentrations were significantly lower than controls on day 8. This shows that bisphenol-A can affect calcium metabolism in teleost fish, but the single dose and lack of confirmation of exposure concentration means that these results are not suitable for use in deriving a PNEC.

3) Zebrafish *Danio rerio*

Bayer AG (1999a) report a 14-day NOEC of 3.2 mg/l and a LOEC of 10.15 mg/l from semi-static tests performed according to OECD guideline 204. The endpoints studied were mortality and visual effects on appearance and behaviour; the specific effect on which the NOEC was defined is not given.

Schäfers *et al*. (2001) studied the estrogenic impact of bisphenol-A in a full life cycle study (only an extended abstract on the work has been seen, but see further references later in this sub-section). They found that bisphenol-A exposure affected juvenile growth, time until first spawning, egg production and fertilisation rate. The $EC_{50}$ and NOEC for fertilisation rate were 1.45 mg/l and 0.76 mg/l, respectively. Bisphenol-A showed a lower estrogenic potency than ethinylestradiol. Similar results were found by Fenske *et al*. (2001) who looked at alterations in vitellogenesis and reproduction in zebra fish exposed to ethinylestradiol and bisphenol-A.

Segner *et al*. (2003a)[17] report a full life cycle study in which zebrafish were exposed to 94-1,500 µg/l bisphenol-A, with analytical confirmation of exposure concentrations. The LOEC for vitellogenin induction and changes in gonad histology was 375 µg/l (the NOEC was 188 µg/l). The LOEC for juvenile growth, time to spawning, mating behaviour, eggs per female and fertilisation success was 1,500 µg/l (the NOEC was 750 µg/l). There was no effect on the hatching rate of offspring. The absence of a considerable number of pertinent experimental design details, lack of discussion on analytical details and sparse presentation of results mean that this study should be classed as "valid with restriction". Nevertheless, it is considered suitable for the PNEC derivation and SSD, even though the most sensitive end points cannot be related directly to demographic parameters such as survival, growth or reproduction.

Lindholst *et al*. (2003) examined the toxicokinetics of bisphenol-A in zebrafish and rainbow trout. It was suggested that zebrafish may be less sensitive than rainbow trout because of more rapid metabolism of bisphenol-A in the zebrafish liver. However Van den Belt *et al*. (2003) compared vitellogenin induction in zebrafish and rainbow trout after a three week semi-static exposure to 40, 200 and 1000 µg/l bisphenol-A and found no evidence for a difference in sensitivity, with significant induction in both species occurring at only the highest concentration.

Drastichová *et al.* (2005) exposed zebrafish (*Danio rerio*) to bisphenol-A in their food. The exposures were begun with 20-day old fry, a stage which is prior to differentiation between males and females. Bisphenol-A in ethanol solution was mixed with decapsulated brine shrimp (*Artemia salina*) eggs at 500, 1000 and 2000 mg/kg. The fish were fed three times a day over the 45 day exposure period, and the water in the exposure vessels was changed three times per week. The sex of each fish was established from the morphology of the gonads at the end of the exposures. The sex ratio in the controls was 1:1. The ratios in the exposures were (female:male) 1.4:1 at 500 mg/kg, 3.8:1 at 1000 mg/kg and 11.5:1 at 2000 mg/kg. The ratios were significantly different from the controls at 1000 and 2000 mg/kg. Fish exposed to 20 mg/kg 17β-estradiol as a positive control all developed as females. The exposure route means that the result is not suitable for use in the risk assessment.

In summary, the NOEC of 750 µg/l for multiple end points from a *D. rerio* full life cycle study is considered suitable for use in the PNEC derivation and SSD. It is noted that vitellogenin induction and changes in gonad histology were observed at this concentration.

4) Rainbow trout *Oncorhynchus mykiss*

Lysak and Marcinek (1972) report a 24-hour $LC_{100}$ of 7 mg/l bisphenol-A and a 48-h NOEC of 5 mg/l for rainbow trout (*Oncorhynchus mykiss*), while Reiff (1979) reports a 96-hour $LC_{50}$ of 3-5 mg/l. Test methods were not stated and concentrations of bisphenol-A were not measured.

Bayer AG (1999b) report the results of a 28-day juvenile growth test on rainbow trout using bisphenol-A. The test followed the proposed OECD guideline 215 for "Fish, Juvenile growth test". The NOEC and LOEC for growth rate were 3.64 and 11.0 mg/l respectively (both

[17] Segner *et al*. (2003b) also report the results of a life cycle test with zebrafish, which is very likely the same test reported in Segner *et al*. (2003a). For example, the exposure concentrations appear to be identical (94, 188, 375, 750 and 1,500 µg/l). This study might also be the same as that reported by Schäfers *et al*. (2001). For example, the reproduction $EC_{50}$ is stated to be 6,140 nM (equivalent to approximately 1.4 mg/l), which is similar to the value reported by Schäfers *et al*. (2001). Schäfers is one of the co-authors of the Segner *et al*. papers.

arithmetic means of analytical values). This chronic study is fully valid, was conducted under full GLP and followed an OECD Guideline.

Lindholst *et al*. (2000) studied the estrogenic response to bisphenol-A in rainbow trout, which were exposed to bisphenol-A via a continuous flow-through system. Vitellogenin concentrations were measured during the exposure period (12 days). A significant induction of vitellogenin synthesis was observed in the 500 µg/l bisphenol-A exposure group over the study period. In lower exposure groups (40 and 70 µg/l) steadily increasing levels of vitellogenin were observed between 6 and 12 days only. Based upon the data the NOEC for vitellogenin production is taken as 40 µg/l. In a further study, Lindholst *et al*. (2001) again exposed rainbow trout to bisphenol-A in a continuous flow-through system (at 100 µg/l), and also through intraperitoneal injection (at a tissue concentration of 35 mg/kg). Both male and female fish showed increased levels of vitellogenin in the injection exposures, with a lag period of 3-5 days for females and 5-7 days for males. Measured levels of bisphenol-A in the livers of the fish had decreased almost to the detection limit before the increase in vitellogenin was noted. Fish in the continuous exposures did not show significantly higher levels of vitellogenin up to the end of the experiment after seven days. Neither of these two studies can be used for the PNEC derivation or SSD since the exposure concentrations were not measured and the end point cannot be related to population effects.

As mentioned above for zebrafish, Lindholst *et al*. (2003) considered that rainbow trout may be more sensitive than zebrafish due to differences in liver metabolism, yet Van den Belt *et al*. (2003) found no evidence for a difference in sensitivity regarding vitellogenin induction (with significant induction only occurring at 1,000 µg/l after a three week semi-static exposure).

In summary, the 28-d NOEC for juvenile growth rate of 3.64 mg/l for *O. mykiss* is considered suitable for use in the PNEC derivation and SSD.

5) Atlantic salmon *Salmo salar* (m. *sebago*)

Honkanen *et al*. (2004) exposed 8-day old yolk-sac fry to nominal concentrations of 10, 100 or 1,000 µg/l bisphenol-A for 42 days. Test media were renewed every 48 hours, but there was no chemical confirmation of exposure concentrations. After 6 days, yolk-sac oedemas and haemorrhages around the gill arches and in the front part of the yolk sac were observed in fry exposed at the highest concentration. After 8 days fry at the highest concentration were lethargic and remained inactive, and by 17 days they were darker in colour than fry at other concentrations. At the end of the experiment fry at the highest concentration remained lethargic, were darker, and some still had yolk-sac oedemas, although others appeared to have recovered. There was also some evidence that fry in the highest concentration weighed significantly more than other fry, although they did not weigh significantly more than those in the solvent control. Histological analysis of fry livers revealed strongly stained fragments in the nuclei of hepatocytes in the 100 and 1,000 µg/l groups, plus a reduction in liver cell storage substances and a difference in the shape of cytoplasmic vacuoles. This study is not considered to be of direct use for the PNEC derivation because of the lack of confirmation of exposure concentration.

6) Brown trout *Salmo trutta*

Lindholst *et al.* (poster presentation; 2002) exposed eggs to 50 µg/l of bisphenol-A from fertilisation through to 64 days post fertilisation, corresponding to the time of first feeding. The concentrations of bisphenol-A and bisphenol-A glucuronic acid (BPAGA) were

measured in the eggs and developing fry. A rapid increase in the concentration of BPAGA was observed at 35 days post fertilisation, on hatching, possibly due to increased uptake of bisphenol-A through the gills at this time. The bioconcentration factor measured in developing eggs was 10, and in the fry it was 14. After hatching, fish were kept for up to 400 days in clean water, and observations were made on the gonads and sex of the fish. No changes were seen in the sex ratio compared to the controls. Generally there were a higher number of males in both exposures and controls, but there was no increase in the percentage of mature males at 400 days. There were no significant differences in the gonadosomatic index of male fish in this study. This study is not considered to be suitable for PNEC derivation because only a single exposure concentration was used, and the actual exposure level was apparently unconfirmed.

7) Japanese medaka *Oryzias latipes*

Several short-term results are available. MITI (1977) report a 48-hour $LC_{50}$ of 15 mg/l, Tabata et al. (2001) report 72-hour $LC_{50}$ values of 5.1 mg/l for embryos and 7.5 mg/l for adults exposed in semi-static systems.

Several longer-term studies have been reported as follows:

a) Shioda and Wakabayashi (2000) exposed male *Or. latipes* to a natural estrogen (17β-estradiol) and three estrogenic substances including bisphenol-A. After 14 days' exposure, one male was kept with two females for spawning. The results indicated that bisphenol-A caused a decrease in the number of hatchlings at a concentration of 2.3 mg/l. No effects were observed at the lower concentrations that were tested (68, 230 and 680 µg/l). This study was designed to look at the effects of endocrine disrupters on reproduction due to *in vivo* exposure. Due to the different study protocols used it is not possible to compare the estimated potency of bisphenol-A with that of 17β-estradiol.

b) Tabata *et al*. (2001) studied the effect of bisphenol-A on mature male *Or. latipes*. No concentration monitoring was undertaken to confirm the exposure levels. After two weeks' exposure to 100 µg/l bisphenol-A, female specific proteins could be detected in the fish, but no effects were observed at 0.1 or 10 µg/l exposure. After five weeks' exposure female specific proteins were found in the 10 µg/l exposure group but not in the 0.1 µg/l exposure group. Abnormalities in the gonad tissue were observed in the 100 µg/l exposure group in one animal of the sixteen exposed. There was no observation of any sex bias towards females in any of the bisphenol-A exposure groups. Tabata *et al*. (2003a&b, 2004) also report results for *Or. latipes* exposed in flow-through systems to bisphenol-A for five weeks in what appear to be different studies to Tabata *et al*. (2001) which produced less sensitive results. Tabata *et al*. (2003a) and Tabata *et al*. (2004) report the same study in which the NOEC for vitellogenin induction was 200 µg/l and the LOEC was 500 µg/l, with significant induction at 500 µg/l beginning on day 3 of the study. Weekly chemical analysis confirmed that test concentrations remained within 77.2 – 102.6% of nominal. Tabata *et al*. (2003b) report a study in which the effect of chlorination on bisphenol-A estrogenicity was assessed when fish were exposed to 100 or 1,000 µg/l for five weeks. Chlorination appeared to remove bisphenol estrogenicity.

c) Na *et al.* (2002) studied the effects of bisphenol-A on sex differentiation and gonadal development in *Or. latipes*. Fish were obtained from a stream in the wild, and breeding fish were cultured for three months. Fertilised eggs were removed and incubated until hatching. Newly hatched larvae were exposed to bisphenol-A in a static renewal system at nominal concentrations of 50, 100 and 200 µg/l (there is no indication that actual

concentrations in the exposures were measured). Solutions were renewed every 72 hours for the first month and then every 48 hours thereafter. The total length of the exposures was 70 days. Fish were sampled at 10, 20, 30 and 70 days. Saggital sections of the gonads of the fish (male and female) were examined and the proportion of the section occupied by each type of germ cell was determined. Length and weight (at 70 days only) were also determined.

No differences of gonadal development in the process of sexual differentiation were observed between any groups until 30 days after exposure began. At 70 days, bisphenol-A exposed female fish had greater proportions of the later stages of oocytes, including mature eggs, which were not present in the controls. In males, the proportions of the later stages of spermatogenesis were reduced; at the highest exposure level there were very few spermatocytes or spermatids.

A chi-square analysis of numbers of females and males showed a 1:1 ratio in the controls and the 200 µg/l exposure, but a 2:1 (female:male) ratio in the other two exposures. However, this section of the paper is unclear. The ratios are based on the sum of the numbers at each time interval and a much larger number was sampled at 30 days, so the ratio is dominated by the numbers then. At 20 days, the control ratio was 3:1 f:m.

The lengths of fish exposed to 50 or 100 µg/l were not significantly different from the controls, but fish exposed to 200 µg/l were longer than those in the other groups after 30 and 70 days exposure. Fish in the high exposure group were also heavier. The NOEC for a growth effect is therefore 100 µg/l (for promoting growth).

The authors conclude that bisphenol-A appears to contribute to the accumulation of vitellogenin in oocytes in females. In males, it inhibits spermatogenesis, and exposed fish had less developed testicular structure. Lack of chemical analysis means that these results are not suitable for direct use in deriving a PNEC.

d) Yokota *et al*. (2000) report a fully valid and thoroughly described extended early life stage study that examined a number of ecologically critical endpoints. *Or. latipes* were exposed to bisphenol-A from fertilised eggs through to 60 days post-hatch. Five concentrations were used: 2.28, 13.0, 71.2, 355 and 1,820 µg/l (as mean measured concentrations, detection limit 2.5 µg/l.) Semi-static exposures were used for the embryos, with flow-through exposures for larvae. The low exposure concentrations were more stable in the semi-static exposures (which is unexpected). The parameters monitored were egg hatchability, time to hatching, cumulative mortality and growth (total length and body weight).

An initial pre-test established a 96-hour $LC_{50}$ of 13.0 mg/l. In the main study, no significant effects were seen on hatchability, time to hatch, or mortality at any exposure. (Hatching of some embryos was significantly delayed in the 13 µg/l exposure, but there was no dose response and higher exposures showed no differences from controls.) Growth was reduced at 60 days - this was a dose-related effect, with only the highest exposure level producing a significant reduction ($p=0.005$). Sex ratios were determined from external secondary sexual characteristics. Ratios were 1:1 at concentrations of 71 µg/l and below; at 355 µg/l there were more females than males (5:13); and there were no males at the highest concentration. Sex ratios were also determined through gonadal histological investigation (this allowed some of the fish that did not show clear secondary sexual characteristics to be sexed). These results showed a similar pattern, with the ratio at the highest concentration significantly different from that in the controls (which was

2:1 male to female). The sexual characteristic results were not treated statistically as they are not considered reliable indicators of sex. The examination also looked for cases of testis-ova; cases were only found at the highest exposure concentration. The authors concluded that the lowest effect concentration was between 355 and 1,820 µg/l, although they noted that the study did not investigate whether early life exposure would impair reproduction as adults.

e) Kang *et al*. (2002) examined the effects of bisphenol-A on the reproductive capacity (fecundity and fertility) and estrogenic response of adult *Or. latipes* and studied the transgenerational effects (F1 generation growth and sex) of this substance on the F1 offspring. The test methods used are now being recommended by the OECD for elucidation of effects on survival, growth, and reproduction of potential endocrine disrupting compounds (paired breeding assay and extended early life stage test). Sexually mature *Or. latipes* at four months after hatching (300 mg body weight, 33 mm length) were acclimated to flow through conditions for three weeks in 56 breeding pairs in individual 1 litre chambers. The fecundity of each pair was checked daily, and over the last week of the acclimation period eggs were collected daily, a few hours after deposition, counted and assessed for fertility. From these fish, 32 pairs were selected which spawned every day, with ≥15 eggs per day and mean fertility >90%. These fish were exposed to bisphenol-A for three weeks, at nominal concentrations of 0, 1,000, 2,000 and 4,000 µg/l. The concentrations in the exposure chambers were measured twice each week during the exposures. The levels varied, falling as low as 60% of the nominal concentration on one day, but the average concentrations were 78-86% of nominal. The average measured levels were 837, 1,720 and 3,120 µg/l.

Eggs were collected daily and assessed for fecundity and fertility under a light microscope. All fish were sacrificed at day 21, and histological evaluation and determination of vitellogenin were carried out.

Eggs collected on days 18-20 from the exposure and control groups were used to assess trans-generational effects. Eggs were incubated in dechlorinated tap water and hatched larvae were transferred randomly to four test chambers for each treatment. One week after the mean time for hatching across all treatments, 15 larvae from each chamber were selected randomly and kept until day 60 to assess abnormal development and mortality.

There was no decrease in fecundity or fertility in any of the treatments compared to the controls. One male died in the 1,720 µg/l exposure on day 11, and one female fish died in the 837 µg/l exposure on day 17. Neither of these dead fish showed any pathological changes. The gonadosomatic and hepatosomatic indices of both sexes of fish were unaffected by bisphenol-A exposure. Intersex gonads (testis-ova) were observed in males at all three of the exposure levels – one case at 837 µg/l, six at 1,720 µg/l and four at 3,120 µg/l. No instances of testis-ova were observed in the controls. Cells indicative of normal spermatogenesis were also found in all of the gonads examined. No histological abnormalities were noted in the ovaries of any of the female fish exposed, or the controls.

Vitellogenin levels were significantly elevated above the controls in male fish at the highest exposure concentration used. The levels at this concentration were similar to those found in female fish in the controls and at all exposure levels. Levels of vitellogenin in four of the seven male fish examined from the 1,720 µg/l exposure exceeded the detection limit but were not significantly elevated above the controls.

Bisphenol-A had no observable effect on the survival and growth of offspring at 60 days after hatching. Low mortality was seen at all three exposure levels and was not significant. Length and weight were not significantly affected. The sex ratios did not differ significantly between the controls and the exposed fish, although the controls contained more males than females (1.52:1), the 837 µg/l exposure had more females than males (0.71:1) and the two higher exposure levels had approximately equal ratios (1:1). The authors concluded that although bisphenol-A induced hepatic vitellogenin and gonadal intersex in male fish, these effects are not associated directly with effects on reproduction.

f) Metcalfe *et al*. (2001) examined growth and sexual differentiation endpoints over the course of an extended early life stage test. These are ecologically relevant endpoints and the study is well reported. *Or. latipes* fry were exposed to bisphenol-A in a static renewal system from one day after they had hatched until they reached a length of 1.5 cm (approximately 90 days post-hatch). The fry were then examined histologically to determine phenotypic sex and incidence of testis-ova. Exposure concentrations of bisphenol-A were 0, 10, 50, 100 and 200 µg/l, and test medium was replaced every 48 hours; chemical analysis showed that average concentrations over 48 hours were 59.6% of nominal. Fish exposed to the two highest test concentrations had a significantly higher condition factor (weight divided by total length) than fish in the other groups, but there were no significant differences between treatments in either total length or wet weight alone. Sex ratios did not differ after exposure to any of the bisphenol-A concentrations. Testis-ova were observed in only two males from the lowest test concentration, but not in any fish from the higher concentrations. Male fish at the higher concentrations (50, 100 and 200 µg/l) showed several morphological changes in testes, and female fish at the highest concentration had ovaries in advanced stages of oogenesis in comparison to control females.

g) Kashiwada *et al*. (2002) exposed *Or. latipes* eggs, embryos or adults to nominal concentrations of bisphenol-A for three days, with daily medium renewal. 72-hour $LC_{50}$ values were 9 mg/l for eggs (95% confidence interval 7.1-11 mg/l), 5.1 mg/l for embryos (95% confidence interval 4.2-6.7 mg/l), 6.8 mg/l for adult males (95% confidence interval 5.9-7.7 mg/l) and 8.3 mg/l for adult females (95% confidence interval 7.4-9.4 mg/l). Adult males were also exposed for five weeks under flow-through conditions to nominal concentrations of 0.1, 10 or 100 µg/l bisphenol-A, with chemical analysis confirming that measured concentrations remained within 10% of nominals. Fish were sampled at the end of weeks 1, 2, 3 and 5 for analysis of female specific proteins. These proteins were detected in males exposed to 10 µg/l after 4-5 weeks and in males exposed to 100 µg/l after two weeks.

h) Embryos of medaka (*Or. latipes*) were exposed to bisphenol-A in scintillation vials, with five embryos per vial (Pastva *et al*, 2001). Two concentration of bisphenol-A were used, 20 and 200 µg/l, with five replicates per concentration. Solutions were renewed every 24 hours for nine days, and a new standard solution of bisphenol-A was prepared every day. Individual embryos were observed daily and compared to a published atlas of normal medaka development. Abnormalities for each embryo were recorded and a score (severity index) for each test vessel. Larval stages were also exposed to 200 µg/l for 96 hours with a similar solution renewal pattern.

The data for the severity index were analysed using a repeated measures function, to take account of the non-independence of the observations – if a fish had a deformity on day 6 it was likely to have the same one on day 7. No deformities were noted until after day 3.

The severity index in the 200 µg/l exposures was greater than that in the controls for days 5 to 8, but by day 9 it was not significantly different, due to reduced severity of lesions in some individual embryos. Hence the effects were largely transient. Most embryos did not show deformities. There were no mortalities in the exposed larvae.

i) Ishibashi *et al.* (2005) exposed eggs of medaka (*Or. latipes*) from a few hours after fertilisation to bisphenol A at nominal concentrations of 1563, 3125, 6250, 12500, 25000 and 50000 µg/l for 14 days. There were two replicates at each concentration, with 30 eggs per replicate. A semi-static exposure regime was used, with solutions changed every 24 hours. The 14-day $LC_{50}$ value determined in these exposures was 14.8 mg/l. The hatchability of eggs was decreased compared to the controls at concentrations above 12,500 µg/l. The time to hatching was not affected.

The same authors also exposed eggs under similar conditions to MBP (4-methyl-2,4-bis(4-hydroxyphenyl)pent-1-ene, a metabolite). Concentrations used were 313, 625, 1250, 2500 and 5000 µg/l. This study gave a 14-day $LC_{50}$ of 1,730 µg/l; hatchability was affected at concentrations above 1,250 µg/l and the time to hatching increased at all exposure concentrations.

Adult male medaka were exposed from three months old to nominal concentrations of 250, 500, 1000 and 2000 µg/l bisphenol-A for 21 days. Seven males were used per concentration, and the solutions were changed every 24 hours. At the end of the exposures the body weight, and total length were measured. Livers and gonads were sampled, and the HIS and GSI were calculated as the ratios of the organ to body weight. Hepatic vitellogenin levels were measured. Bisphenol-A did not affect growth (weight or length) and there were no effects on survival at 2,000 µg/l. Similarly there were no effects on HIS or GSI over 21 days. Vitellogenin levels in the liver were significantly higher in the 1,000 and 2,000 µg/l exposures.

The metabolite MBP was also tested under similar conditions to the above. The 21-day $LC_{50}$ was estimated as 63.4 µg/l. There were no effects on the GSI up to 1,000 µg/l, but the HIS was significantly higher than in the controls at 37 µg/l. Vitellogenin levels in the liver were significantly increased over the controls at 4.1 µg/l and above.

j) Three other studies on Japanese medaka have recently been completed in Japan. Full details are unavailable, but the text for the results tables is available (Japanese Ministry of the Environment, 2006):

- In one study fish were exposed for 21 days to 0, 58.5, 141, 334, 772 and 1,740 µg/l mean measured concentrations of bisphenol-A. All fish survived at concentrations up to 334 µg/l; there was 3.3% and 13.3% mortality at 772 and 1,740 µg/l, respectively. At 21 days the hepatosomatic index increased significantly at 334 µg/l and vitellogenin concentrations were significantly higher at the same level.
- In a second study (a partial life-cycle test) groups of 20 fish were exposed to 0, 220, 470, 890, 2120 and 4,410 µg/l mean measured bisphenol-A. Hatching rate was unaffected at all concentrations, but time to hatching was significantly greater at the highest concentration. Body length was significantly greater than controls at 470 and 890 µg/l, but not at the two highest concentrations. Body weight was significantly greater than controls at 220 and 470 µg/l, and significantly lower at 4,410 µg/l, with no significant difference at 890 and 2,120 µg/l. The gonadosomatic index was unaffected in this study, but there were significant effects on incidence of testis-ova at 890 µg/l, male hepatosomatic index at 4,410 µg/l, female hepatosomatic index at

2,120 µg/l, male liver vitellogenin at 470 µg/l and female live vitellogenin at 2,120 µg/l.

- In a third study (a full life-cycle test), groups of 20 medaka were exposed to 0, 2, 9.3, 49.7, 247 and 1,179 µg/l mean measured bisphenol-A. There were no effects on F0 hatching rate, days to hatching, body length, body weight, gonadosomatic index, number of eggs, incidence of testis-ova, liver vitellogenin and female hepatosomatic index, but there was a significant increase in mortality at the highest test concentration and in the male hepatosomatic index at 49.7 µg/l. In the F1 generation there were no significant effects on survival, days to hatching, gonadosomatic index or female liver vitellogenin. There were effects in the F1 generation on testis-ova and male liver vitellogenin at the highest concentration. Differences in body length and weight were small and although some were significant there were no linear or U-shaped dose-response relationships. There was a significant reduction in hatching rate at 2 µg/l of about 10%, but no significant reductions at any of the other test concentrations. Taken together, these results suggest that the most sensitive reliable NOEC for *Or. latipes* is 247 µg/l for F0 survival (28% mortality compared with 11-12% in the controls) with a LOEC of 1,179 µg/l. Measured effects below this NOEC are either difficult to interpret or do not appear to have influenced survival, growth or reproduction.

k) Several other authors have also measured vitellogenin induction or gene expression in *Or. latipes* exposed to bisphenol-A. Yamaguchi *et al*. (2005) exposed adults to nominal concentrations of 800 or 8,000 µg/l bisphenol-A for 8 hours and then analysed liver vitellogenin. There was significant induction of vitellogenin II and ERα at 8,000 µg/l, but not at 800 µg/l, and no induction of vitellogenin I at either concentration. Nagae *et al*. (2005) exposed fish to nominal vitellogenin concentrations of 100, 500, 1,000, 5,000 and 10,000 µg/l bisphenol-A for three days, with renewal of test medium every day. Induction of vitellogenin I and II was only apparent at concentrations above 5,000 µg/l. Chikae *et al*. (2003) exposed adult males to 0, 0.02, 0.2, 2, 20 and 40 mg/g bisphenol-A in their diet for 14 days and estimated an $EC_{50}$ for plasma vitellogenin induction of 1.6 mg/g. Lee *et al*. (2002) exposed adult males to nominal concentrations of 5, 50, 100, 200 or 500 µg/l bisphenol-A for 144 hours and found that choriogenin mRNA, which is involved in egg formation in females, began to be expressed in males exposed to ≥50 µg/l.

Many of the studies reported above provide results for secondary supplemental end points (such as vitellogenin, other proteins, histology and other biomarkers) which provide useful information on possible mechanisms of action. However, only long-term end points related to mortality, growth and reproduction (i.e., endpoints of demographic importance) should be used to derive the PNEC. In this regard several of the studies are highly relevant and of high quality, and include measurement of exposure concentrations (particularly Yokota *et al*. (2000), Kang *et al*. (2002), Metcalfe *et al*. (2001) and Japanese Ministry of the Environment (2006)). Inclusion of more than one study for a single species in an SSD would introduce bias, and calculation of a geometric mean for *Or. latipes* is not possible because the study durations differ. After consideration of all of the studies, the new results from the Japanese Ministry of the Environment (2006) are considered to be the most useful for inclusion in an SSD. Although full details are lacking, results are presented for end points of clear demographic importance from a multi-generation study with measured test concentrations.

The NOEC of 247 µg/l for multiple end points in a full life cycle study with *Or. latipes* is considered the most relevant for use in the PNEC derivation and SSD. Effects observed below this NOEC are either difficult to interpret or do not

appear to have influenced survival, growth or reproduction.

8) Fathead minnow *Pimephales promelas*

Two short-term results are available. Alexander et al. (1985a and 1988) report 96-hour $LC_{50}$ values of 4.7 (static) and 4.6 mg/l (flow-through) (nominal concentrations). The test conditions and methods are fully described in the test report, and the studies are considered valid.

Sumpter et al. (2001) (partly published as Sohoni et al., 2001) report a multigenerational study on P promelas that examined effects of bisphenol-A on the F0, F1 and F2 generations. Exposure was to nominal concentrations of bisphenol-A (1 µg/l, 16 µg/l, 160 µg/l, 640 µg/l and 1,280 µg/l) in a flow-through system. Nominal test concentrations were confirmed by measurements of bisphenol-A in the test media. Fish were also exposed to a dilution water control throughout the experiment. The study began with adult fish at 120 days post hatch, with 60 fish per treatment level. At day 42 of the study, eight breeding pairs per treatment were randomly selected and used to assess the fecundity of the F0 generation. Spawnings of 50 embryos from single females were used in hatchability trials. Two cohorts of eggs from these breeding pairs were taken and used in two separate early life stage studies (commencing on days 56 and 155 of the study). Fish larvae from the hatchability trials were discarded at the end of the trials, but those from the early life stage studies were transferred to the progeny tanks to form the F1 generation. The F0 breeding pairs were sacrificed on day 164 of the study. Other adult fish in the F0 generation were sacrificed after 43 and 71 days of the exposure.

Fish of the F1 generation were continuously exposed through to sexual maturity. On day 275 of the study (when the F1 fish were an average of 150 days old) eight breeding pairs were randomly selected and a similar series of tests to those above conducted: fecundity measurements on the F1 generation; hatchability trials on the F2 generation; and an early life stage test on the F2 generation. Adults from the F1 generation not selected for breeding were sacrificed on day 295 of the study. The study was terminated at 431 days from the start with the sacrifice of the F1 breeding pairs.

During the experiment information was recorded on fish survival, fecundity and hatchability of eggs. Upon sacrifice, intact fish, dissected gonads and blood plasma of the F0 and F1 fish were analysed for vitellogenin, gonad growth and histology of the gonads. For male fish, the gonad histology included a scoring of the various testicular cell types in order to assess the progression of spermatogenesis. The study concluded that bisphenol-A acts as a weak estrogen in vivo to fathead minnow exposed to bisphenol-A via water. The overall NOEC for conventional endpoints of survival, growth and reproduction based on the hatchability of the F2 generation is 16 µg/l. For vitellogenin production a NOEC of 16 µg/l is determined. Some growth endpoints, including gonad size, show NOEC values of <16 µg/l at individual monitoring points, but not consistently over the course of the experiment.

The observations on the testes of the male fish showed that exposure to bisphenol-A had a significant effect on the development of sex cell types compared to the controls. Measurements were made on the relative proportions of each cell type in the tissue, not the absolute numbers of cells. The cells develop from spermatogonia through spermatocytes and spermatids to spermatozoa. For the F0 generation, regression analysis showed that there were dose-related effects of bisphenol-A on the proportion of different cell types. The lowest effective concentration for these responses was 640 µg/l (spermatogonia) and 16 µg/l (spermatozoa). The highest exposure concentration (1,280 µg/l) caused a five-fold decrease

in the relative occurrence of mature spermatozoa while spermatocytes, spermatids and other cell types varied by up to 10%. The relative proportion of spermatogonia increased from ~12% in the controls to 83% at the highest concentration. The NOEC for a reduced proportion of spermatozoa is 1 µg/l. For the F1 generation, there was a positive dose-related effect of bisphenol-A on the proportion of spermatogonia, and an inhibitory effect on the proportion of the testes occupied by spermatozoa. The lowest effect concentration for these responses was 1 µg/l for both spermatogonia and spermatozoa. (This aspect of the study has since been questioned, see comments below following the study conclusions.)

From the data it is not possible to say that inter-generational sensitivity increased or decreased because the F0 generation fish were introduced to the test system as sub-adults, whereas the F1 generation was exposed to bisphenol-A throughout their lives.

From the data the report derived the following conclusions:

- LOEC (survival, 60 days) 640 µg/l (for F1, LOEC>640 µg/l for F0 and F2)
- NOEC (growth, 164 days) 160 µg/l.
- The size of the gonads of female F0 fish, were significantly greater than that of the controls at 1 µg/l on day 43. However, no significant effects were seen at 16 µg/l and subsequently the NOEC rose to 1,280 µg/l (day 71) and 160 µg/l (day 164). In males the NOEC for effects on gonad size was <1 µg/l on day 43 but subsequently rose to 1,280 µg/l (day 71) and 160 µg/l (day 164). Therefore, the NOEC for consistent or dose-related effects is taken as 160 µg/l.
- NOEC (egg production) 160 µg/l for the F1 generation and 640 µg/l for the F0 generation. This is based upon the number of eggs produced per female per day.
- NOEC (hatchability of eggs) 160 µg/l for the F1 generation and 16 µg/l for the F2 generation.
- NOEC (vitellogenin production) 16 µg/l, for F0 males and F1 generation males and females.
- Effects on the different stages of male spermatozoa development were seen at lower concentrations, with a NOEC value for the proportion of spermatogonia and spermatozoa of 1 µg/l for the F0 generation and a LOEC of 1 µg/l for the F1 generation. The hatchability of eggs was affected only at 160 µg/l or greater.

Overall, effects based upon the survival, and reproductive fitness of fathead minnows exposed to bisphenol-A from F0 breeding adults to F2 offspring occurred at concentrations of 640 µg/l bisphenol-A and higher, with hatchability of F2 eggs slightly but significantly reduced at 160 µg/l.

Two independent experts in fish histopathology subsequently reviewed the parts of this study relating to spermatogenesis (D Dietrich, personal communication). It was noted that the study was designed to look for effects on reproduction, hatching and growth. The sampling and examination of gonad tissues for sperm cell types was added after the study design had been implemented, and so the experimental design was not optimised to look at these effects. Some short-comings of this part of the study were identified in relation to the number of fish sampled from each exposure level, the taking of tissue samples from the testes and their preparation for counting, and the number of cells counted in each sample. In addition, the statistical methods used to compare the proportions of cell types in the controls and exposed fish were not appropriate, as the relative proportions of each cell type are not independent of

each other. While these short-comings and general test design are not considered to make the study invalid for population effects in terms of reproduction, hatchability and growth, the experts concluded that the weaknesses in the spermatogenesis data make them unsuitable as the basis for deriving a PNEC. This view was supported by one of the main authors of the study.

The published risk assessment for bisphenol-A (EC, 2003) concluded that further work was needed on this endpoint. As a result a series of studies has been carried out on fathead minnows to investigate further the possible effects on sperm cells and on ovarian cells (Rhodes *et al*, 2007). The initial phase of the work was to develop the methods necessary to visualise and quantify the individual gonadal cell types (Wolf *et al*., 2004). In this phase of the work the fish were exposed to 17β-estradiol. Techniques were developed for the optimal preparation, preservation and processing of gonadal tissues. These tissue samples were used to develop manual tagging procedures for the identification and quantification of gonadal cell types. The developed method allows for a permanent record of all cells identified and counted and therefore facilitates peer review of gonadal cell type assessment.

The second phase of the studies (Caunter *et al*., 2006) was a 42-day range finding study exposing fathead minnows to bisphenol-A in order to demonstrate the above methods. This part of the work also looked at the natural variability of the distribution of cell types, and the consequences for the number of replicates needed in the final study to allow determination of statistically significant effects on gonadal cell type distribution as a result of treatment.

The third phase of the studies was a partial life cycle test over 164 days, with a similar duration and similar bisphenol-A concentrations to those in the P (F0) and F1 parts of the Sumpter *et al.* (2001) study (Rhodes *et al*., 2007). In addition to the cell types, endpoints covered included survival, growth, reproduction, gonadosomatic index and vitellogenin levels. The study involved flow-through exposures to nominal concentrations of 1.0, 16, 64, 160 and 640 µg/l, together with controls. Concentrations were measured regularly during the exposures, and the mean measured levels were 1.19, 13.4, 52.8, 130 and 567 µg/l. These were 81-89% of nominal with the exception of the lowest concentration which was higher than nominal; all exposure levels were reasonably consistent throughout the test. Concentrations in this summary refer to the nominal. The concentration of bisphenol-A in the controls was less than 0.293 µg/l (the analytical limit of quantitation). Other environmental properties were also monitored routinely – dissolved oxygen, temperature, pH, conductivity, alkalinity and hardness – with no notable deviations from the required values.

Testes were fixed, embedded, sectioned and stained according to the methods developed in the earlier phases of the work. Four digital images of each testis (left and right) were obtained at 40X magnification (hence eight images per fish). A grid with 400 intersection points was superimposed on the images, and the intersection points were manually identified as a cell type. The cell types included were spermatozoa, spermatid, spermatocyte, spermatogonium, vacuolated cell (VC), apoptic body cell (ABC), interstitial (Leydig) cell, Sertoli cell, interstitial tissue or unknown cell (ITUC), or empty space. A total of 3,200 points were counted per male fish. The relative frequency of each sperm cell type was expressed as the number of cells of a given type as a proportion of the number of cells that were equally or less mature – the sequence runs from more mature to less mature above, from spermatozoa to spermatogonium. The median frequencies of the other cell types (VC, ABC, Leydig, Sertoli, ITUC) were also determined.

Ovaries were fixed, embedded, sectioned and stained according to the methods developed in the earlier phases of the work. Two digital images were obtained from each of the left and

right ovary sections at 4X magnification (hence four images per fish). All ovarian follicles in the images were identified and tagged as one of six types from least to most mature – perinuclear, cortical alveolar, early vitellogenic, late vitellogenic, mature/spawning and atretic. An average of 408.5 follicles from both left and right ovaries combined were counted from the four images per fish. The relative frequency of each oocyte type was expressed as the number of a given type as a proportion of those equally or less mature.

The gonadal tissue slides were examined microscopically for morphological abnormalities and potential exposure-related changes. These were graded on a severity scale from 1 (minimal) to 5 (severe/high). Gross observations were also made during necropsy and sample preparations, and were related to microscopic observations where possible.

Statistical assessments were carried out on 37 variables for males and 27 for females, using a variety of statistical techniques (for most variables several techniques were employed). Variable-wise comparisons with the control values were carried out for each variable at a significance level of 5%. At this level of significance, on average one in twenty comparisons will show a difference by chance, i.e. a false positive will be detected. To address this, simultaneous significance tests were also carried out, where the level of significance was distributed across the number of endpoints addressed. This was done by initially grouping the variables into five types – size variables (weight, length etc), histopathological tissue lesions, gonad cell type frequencies, reproduction variables (e.g. fecundity, egg production), and others (survival, vitellogenin etc). The significance level was split equally between the five groups, and then further divided between the variables within each group. Splitting the significance level between groups of similar endpoints, such as size or histopathology endpoints, maintains an equal importance or power to detect an effect for each group so that a group with more variables (e.g. histopathology) does not dilute the significance of anther group of endpoints. An effect was considered to be statistically significant if it was significant in both the variable-wise and the simultaneous tests. If an effect was only significant in a variable-wise comparison this was considered an indication of an effect, but not sufficient to conclude an effect at the 5% significance level[18].

For studies with similar methodology and replication, one possible consequence of splitting the significance across the variables in this way is a reduction in the power of the tests to identify a real effect, i.e. an increased possibility of a false negative. A comparison of the statistical power available in the Phase 3 study with the power available in the Sumpter *et al.* study clearly demonstrates a much higher power (lower minimum significant difference which can be detected) in the Phase 3 study. This is due to the improved methodology used for gonadal cell determinations as well as a result of the high replication employed. Thus in the Sumpter *et al*. study, up to eight fish were available for assessment per treatment, compared to up to 32 fish of the same sex in the Phase 3 study. The minimum significant difference of the one-sided Dunnett test in logit units ranged from 1 to 1.2 for the male gonadal cell types in the Sumpter *et al*. study, compared with 0.5 to 0.8 for the same endpoints in the Phase 3 study (calculated on the assumption that the fish were independent of each other). Consequently, even with the splitting of the significance level the Phase 3 study had a much higher likelihood of finding a treatment related effect than the original Sumpter *et al.* study.

[18] Variable-wise significant effects which were not simultaneously significant in any statistical test were observed for male wet-weight at 640 µg/l, for the effects on the number of spawns and the time of first spawning at 640 µg/l, the VTG level in males at 16 µg/l and in females at 16 and 1 µg/l, for the lesion testicular cysts in testis at 640 µg/l, the lesion cellular infiltrates, mononuclear cells in ovaries at 640, 160 and 64 µg/l, and the frequency of VC in the group of VC and ABC in testis at 640 µg/l.

The survival of male fish was significantly reduced at 640 µg/l; no effect was seen on survival of females at any concentration. No statistically significant effects on growth were seen in either males or females, or on gonad weight or gonadosomatic index. Among the breeding pairs of fish there were no significant differences from controls at any concentration in the mean numbers of eggs, the mean number of spawns and the mean number of eggs per spawn. There were no statistically significant effects on hatching, with no significant trend with concentration and no significant differences between treatments.

The levels of vitellogenin were significantly elevated above those in the control fish in both males and females at concentrations of 64 µg/l and above.

The incidence and severity of the histopathological lesions observed increased in male fish at 160 and 640 µg/l, and in female fish at 640 µg/l. The main observation was proteinaceous fluid in the testes and ovaries. These observations may be related to the induction of vitellogenin. In male fish the bisphenol-A concentration accounts for 65% of the variance in the results. In the majority of male fish exposed to BPA at 640 µg/l, and to a lesser extent at 160 µg/l, macroscopic enlargement of the kidneys was associated with a variety of degenerative changes that are considered to be consistent with chronic protein (vitellogenin) overload. Other histopathological observations were not considered to be related to bisphenol-A exposure (no dose responses, occurrence in the controls, historical incidence).

For the sperm cells, the relative proportions of cell types to those of an equal or lesser stage of development were calculated as indicated above. A comparison of these relative frequencies between the controls and treatments is not the best way to express the size of a treatment effect. Small changes in the relative frequency are more important when the relative frequency is very small or very large – so in the margins - compared to when the relative frequency is intermediate. To address this, the relative frequency values for each gonad were converted to logit values, the logit values for the left and right gonads were averaged, and the comparisons between controls and treatments carried out on these values. From these comparisons, there was a statistically significant shift to less mature cell types at 160 and 640 µg/l in male fish (for spermatocytes as a proportion of equally and less developed cells at both concentrations, for spermatids as a proportion of equally and less developed cells at 640 µg/l). There was also a decrease in the proportion of Leydig cells relative to the ITUC at the same concentrations. In female fish, a shift to less mature cell types in the ovaries was observed at 640 µg/l.

From this study, the lowest effect concentration for a "conventional" endpoint was 640 µg/l for survival in male fish, giving a NOEC of 160 µg/l. The gonadal cell distribution was significantly affected at concentrations of 160 and 640 µg/l in male fish, hence a NOEC of 64 µg/l, and vitellogenin induction was significant at 64 µg/l, giving a NOEC of 16 µg/l.

The results from the two long-term studies on fathead minnow are compared in Table 3.22.

The Phase 3 study is comparable to that on the F0 generation in the Sumpter *et al.* study in terms of the concentration range used and the duration of exposure. The concentrations used in the comparison are nominal values as in most cases the same nominal levels were used. The overall effect levels for survival are the same for both studies, though for different generations. Growth was not significantly affected in the Phase 3 study, whereas effects were seen at 160 µg/l in the earlier study. Both studies reported a NOEC of 16 µg/l (nominal) for the production of vitellogenin[19]. The results for egg production are similar for the F0

[19] The levels of vitellogenin in the control fish in the Phase 2 and 3 studies were notably higher than those in the Sumpter *et al.* study. Work by the OECD and others has shown that there can be considerable variation between

generation. There is a difference in the results for hatchability. No effects were seen in the new study at 640 µg/l, whereas effects were seen at 640 µg/l in the F1 eggs and at 160 µg/l in the F2 eggs in the earlier study. The F2 eggs in the Sumpter *et al.* study come from fish which had been exposed to bisphenol-A throughout their lifetime up to egg laying, and so had a longer exposure than those in either of the two F0 cases. Although the replication was not as great in the Sumpter *et al.* study, and hence the possibility of a false positive finding is greater, the original study is considered to be suitable for use in the assessment for this endpoint, and so the NOEC of 16 µg/l for hatchability will be taken.

VTG levels in control fish in different studies, even when similar assays are used. As a result, comparisons within studies are considered relevant but comparisons between studies are not.

Table 3.22 Comparison of results from Phase 3 study with original Sumpter *et al.* study

| | NOEC values (µg/l) | | | LOEC values (µg/l) | | |
|---|---|---|---|---|---|---|
| **Endpoint** | **Phase 3 (F0)** | **Sumpter F0** | **Sumpter F1** | **Phase 3 (F0)** | **Sumpter F0** | **Sumpter F1** |
| Survival | 160 (m) | NA | 160, 640[d] | 640 (m) | NA | 640, >640[d] |
| Growth (length, weight) | >640 | 160 (m) | 160 (m) | >640 | 640 (m) | 640 (m) |
| Gonad weight | >640 | 160 | NA | >640 | 640 | NA |
| GSI | >640 | 160 (m) | NA | >640 | 640 (m) | NA |
| Egg production | >640 (f) | 640 (f) | 160 (f) | >640 (f) | 1280 (f) | 640 (f) |
| Hatchability | >640[a] | 160[a] | 16[b] | >640[a] | 640[a] | 160[b] |
| Vitellogenin | 16 | 16 (m) | 16 | 64 | 160 (m) | 160 |
| Histopathological lesions | 64 (m) | NA | NA | 160 (m) | NA | NA |
| Gonad cell distribution | 64 (m) | c | c | 160 (m) | c | c |

Notes: m, f – male, female, if neither included then value applies to both
>: no effect at highest concentration tested
<: effect at lowest concentration tested
NA: not assessed
a: relates to F1 eggs
b: relates to F2 eggs
c: figures for this endpoint not considered reliable
d: results from two separate early life stage studies at 60 days. No results for F0 survival reported. F2 ELS studies had LOEC >640 µg/l.

Brian *et al*. (2005) exposed *Pi. promelas* to bisphenol-A in a study designed to assess the effects of mixtures of endocrine disrupters on plasma vitellogenin induction. The individual dose-response curves for vitellogenin induction were fully characterised for bisphenol-A, estradiol, ethinylestradiol, nonylphenol and octylphenol by exposing adult fish under flow-through conditions for two weeks, with chemical analysis of test concentrations. There were problems with the analysis of test concentrations during this phase of the study, resolved later for the mixture stage, so nominal concentrations were used to report the single substance studies. The $EC_{50}$ for vitellogenin induction by bisphenol-A was 158 µg/l (95% confidence interval 119-205 µg/l).

Prediction of the overall effect on vitellogenin induction of a mixture of the five chemicals, based on concentration addition, was supported by the empirical results. This shows that the co-occurrence of several estrogenic chemicals in the environment may lead to greater biological effects than individual substance risk assessments might suggest.

The NOEC of 16 µg/l for F2 generation egg hatchability in a full life cycle study with *Pi. promelas* is considered suitable for use in the PNEC derivation and SSD.

9) Guppy *Poecilia reticulata*

Haubruge et al. (2000) exposed adult males to bisphenol-A at 274 and 549 µg/l. The exposure solutions were renewed every 48 hours. After 21 days a significant decline on total sperm count was noted, by 40-75%. It was considered that the short-term decline in sperm count was unlikely to be due to endocrine mediated alteration of the germ line, and no change was found in testis size or sperm length. The authors speculate that the effect may be due to interference with the function of Sertoli cells, which facilitate the transport of maturing sperm. These cells are directly sensitive to the action of xenobiotics.

Kinnberg and Toft (2003) exposed groups of 30 sexually mature males for 30 days to nominal concentrations of 5, 50, 500 and 5,000 µg/l bisphenol-A in a flow-through system. Concentrations were analysed and were all higher than nominals, with a maximum difference of 21%, except for one sample which was 129% higher. During the first 21 days of exposure 77% of the fish in the highest concentration died and this treatment was terminated. No fish died in any of the other treatments. The gonad histology of fish in the highest treatment showed pronounced effects, with testes filled with spermatozeugmata, some of which had ruptured resulting in free spermatozoa, and virtually no spermatogenic cysts. No effects were reported at the other treatment levels.

The 30-d survival NOEC of 500 µg/l for *Po. reticulata* is considered suitable for use in the PNEC derivation and SSD.

10) Swordtail *Xiphophorus helleri*

Kwak et al. (2001) conducted short-term tests (72 hours) to determine the effect of bisphenol-A on vitellogenesis and damage to testes, and long-term tests (60 days) to examine the effect on sword (tail) length (a secondary sexual characteristic in males). Semi-static exposure conditions were used, but no concentration monitoring was undertaken. Vitellogenin expression was noted in a dose dependant manner with no induction at 0.4 mg/l bisphenol-A, but induction was observed at 2 and 10 mg/l. Binding studies to detect cell damage (apoptosis or necrosis) showed a reduction in the proportion of healthy cells at all three exposure concentrations. However, histological examination of testis tissue taken from

fish exposed to 0.4 or 2 mg/l bisphenol-A failed to show any apoptotic cells. Apoptotic cell masses and other injured cells were observed at 10 mg/l bisphenol-A though no lesions were observed. In tests on swordtail length, a significant reduction in length was observed at 0.002 and 0.02 mg/l bisphenol-A but not at 0.0002 mg/l bisphenol-A. The authors also determined a 96-hour $LC_{50}$ of 17.93 mg/l, based upon OECD guideline 204 and semi-static exposure.

The significance of the changes in sword length is not understood, but it is thought that the length of the sword has an influence on mating success, with female fish preferring males with longer swords. It is not clear what degree of change should be considered to be significant. The separation between exposure levels was an order of magnitude, and there was no measurement of concentration during the exposures. The study is therefore not considered suitable for use in PNEC derivation, but it is noted that the LOEC from this study is higher than the NOEC from the full life cycle test with Pi. promelas.

Summary of freshwater fish studies

Toxicity data are now available for ten species of freshwater fish. Whilst some of these are warmwater or even tropical species, most are 'standard' species for ecotoxicological assessment. Bisphenol-A is estrogenic to fish as shown by the concentration-related increase in the plasma vitellogenin concentration observed in the fathead minnow (Sumpter *et al*., 2001), rainbow trout (Lindholst *et al*., 2000), male carp (Smeets *et al*., 1999), and other studies reported above. Vitellogenin synthesis in fish is widely considered to be a reliable and sensitive indicator of exposure to estrogenic chemicals (Sumpter and Jobling, 1995). Sumpter *et al*. (2001) report a LOEC of 160 µg/l and a NOEC of 16 µg/l for vitellogenin production. The conclusion (i) test programme also found a NOEC of 16 µg/l for the same endpoint. These values fit with the LOECs of 23 µg/l and 40 µg/l for vitellogenin production reported by Pawlowski *et al*. (2000) and Lindholst *et al*. (2000). While both of these studies did not test concentrations low enough to derive NOEC values they did measure the relative potency of bisphenol-A to 17β-estradiol. All of the studies showed a similar relative potency of bisphenol-A to that of 17β-estradiol of around $10^{-4}$. This and the similar concentration for LOEC values between the studies suggests that the NOEC values from these other studies should be in a similar concentration range to the NOEC of 16 µg/l. Based upon the available data a NOEC of 16 µg/l can be assumed for vitellogenin production in fish.

Bisphenol-A can also bind to the estrogen receptor of fish (Kloas *et al*., 2000) though with a lower affinity than estradiol has for the receptor.

Although vitellogenin is a biomarker for exposure to estrogenic substances, the ecological significance of its presence is not yet known - the relationship between biomarkers for endocrine disruption and ecological effects is currently being investigated by a number of workers. The most sensitive end point for population-relevant effects from the existing fish studies is the NOEC for egg hatchability for the F2 generation of 16 µg/l reported by Sumpter *et al*. (2001). This is the same as the NOEC for vitellogenin production from the same study.

Other parameters can be sensitive to both estrogens and xenoestrogens. These include inhibition of testis growth by natural and synthetic estrogens and xenoestrogens (Panter *et al*., 1998; Jobling *et al*., 1996). Estrogens are also known to inhibit spermatogenesis in male fish (Billard *et al*., 1981) and exposure of fish to estradiol and nonylphenol has been shown to affect testicular structure (Miles-Richardson *et al*., 1999; Flammarion *et al*., 2000; Jobling *et al*., 1996). High concentrations of both estrogens and xenoestrogens can induce the development of ovotestes in male fish or cause complete feminisation (Hartley *et al*., 1998; Gary and Metcalfe, 1997).

Bowmer and Gimeno (2001) observed a NOEC for oviduct formation in male carp of 16 µg/l. It is noted that this is the same as the NOEC for egg hatchability observed by Sumpter *et al*. (2001).

The study on swordtail fish (Kwak *et al*., 2001) largely showed responses at similar concentrations to other studies and support these data. As noted above, this study is not considered suitable for use in defining the PNEC, but it is noted that the LOEC from this study is higher than the NOEC from the full life cycle test with fathead minnow *Pi. promelas*.

To summarise, the results from many tests indicate that bisphenol-A acts as a weak estrogen in fish, though it is a lot less active than either estradiol or ethinylestradiol. The NOEC for egg hatchability in fathead minnows (16 µg/l) will be taken forward for further discussion in the PNEC derivation as the most sensitive measure of fish toxicity. Long-term results for a further five fish species may also be considered for the derivation of an SSD:

- *Cyprinus carpio* 49-d growth NOEC of 100 µg/l,
- *Danio rerio* NOEC of 750 µg/l for multiple end points (full life cycle study),
- *Oncorhynchus mykiss* 28-d juvenile growth rate NOEC of 3,640 µg/l,
- *Oryzias latipes* NOEC of 247 µg/l for multiple end points (full life cycle study), and
- *Poecilia reticulata* 30-d survival NOEC of 500 µg/l.

Saltwater species

1) Sheepshead minnow *Cyprinodon variegatus*

   Emmitte (1978) reports a 96-hour $LC_{50}$ of 7.5 mg/l (measured concentration) in a flow-through exposure. The test method used appears to be acceptable, although no information is given on temperature, pH or dissolved oxygen during the test. Whilst apparently reliable, this test only considers short-term lethality.

2) Atlantic silverside *Menidia menidia*

   Springborn Bionomics (1985a) and Alexander *et al*. (1988) report a 96-hour $LC_{50}$ of 9.4 mg/l measured bisphenol-A in a flow-through test. Whilst valid, this study only considers short-term lethality.

3) Japanese common goby *Acanthogobius flavimanus*

   Mochida *et al*. (2004) exposed *A. flavimanus* to 0.2, 1, 5 or 25 µg/l bisphenol-A for three weeks in a flow-through system. Chemical analysis at least once per week showed that mean concentrations were 0.28, 0.79, 3.02 and 19.1 µg/l. Exposure had no effect on histology, serum vitellogenin or the expression of ubiquitin C-terminal hydrolase mRNA in either the testis or brain. This study is not considered to be suitable for PNEC derivation because the measured parameters cannot be directly related to demographically important end points.

4) Killifish *Fundulus heteroclitus*

   Pait and Nelson (2003) investigated the production of vitellogenin in males following injection with bisphenol-A. The injection levels used were 0, 10, 50, 100 and 150 mg/kg body weight fish. They compared the results obtained for fish from "clean" stocks with fish taken from contaminated areas (general contamination, not specifically with bisphenol-A). In

the clean fish there were significant increases in vitellogenin levels at 50, 100 and 150 mg/kg doses. In fish from contaminated areas the production of vitellogenin was reduced compared to that in the clean fish, although only significantly so at the middle two doses. The administration route makes this study unsuitable for use in the risk assessment, and the measured parameters cannot be related directly to demographically important end points either.

1) Turbot *Psetta maxima*

Labadie and Budzinski (2006) exposed juvenile turbot (Psetta maxima) to bisphenol-A for three weeks under flow through conditions in natural seawater. The one exposure concentration was confirmed by GC-MS as 59±11 µg/l. The levels of sex steroids in the fish were measured at the end of the exposure. Bisphenol-A had no effect on androgen levels. It increased levels of E1 (estrone), which the authors suggested was due to up-regulation of aromatase activity.

2) Korean rockfish *Sebastes schlegeli*

Lee et al. (2003) exposed fry of the Korean rockfish (Sebastes schlegeli) to bisphenol-A in their diet. Food was prepared by adding a solution of bisphenol-A in ethanol to powdered fish diet at the appropriate level, drying at room temperature and storing in a refrigerator until used. Exposure levels were 0.05, 0.5, 5, 50 and 100 µg/g. Fish were fed 2.52 g of food per day. Three replicates for each exposure were used, with 70 fry in each, with exposures over 29 days. The fry were exposed from 51 days old, a time at which they have undifferentiated gonads. The study found no difference in the male to female ratio between the controls and any of the exposure levels. No effects on fry length were noted. The exposure route means that the result is not suitable for use in the risk assessment.

In summary, the limited data available for saltwater species does not suggest any significant difference in sensitivity compared to freshwater species during short-term exposures.

#### 3.2.1.4.2 Amphibians

Experiments have been conducted with five species.

1) European common frog *Rana temporaria*

Koponen and Kukkonen (2002) investigated the effect of bisphenol-A alone and together with artificial UVB radiation. Eggs and larvae were exposed for 20 days in Pyrex dishes, 30 embryos to a dish. The exposures were ended after 20 days because by this time almost all of the UVB-exposed larvae had died. Control larvae were at Gosner stage 25-27 at this time. In the exposures without UVB, bisphenol-A had no effects on survival at concentrations up to 100 µg/l, with significant reduction in survival at 1,000 µg/l. The UVB exposures showed mortality with or without bisphenol-A. The authors concluded that the combined effect at the highest bisphenol-A concentration was greater than that from UVB alone. This study is not considered to be suitable for PNEC derivation because there was no chemical analysis of exposure concentrations.

Rouhani Rankouhi *et al*. (2005) found that bisphenol-A did not induce estrogen-receptor mediated vitellogenesis in *R. temporaria* primary hepatocytes at concentrations up to 100 µM.

2) African clawed frog *Xenopus laevis*

Several studies have been performed with this species, and these are summarised below.

a) Kloas *et al*. (1999) reported the development of a model for the investigation of endocrine-disrupting chemicals using this species. As part of this work tadpoles at 2-3 days post-hatch were exposed to nominal concentrations of bisphenol-A. Solutions were renewed three times per week, and exposure continued until metamorphosis occurred in approximately 90% of all animals - this took around 12 weeks. The two exposure concentrations used were $10^{-7}$ M (23 µg/l) and $10^{-8}$ M (2.3 µg/l). After exposure the animals were examined for differentiation into males and females. The higher exposure concentration produced a statistically significant increase in the number of female phenotypes in relation to the controls. The ratio of the sexes in the control exposures was 60:40 male:female and in the 23 µg/l exposure group was 36:64 male:female. A decreased male:female ratio was also observed in the 2.3 µg/l test group though the result was not significant comparable to the controls.

   It should be noted that this was only a method development study, which was not optimally designed to establish a NOEC (e.g., only two exposure concentrations were used, separated by an order of magnitude). The lack of information on test conditions (e.g., temperature, water quality), limited test vessel replication and lack of analytical confirmation of test concentrations means that this study cannot be used directly in the PNEC derivation or SSD.

b) Pickford *et al*. (2000; published in Pickford *et al*., 2003) reported the results of a study investigating the effects of bisphenol-A on larval growth, development and sexual differentiation on *X. laevis*. This study was conducted in an attempt to repeat the original findings by Kloas *et al*. (1999) and establish a dose-response relationship. The test was initiated with 4-day-old larvae. Hatching of larvae occurred principally on day 2 post-fertilisation; exposure to the test substance therefore commenced approximately 2 days post-hatching. A dynamic flow-through test system was used with four replicate test vessels for each test concentration, dilution water and positive control. In the experiments 17β-estradiol was used as a positive control. Larvae were exposed to 1, 2.3, 10, 23, 100 and 500 µg/l nominal concentrations of bisphenol-A. The larvae were observed daily for mortality, behaviour and appearance. Test conditions were monitored throughout the study. Growth and development assessments were performed on all larvae from one replicate per treatment group on exposure days 32 and 62. Larvae were sacrificed upon reaching the froglet stage of development for analysis. The test was terminated at day 90, which corresponds to 94 days after fertilisation.

   The NOEC for larval survival was calculated as 500 µg/l based upon pooled data results. At 32 days and 62 days post fertilisation there were no significant differences in growth or development between the test concentrations, the positive control or the dilution water control. The sex ratios were assessed pre- and post- fixation to allow comparison with the method used by Kloas *et al*. (1999), with statistical analysis being undertaken on the post-fixation results only. No significant difference from the expected 50:50 sex ratio were observed in any of the test concentrations or the dilution water control, while a significant feminisation was observed in the positive control group. The exposure of larvae to bisphenol-A did not result in an increase in gross gonadal abnormalities in stage 66 froglets. There was no significant difference in time to metamorphosis in any of the test concentrations of bisphenol-A compared to the dilution water control. There was no significant difference in total lengths in any of the test concentrations compared to the dilution water control. There were no significant differences in weight between any of the test concentrations of bisphenol-A, and the dilution water control.

This 90-d study was conducted under full GLP and was thoroughly reported, so is considered fully valid.

c) Kloas and co-workers (Levy *et al*. 2004) carried out a further study on *X. laevis* as a follow-up to their original 1999 study. The bisphenol-A used in the experiments was 99% pure. Tadpoles were raised in tanks to development stage 42/43, in deionised distilled water with 2.5 g/l added sea salt. They were then randomly assigned to groups of forty tadpoles. Two experiments were then conducted with different exposure regimes.

*Experiment 1*: This consisted of exposures to $10^{-7}$ and $10^{-8}$ M bisphenol-A (23 µg/l and 2.3 µg/l respectively) in duplicate. The test medium was changed three times per week, on Monday, Wednesday and Friday, and food and test substance were added at the same time to give a semi-static exposure regime. Exposures at the same molar concentrations were also conducted with 17β-estradiol (E2). After metamorphosis was complete, the froglets were sacrificed, and their gonads fixed *in situ*. Sex determination was based on gross morphology. The same procedure was applied to tadpoles that had not completed metamorphosis by 120 days after the first chemical application.

There were no signs of general toxicity at either of the applied concentrations. An average of 75% of the surviving animals reached metamorphosis in the experiment, with mortality at 20-30%. There were no significant differences between the replicates in terms of mortality, time to metamorphosis, and other end points so the groups were pooled. The control organisms had 56% male and 44% female froglets. The organisms from the 23 µg/l nominal exposure were 69% female (significantly different from controls at $P<0.005$), and at 2.3 µg/l nominal 65% were female (not statistically significant). For comparison, E2 produced 81% and 84% females respectively.

*Experiment 2*: Three exposure levels were used ($10^{-6}$, $10^{-7}$ and $10^{-8}$ M, or 230, 23 and 2.3 µg/l), in duplicate, with $10^{-7}$ M E2 as a positive control. A different food was used in this experiment. After metamorphosis, the froglets were weighed, and sex determined by gross morphology. The gonads and kidneys were removed completely and fixed. Tadpoles not completing metamorphosis after 120 days were treated in the same way, but without weighing. Testes from this experiment were examined to confirm the identification as males, and to look for possible cellular irregularities. Only a random sub sample of ovaries was examined, as bisphenol-A is not expected to produce effects on ovaries.

The content of bisphenol-A in the water from all vessels from experiment 2 was analysed. Samples were taken immediately after the application of the nominal concentration and at six-hour intervals over the 48 hours between solution changes. Samples were taken from the experimental solutions, solutions without tadpoles, and from test medium with only bisphenol-A. Water samples were sterilised with mercuric chloride after collection and stored at -20°C before analysis, which was by solid phase extraction and HPLC determination. The concentration of bisphenol-A in the controls and the pure test medium was below the limit of detection, which was 0.2 µg/l ($9 \times 10^{-9}$ M). The measured concentrations in the exposures at time zero (immediately after the solution change) were 90-105% of nominal levels. Samples from the actual exposures (containing medium, food and tadpoles) decreased to 15-30% of nominal over the 48-hour period between solution changes. Samples of the medium with food, and the medium alone, remained at 70% or higher of nominal (with one exception, the $10^{-8}$ M solution with food dropping to 50% nominal).

An average of 80% of the surviving animals reached metamorphosis, and the mortality in the exposures was 10-20%. As for experiment 1, the data for the duplicate exposures were pooled. The mean body weight of the organisms increased at all three bisphenol-A exposure levels, with a possible trend of higher weights at lower concentrations, but the changes were not statistically significant. Animals exposed to E2 had a similar mean weight to the controls. The middle bisphenol-A nominal concentration of 23 µg/l resulted in a statistically increased proportion of females (70%) compared to the controls (48% in this experiment). The other two bisphenol-A exposures resulted in ratios not significantly different from the controls (51% female at 2.3 µg/l; 53% female at 230 µg/l). No morphological irregularities were noted in the gonads from any of the bisphenol-A exposure groups (nor from the E2 exposure) following examination of gross morphology. None of the developed testes were affected by bisphenol-A or E2 exposure. The incidence of testis-ova was only 1.1%.

The paper gives no information on metabolism, but studies on mRNA also reported in this paper suggest that bisphenol-A may bind effectively to the endocrine receptor *in vivo*. The authors conclude that bisphenol-A is responsible for sex reversal in this species.

It is not entirely straightforward to derive a NOEC from this study. In the first experiment, the $10^{-8}$ M exposure affected sex ratio (although the effect was not statistically significant), while the same concentration had no effect in the second experiment. The $10^{-7}$ M exposure showed effects in both experiments, so could be considered to be the LOEC. If the lower concentration were taken as showing no effect, then the NOEC would be $10^{-8}$ M, or 2.3 µg/l. There is a large gap between the concentrations (one order of magnitude), so the geometric mean will be taken to indicate a NOEC of 7.3 µg/l (and it is noted that it could be higher still). The validity of this study is discussed at the end of this section.

d) Iwamuro *et al*. (2003) carried out studies on embryos and larvae of *X. laevis*. Adult frogs were mated and eggs were removed the next morning and kept for sixteen hours in dechlorinated water. Fertilised embryos were transferred to containers with the experimental solutions, or kept in dechlorinated water for experiments at more advanced stages of development. Embryos from different parents were well mixed when larger numbers of individuals were needed for the experiments.

Embryos (60-100, development stage 7) were exposed for 72 hours to concentrations of bisphenol-A of $10^{-5}$, 2 x $10^{-5}$, 2.5 x $10^{-5}$, 3 x $10^{-5}$, 5 x $10^{-5}$ and 1 x $10^{-4}$ M (i.e., 2.3 – 23 mg/l). They were transferred to dechlorinated water, and the number of surviving embryos counted at 48, 96 and 120 hours. The survival rates at 96 and 120 hours were expressed as a percentage of those alive after 48 hours. The number of tadpoles showing morphological abnormalities was recorded at 5-7 days after fertilisation.

Tadpoles developed to stage 52 were immersed in 2.5 x $10^{-5}$ M bisphenol-A for 22 days, with the exposure solution being changed every two days. Development was monitored every three days under a microscope. *In vitro* studies were also carried out on tails removed from stage 52-54 tadpoles.

The survival rate of embryos exposed to bisphenol-A was reduced at 2.5 x $10^{-5}$ M, with no significant effect at 2 x $10^{-5}$ M. The median lethal dose was calculated as 2.1 x $10^{-5}$ M (4.8 mg/l). No apparent abnormalities were seen in embryos immersed in $10^{-5}$ M bisphenol-A for seven days. At 2.5 x $10^{-5}$ M, most of the abnormalities were seen in dead

tadpoles. The abnormalities seen were winding vertebrae (scoliosis) or malformation of the head region (reduced distance between the eyes).

Stage 52 embryos kept in bisphenol-A solution ($10^{-5}$ M or above) showed a retardation of metamorphosis by 1-2 stages compared to the controls, and the effect was dose-dependent. The hormone $T_4$ (L-thyroxine) promoted metamorphosis by four stages from the controls; in combination with bisphenol-A this was retarded by 2-4 stages, again dependent on concentration. The hormone $T_3$ promoted the reduction of the length of tail sections taken from stage 52-54 larvae; $10^{-5}$ and $10^{-4}$ M bisphenol-A blocked this shortening in a concentration dependent manner.

The parameters measured in this study cannot be readily related to demographic effects, so are unsuitable for use in PNEC derivation. In any case, the test concentrations were significantly higher than the NOECs derived in the other studies reported above.

e) Oka *et al*. (2003) exposed *X. laevis* embryos to 10-100 µM bisphenol-A until the early tadpole stage, when they had reached stage 6 or late stage 10. Developmental abnormalities were absent at 10 µM (2.3 mg/l) but began to occur at 20 µM (4.6 mg/l), with crooked vertebrae and development defects of the head and abdomen. At 40-100 µM embryos died rapidly during the gastrula stage. When embryos were exposed to similar molar concentrations of ethinylestradiol different abnormalities were induced, suggesting to the authors that the effects of bisphenol-A were due to non-estrogenic effects on developmental processes. The paper does not report whether the test medium was renewed and there does not appear to have been any chemical analysis of test concentrations, so it cannot be used for PNEC derivation.

f) Trudeau *et al*. (2005) exposed *X. laevis* tadpoles for 48-hours to nominal concentrations of 50 nM bisphenol-A (11.5 µg/l). They then injected an estrogen response element-thymidine-kinase-luciferase (ERE-TK-LUC) construct into the tadpoles' brains before returning them to fresh test medium for a further 48 hours before sacrifice and determination of total brain luciferase activity. Bisphenol-A increased luciferase activity 1.5-fold over controls. This study showed that exposure to bisphenol-A can modulate tadpole brain activity. However, the individual or demographic consequences remain unknown, so the study cannot be used for PNEC derivation.

g) Several papers evaluate the ability of receptors of *X. laevis* and other amphibians to bind bisphenol-A *in vitro* or *in vivo*. Kudo and Yamauchi (2005) suggest that bisphenol-A could interfere with the *X. laevis* thyroid system at environmentally realistic concentrations. However, this conclusion was based solely on results from *in vitro* transthyretin and thyroid hormone receptor β binding assays with bisphenol-A, and the relevance of this *in vivo* remains uncertain. Suzuki *et al*. (2004b) developed an *in vitro* estrogen binding assay and found a relative binding affinity of bisphenol-A of 0.957% when compared with diethylstilbestrol. This is rather a low value, but greater than the binding affinity of bisphenol-A to quail ERα. Lutz *et al.* (2005) studied the time course of free estrogen receptor (ER) in cultures of primary cultured hepatocytes of *X. laevis*. Bisphenol-A, nonylphenol and E2 all led to immediate drops in the free ER levels, followed by significant increases. Bisphenol-A produced a significant increase at $10^{-7}$ M (~23 µg/l).These studies provide useful information on possible mechanisms of action but are not relevant for PNEC derivation.

3) Wrinkled frog *Rana rugosa*

Goto *et al.* (2006) carried out a number of studies on the effects of bisphenol-A on the $T_3$-induced tadpole tail regression in *Rana rugosa* (the wrinkled frog). Tadpoles were exposed to bisphenol-A (2.3, 23 and 230 µg/l) for five days with a chlorine-free water control. After five days, $T_3$ ($5x10^{-8}$ M) was added to half of the vessels in the treatment and control groups for one day. This addition resulted in induced metamorphosis (measured by tail shortening) in the treated tadpoles not exposed to bisphenol-A. Tadpoles in the untreated water controls and the untreated bisphenol-A exposures did not exhibit tail shortening. Tadpoles in the treated bisphenol-A exposures showed a lesser degree of tail shortening, significantly less than the $T_3$-treated tadpoles at 23 and 230 µg/l.

DNA fragmentation in the tails of the tadpoles was also investigated. $T_3$-treated tadpoles showed marked fragmentation and the development of a ladder-like profile. This was not seen in untreated controls (tadpoles kept in water), those treated with bisphenol-A alone (230 µg/l) and those treated with both $T_3$ and bisphenol-A (230 µg/l).

These results were interpreted as showing possible competition between bisphenol-A and $T_3$ for the thyroid hormone receptor. The study is not suitable for use in the risk assessment as the metamorphosis was artificially induced.

4) Tropical clawed frog *Silurana tropicalis*

Goto *et al.* (2006) investigated the effects of bisphenol-A exposure on spontaneous metamorphosis, tail shortening and hindlimb elongation in tropical clawed frog *Silurana tropicalis* tadpoles. Stage 57 tadpoles were exposed to either 230 µg/l bisphenol-A or a 1 mM solution of methimazole (thyroid hormone synthesis inhibitor) for up to ten days. Tadpoles raised in chlorine-free tap water acted as the control population. At various times during the test, the stage of metamorphosis, tail length and hind limb length was determined. Exposure to bisphenol-A at 230 µg/l elicited a similar response as methimazole, and resulted in suppressed spontaneous metamorphosis, tadpole tail length shortening and hindlimb elongation compared with the control population. As only one concentration was used this result cannot be used in the risk assessment but will be considered in the discussion.

5) Black spotted pond frog *Rana nigromaculata*

Yang *et al.* (2005) exposed tadpoles of the black spotted pond frog *Rana nigromaculata* to bisphenol A from five days after hatching. Embryos were collected from the field. Concentrations of 2, 20 and 200 µg/l were used, and half of the exposure solution in each vessel (one vessel per concentration) was replaced every three days. Five tadpoles were sampled from each vessel on days 15, 30 45 and 60 of the exposures. These were weighted individually, then pooled for analysis. The samples were analysed for testosterone, total thryoxin (TT4) and plasma vitellogenin (as alkaline-labile phosphate). (Note: the paper indicates that the five tadpoles were pooled for analysis, but the results are presented as the average for five tadpoles, so the basis of the results is not clear.)

Malformations of tail flexure were noted in the highest exposure concentration at a level of 10%. These animals grew into young frogs. Inhibition of TT4 compared to the controls at 60 days was noted, but not significant. Testosterone levels were not different from those in the controls. Alkaline-labile phosphate levels were increased at all concentrations, but again not significantly. The lack of clarity in what the results represent and the lack of measurement of concentrations means this study is not suitable for the risk assessment.

Discussion of amphibian toxicity data

It is not clear why the three experiments by Kloas *et al*. (1999), Pickford *et al*. (2000 & 2003) and Levy *et al*. (2004) on the same species of amphibian produced such different results. The original study by Kloas *et al*. (1999) was aimed at developing a method to investigate endocrine effects rather than to determine a no-effect level, and can be disregarded given the other two studies now available.

Differences in experimental design might be an important factor. The range of concentrations in the Pickford *et al*. study covers the range of nominal concentrations used by Levy *et al*. (2004), as well as the actual range based on measurements (with the exception of the lowest concentration towards the end of the period between changes). The only clear difference between Levy *et al*. (2004) and Pickford *et al*. (2000 & 2003) is the exposure regime, with semi-static renewal used in the former instead of a flow-through design. As the bisphenol-A concentration declined significantly during the period between solution changes, it is likely that degradation was occurring. It is noted that this did not appear to occur in solutions unless tadpoles were present. However, this does not necessarily suggest that tadpole metabolism was the cause: the tadpoles have a microbial flora on their skin, and in any case, uptake would have occurred in both studies, so metabolism should also have been the same.

Pickford (2003) identified a number of other issues from a pre-publication manuscript of the Levy *et al*. (2004) study, as follows:

- There were two replicate vessels per test concentration, but pooling the data effectively reduced the number of replicates to one. The experimental error associated with the sex ratio end point therefore cannot be estimated.
- The most appropriate statistical method for analysis of sex ratio data is a test based on a binomial distribution of frequency data (e.g., Chi-squared test). In contrast, Levy *et al*. reduced the sex ratio of the duplicate tanks to one average numeric value for per cent males, and compared this by a non-parametric method to the solvent control value (as in Kloas *et al*., 1999). Since the solvent control sex ratio is slightly skewed in favour of males, this could have introduced a statistical bias.
- No concentration-response relationship is apparent. The experiments were not conducted with sufficient replication and statistical rigour to infer that a non-monotonic (i.e., inverted-U) response was involved.
- The absence of significant incidences of gonadal abnormalities at the histological level does not seem to be consistent with the presumed effect of bisphenol-A on gonadal development. Evidence of intersex condition in some larvae would be expected.
- Given the generally lower estrogen receptor binding affinity of bisphenol-A compared to estradiol, the similarity in level of mRNA induction at the same concentration is rather surprising. As there are no complementary protein expression data (e.g., immunohistochemistry), it is not clear whether this level of upregulation has any biological significance. It is not even clear whether the upregulation was in the presumptive (gonad) target tissue. Consequently it is not possible to relate the apparent mRNA upregulation mechanistically to the apparent effect on the sex ratio.

The Pickford *et al*. (2000 & 2003) study is of high quality and was specifically designed to establish a no-effect level for a range of effects. The Levy *et al*. (2004) study suggests a lower NOEC, but there were some drawbacks to the methodology used, and the apparent effect could

be an artefact. The true NOEC value is also uncertain given the wide separation of test concentrations. However, given that an effect on sex ratio is a potentially important finding, and the results cannot be rejected as invalid, the study is still considered in the PNEC derivation, though classed as 'valid with restriction'.

This means that two NOEC values are considered for this species. Since there is a large gap between them (two orders of magnitude), the geometric mean NOEC of 60.4 µg/l is used as the preferred value for PNEC derivation. It should be noted that the highest NOEC of 500 µg/l was in fact the highest concentration tested in the study, so the true NOEC could be higher. The geometric mean is therefore considered to be a conservative value. Finally, there are also still questions in relation to the use of a parameter such as the sex ratio in risk assessment: for example, what other factors influence the ratio, and what is the normal range of values for the ratio in healthy populations? The geometric mean value is below the concentration which retarded metamorphosis in *Silurana tropicalis*.

| In summary, the geometric mean chronic sex ratio NOEC of 60.4 µg/l for *X. laevis* is considered in the PNEC derivation and SSD. This is derived from two significantly different NOECs, i.e., 7.3 and 500 µg/l. |
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#### 3.2.1.4.3 Reptiles

Stoker *et al*. (2003) studied the effect of topical administration of bisphenol-A to eggs of the broad snouted caiman *Caiman latirostris* (a member of the *Crocodylidae* family). Sex determination in this species is temperature dependent. Bisphenol-A was applied to the eggs at doses of 1.4 and 140 ppm, and exposures were at two temperatures, i.e., 30°C (female producing temperature) and 33°C (male producing temperature).

No effects were seen on animals exposed to bisphenol-A at 30°C. At 33°C, all animals hatched as females at a bisphenol-A dose of 140 ppm. The same result was observed with 17β-estradiol at a dose of 1.4 ppm at this temperature. At the lower bisphenol-A dose of 1.4 ppm, all of the animals hatched as males, but significant disruption of the seminiferous tubule histoarchitecture was observed.

The topical method of application of bisphenol-A in this study means that these results are not suitable for derivation of a PNEC, although it does provide additional evidence of an endocrine effect.

#### 3.2.1.4.4 Mesocosm studies

One stream mesocosm study is available in which the effect on aufwuchs biomass was examined (Licht *et al*., 2004) ("aufwuchs" is a term used to describe the organisms and detritus that coat rock and plant surfaces in aquatic systems). In this study the aufwuchs were collected from a German river and allowed to colonise unglazed ceramic tiles. These tiles were then placed in unreplicated artificial streams (3.7 m long x 0.5 m wide) located in a greenhouse. The bisphenol-A was added at nominal concentrations of 5, 50 and 500 µg/l as weekly pulses and analysis of concentrations showed that nominal concentrations were achieved initially, with rapid degradation (DT50 ~1 day) leading to almost complete disappearance of the substance between doses. The authors converted nominal concentrations into what they termed 'effective concentrations' by using the geometric mean of the initial concentration and the concentration after 7 days (or the limit of detection). Three of the aufwuchs-colonised tiles were removed from

each stream at 14-day intervals and the ash-free dry weight of the aufwuchs was determined. The overall exposure period was 103 days.

There was some evidence that exposure of aufwuchs to 500 µg/l bisphenol-A was associated with significantly lower ash-free dry weights, but there was little evidence of effects at 50 or 5 µg/l. However, the authors report an $EC_{10}$ of 11 µg/l and $EC_{50}$ of 46 µg/l for the area under the aufwuchs biomass/time curve, or an $EC_{10}$ of 20 µg/l and $EC_{50}$ of 73 µg/l when these values were normalised to the percentage of initial biomass in each treatment. These low values result from the calculation of exposure concentrations as the geometric means of initial and 7-day concentrations. If nominal concentrations are used then the $EC_{10}$ and $EC_{50}$ for the area under the aufwuchs biomass/time curve are 38 and 450 µg/l respectively, or 239 and 806 µg/l, respectively, if normalised to the percentage of initial biomass.

This study is not suitable for derivation of a PNEC because treatments were not replicated, and the relationship between exposure and effects on aufwuchs is difficult to interpret because of the pulsed dosing design.

The same artificial streams were used for exposures of the crustacean *Gammarus fossarum* to bisphenol-A at the same nominal concentrations (Schirling *et al*, 2006b). The effects noted in the study were an accelerated maturation of oocytes in females and a reduction in the size and number of early vitellogenic oocytes. The pulsed dosing system again makes the actual exposures difficult to estimate, and this and the lack of replication mean that the results are not suitable for the risk assessment.

#### 3.2.1.4.5 Field studies

Vethaak *et al*. (2005) report a field monitoring study in which concentrations of several xenoestrogens, including bisphenol-A were measured at several freshwater and saltwater sites across the Netherlands. The *in vitro* reporter assay ER-CALUX was used to assess the estrogenic activity of the water samples, and samples of flounder (*Platichthys flesus*) and bream (*Abramis brama*) were also collected from selected sites for assessment of blood vitellogenin and ovotestis in males, and muscle concentrations of xenoestrogens. Two case studies were also performed as part of this study in which caged rainbow trout (*Oncorhynchus mykiss*) and carp (*Cyprinus carpio*) were exposed on-site to sewage effluent. Multivariate statistical techniques were then used to relate measured concentrations of xenoestrogens to estrogenic activity and effects on fish. Steroid hormones (particularly ethinylestradiol), alkylphenols and alkylphenol ethoxylate concentrations were associated with estrogenic effects, but the authors state that 'Estrogenic effects of [bisphenol-A] can be more or less ruled out.'

This study is not suitable for either deriving a PNEC or for assessing the environmental realism of the PNEC based on laboratory-derived data, since a mixture of substances was present, and only fish were analysed.

### 3.2.1.5 PNEC derivation for fresh surface water

#### 3.2.1.5.1 Assessment factor approach

In deriving the $PNEC_{water}$ consideration needs to be given to short-term and chronic toxicity studies for fish, amphibians, aquatic invertebrates and algae. The guidelines given in the TGD

are based upon population effects (e.g. effects on ability to reproduce and species mortality) and do not directly cover endocrine disruption as an endpoint. Ideally, the data used to derive the $PNEC_{water}$ should be obtained from studies conducted to standard guideline methods that have been adequately ring tested, and performed to appropriate quality assurance standards. In this case, data are available for many species but most do not involve standardised methods. Nevertheless, these studies can still be relevant provided that the methods and results are sufficiently described.

A number of acute toxicity studies are available for fresh and saltwater fish, invertebrates and algae. No group appears to be significantly more sensitive than the others, and $L(E)C_{50}$ values are typically in the range 1-10 mg/l. There are no new acute studies with $L(E)C_{50}$ values below 1 mg/l, so the environmental classification proposal is unaffected.

For bisphenol-A the most sensitive effect that has a clear ecological relevance is egg hatchability in the fathead minnow, with a NOEC of 16 µg/l. This is also the NOEC for vitellogenin production in males of the same species (seen as an indicator of endocrine effects) and oviduct formation in male carp, and the study is of high quality and is considered reliable.

As there are long-term NOEC values available for fish, invertebrates and algae a factor of 10 can be used on the NOEC in accordance with the usual TGD method to give a **$PNEC_{water}$ of 1.6 µg/l**.[20]

This leaves out the consideration of effects on snails, in particular *Marisa cornuarietis*. The (conservative) NOEC from the most reliable study is 25 µg/l, and so is covered by the derivation above. The other, less reliable, values identified in Section 3.2.1.3.1 relate to the stimulation of egg production during a period of non-spawning. Such an effect is clearly important for seasonally breeding species, when chemical stimulation of breeding could effectively be forcing the organism to use energy reserves at a time of sexual repose, with a consequent possible reduction in fecundity during the following normal breeding season. There may also be an impact on offspring survival since eggs may hatch during periods of low natural food availability. Finally, the female-specific mortality caused by oviduct malformations might have an impact on sex ratio. Therefore this is a potentially important adverse effect, although ideally a full life cycle study would help clarify the actual relevance of each of these considerations. If the lowest $EC_{10}$ value of 0.0148 µg/l[21] from Oehlmann *et al.* (2006) were used with an assessment factor of 10, the $PNEC_{water}$ would be 1.48 ng/l, which is extremely low. The derivation of this value is not clear in the paper and could not be duplicated (e.g. van der Hoeven, 2005). An alternative value of 2.1 µg/l was derived from the same raw data; this would give a $PNEC_{water}$ of 0.21 µg/l with an assessment factor of 10. It should be noted that this study is not considered to be as reliable as the conclusion (i) study, but this is discussed further in the risk characterisation section.

[20] For the majority of industrial chemicals, the $PNEC_{water}$ can be derived from just five tests perhaps involving only three species – one algal test (providing both acute and chronic data), an acute and a chronic *Daphnia* test, and an acute and a chronic fish test. For bisphenol-A, chronic NOECs for fish, *Daphnia* and algae are 3,640 (from the juvenile fish growth test), >3,146 and 1,360 µg/l respectively. If these were the only data available, the $PNEC_{water}$ would be 136 µg/l based on an assessment factor of 10 (with algae being the most sensitive trophic level). This shows the importance of measuring reproductive effects for suspected endocrine disrupters.

[21] The German competent authority believes that this value is reliable enough for the PNEC derivation.

#### 3.2.1.5.2 Statistical approach

The TGD allows the use of statistical extrapolation to derive a $PNEC_{water}$ if there are sufficient data. The suggested minimum data requirements are that there should be at least 10 NOECs from at least 8 taxonomic groups, including:

- Fish
- A second family in the phylum Chordata (fish, amphibian, etc.);
- A crustacean (e.g., cladoceran, copepod, ostracod, isopod, amphipod, crayfish etc.);
- An insect (e.g., mayfly, dragonfly, damselfly, stonefly, caddisfly, mosquito, midge, etc.);
- A family in a phylum other than Arthropoda or Chordata (e.g., Rotifera, Annelida, Mollusca);
- A family in any order of insect or any phylum not already represented;
- Algae; and
- Higher plants.

Suitable data (including some from studies that are classed as valid with restriction) are listed in Table 3.20, and these show that the above requirements are met. With the exception of molluscs, the data are the most reliable long-term values for each of the species, and the reasons for their selection are discussed in Sections 3.2.1.2 to 3.2.1.4. Fish provide around one third of the chronic data points. It could be argued that only data from full life cycle tests should be used, since these should cover all relevant life stages. It should also be noted that this table only considers data for freshwater organisms. At least one marine species has a chronic value that could be suitable for inclusion (*Skeletonema costatum*).

The data in Table 3.20 were used to construct species sensitivity distributions (SSDs) using the software program ETX 2.0, available from RIVM in the Netherlands. The value selected for *Marisa* snails is open to challenge since it is not from the most reliable study, and represents a recalculated value. Therefore, calculations have also been performed with the 5-month egg production $EC_{10}$ as derived by the original study authors (for illustrative purposes only, given the low reliability of the actual value), as well as the result of the fully valid conclusion (i) study, to illustrate how the SSD would be affected. Plots of the resulting SSDs are shown in Figure 3.2 to Figure 3.4, and the resulting HC5 values are presented in Table 3.24. The table also contains the results of the estimation of the goodness of fit to a normal distribution using three different measures.

Table 3.23 Freshwater toxicity data used to construct a species sensitivity distribution for bisphenol-A

| Taxonomic group | Species | Common name | Endpoint | Result (µg/l) | Reference |
|---|---|---|---|---|---|
| Fish | *Cyprinus carpio* | Common carp | 49-d growth NOEC | 100 [a] | Bowmer & Gimeno (2001) |
| | *Danio rerio* | Zebrafish | Full life-cycle multiple end point NOEC | 750 | Segner *et al*. (2003a) |
| | *Oncorhynchus mykiss* | Rainbow trout | 28-d juvenile growth NOEC | 3,640 | Bayer AG (1999) |

| Taxonomic group | Species | Common name | Endpoint | Result (µg/l) | Reference |
|---|---|---|---|---|---|
| | *Pimephales promelas* | Fathead minnow | Multi-generation F2 egg hatchability NOEC | 16 | Sumpter *et al*. (2001) |
| | *Oryzias latipes* | Japanese medaka | Multi-generation multiple end point NOEC | 247 [a] | Japanese Ministry of the Environment (2006) |
| | *Poecilia reticulata* | Guppy | 30-d survival NOEC | 500 | Kinnberg & Toft (2003) |
| Amphibia | *Xenopus laevis* | African clawed frog | 12-week sex ratio NOEC | 60.4 | Geometric mean of 500 (Pickford *et al*., 2000 & 2003) and 7.3 (Levy *et al*., 2004) |
| Crustacea | *Daphnia magna* | Water flea | 21-d reproduction NOEC | 3,146 | Bayer AG (1996) |
| | *Hyalella azteca* | Scud | 42-d reproduction NOEC | 490 | Springborn Smithers (2006b) |
| Insects | *Chironomus riparius* | Midge | Life-cycle time to moult & growth NOEC | 100 | Watts *et al*. (2003) |
| Rotifers | *Brachionus calyciflorus* | Rotifer | 48-h intrinsic rate of increase NOEC | 1,800 | Springborn Smithers (2006a) |
| Molluscs | *Marisa cornuarietis* | Ramshorn (apple) snail | 5-month egg production $EC_{10}$ | 2.1 | Van der Hoeven (2005), recalculated from Oehlmann *et al*. (2006) |
| Cnidarians | *Hydra vulgaris* | Hydra | 6-week polyp structure NOEC | 42 | Pascoe *et al*. (2002) |
| Poriferans | *Heteromyenia sp.* | Sponge | 9-d growth NOEC | 1,600 | Hill *et al*. (2002) |
| Algae | *Pseudo-kirchneriella subcapitata* | Alga | 96-h cell count $EC_{10}$ | 1,360 | Alexander *et al*. (1985b & 1988) |
| Macrophytes | *Lemna gibba* | Duckweed | 7-d growth NOEC | 7,800 | Putt (2003) |

a) A full study report is not currently available, but the data are considered adequate based on abstract information

Figure 3.2 Species sensitivity distribution using whole data set with mollusc value of 0.0148 µg/l

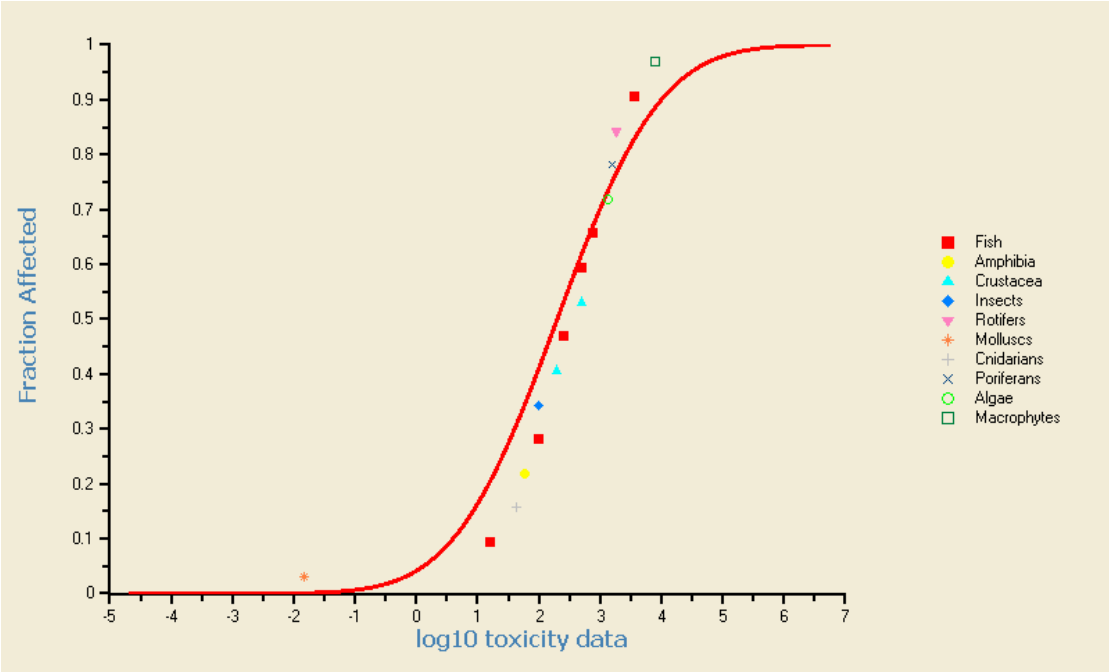



Figure 3.3 Species sensitivity distribution using whole data set with mollusc value of 2.1 µg/l

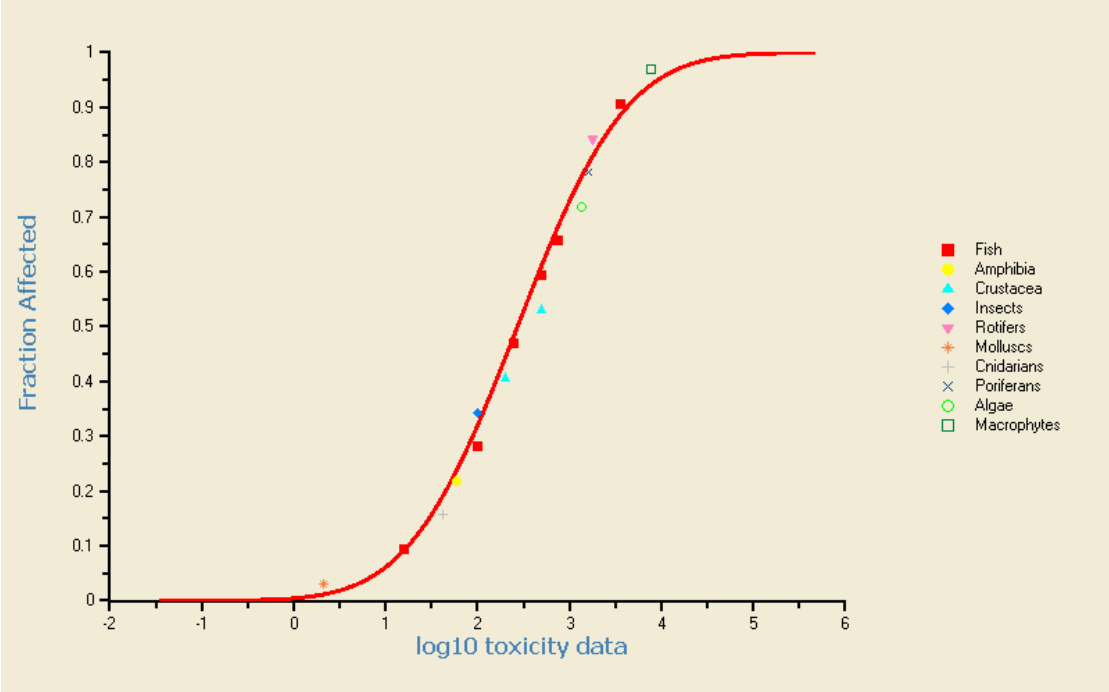
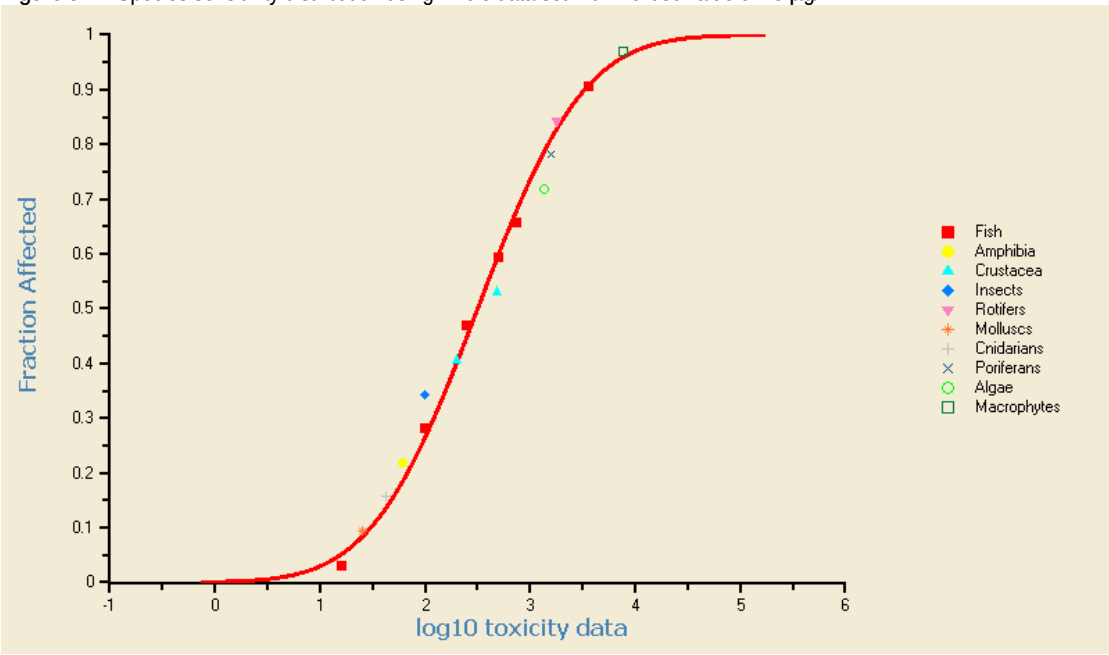


Figure 3.4 Species sensitivity distribution using whole data set with mollusc value of 25 µg/l




There are indications (not necessarily in relation to bisphenol-A) that many invertebrates have physiological systems that could potentially be affected by endocrine-disrupting substances. Fish are known to be affected by such compounds, so it is considered valid to combine the data for the invertebrates and fish in the SSD. It might be expected that algae and plants could respond differently to bisphenol-A. The results of leaving the data for these out of the data set are therefore also shown in Table 3.21 (plots are not shown).

Table 3.24 HC5 values

| Data set | HC5 | 90% interval | Goodness of fit |
|---|---|---|---|
| Mollusc 2.1 µg/l | 7.5 | 1.23 – 24.3 | All accepted |
| Mollusc 2.1 µg/l<br>Algae and macrophytes removed | 6.36 | 0.97 – 20.7 | All accepted |
| Mollusc 25 µg/l | 14.7 | 3.12 40.2 | All accepted |
| Mollusc 25 µg/l<br>Algae and macrophytes removed | 13.6 | 2.87 – 36.2 | All accepted |
| The following results are included for comparative purposes | | | |
| Mollusc 0.0148 µg/l | 1.19 | 0.09 – 6.4 | A-D rejected at 0.025<br>K-S all accepted<br>CvM rejected at 0.1 |
| Mollusc 0.0148 µg/l<br>Algae and macrophytes removed | 0.79 | 0.046 – 4.7 | A-D rejected at 0.025<br>K-S rejected at 0.1<br>CvM rejected at 0.05 |

A-D Anderson-Darling;
K-S Kolmogorov-Smirnov;
CvM Cramer von Mies

The choice of value for *Marisa* has a large influence on the HC5 resulting from the calculation, the difference between the highest and the lowest being over an order of magnitude. In contrast, removing the algal and macrophytes values produced a change of only 35% at most. The complete data set has therefore been used.

If the *Marisa* $EC_{10}$ of 2.1 µg/l is used, the data pass all three tests for normality at the p=0.1 level; this value is also the lowest in the data set. Using the conclusion (i) programme NOEC of 25 µg/l, the data also pass all three tests at the p=0.01 level, but fish are more sensitive.

The lowest $EC_{10}$ value of 0.0148 µg/l for *Marisa* is considered to be the least reliable value for a variety of reasons, as outlined in Section 3.2.1.3.1. When it is included in the data set for the SSD, the data pass the Kolmogorov-Smirnov test for normality at the p=0.1 significance level, but only pass the Anderson-Darling test at the p=0.01 level and the Cramer von Mies test at the p=0.05 level. These latter two tests focus on the fit in the tails of the distribution, and this *Marisa* result is inconsistent with a normal distribution of data. Regardless of the validity of the numerical value of this $EC_{10}$, the HC5 from this SSD would have to be treated with caution because the assumptions of normality are likely to be violated and the value therefore has a high level of uncertainty. It is therefore not considered further in this assessment.

The TGD proposes the use of an assessment factor of between one and five on the HC5 value to arrive at the $PNEC_{water}$. The choice of assessment factor depends on the quality and extent of the data. The data set meets the minimum requirements of 10 NOEC values for eight taxonomic groups, there are in fact 16 values for 10 groups. The main group is fish, with six values, and hence fish could be considered to have too large an influence on the result; however, the individual values for fish are spread out through the data set fairly evenly. There are no valid mesocosm or field data to use to support or confirm the result of the SSD. The data set overall is smaller than that used for some metals where a low factor of one or two has been proposed. There is also the remaining uncertainty over the appropriate value to use for molluscs. It is therefore proposed to use an assessment factor of five.

Applying a factor of five to the HC5 from the data set including the conclusion (i) programme result would give a $PNEC_{water}$ of 3.0 µg/l. Using the recalculated result of 2.1 µg/l in the data set and an assessment factor of five gives a $PNEC_{water}$ of 1.5 µg/l. This lower value is preferred for the risk characterisation given the possibility that the conclusion (i) study might have missed an effect because the snails did not exhibit a seasonal breeding pattern. It is very similar to the $PNEC_{water}$ derived using the assessment factor approach without consideration of the snail data, and is also close to the lower limit of the $90^{th}$ percentile confidence interval on the HC5 value.

### 3.2.1.6 PNEC for marine waters

Information is available on a number of tests with marine organisms. None of these tests provide results that are suitable for direct use in the risk assessment. The results for fish appear to show effects at similar levels to those in freshwater fish and no indication of increased sensitivity in the marine species. The most sensitive organisms appear to be molluscs, with effects at similar levels to those with *Marisa* in freshwater (with the same reservations about the limitations of the studies). There is no specific guidance on adapting an SSD-based PNEC from freshwater organisms to the marine environment. For the assessment factor approach, an additional factor of 10 would be used on a PNEC from freshwater data only, to take account of the wider range of species in the marine environment. The same approach will be adopted here, giving a $PNEC_{marine\ water}$ of 0.15 µg/l.

### 3.2.2 Sediment compartment (fresh and saltwater)

#### 3.2.2.1 Invertebrate toxicity data

##### 3.2.2.1.1 Molluscs

The freshwater snail *Potamopyrgus antipodarum* was exposed to bisphenol-A in artificial sediments for up to eight weeks (Duft *et al*., 2003). The sediment was composed of 95% quartz sand and 5% ground beech leaves. Bisphenol-A was added to the sediment dissolved in ethanol and the sediment left for one day for the solvent to evaporate. Water was added and the sediment allowed to equilibrate for five days with aeration. Exposure concentrations were 1, 10, 30, 100 and 300 µg/kg dry weight. Experiments were carried out at 15±1°C.

Eighty snails were added to the flasks containing sediment at the start of the exposures, and twenty were removed after 0, 2, 4 and 8 weeks. Embryos were removed from the brood pouch and the number of 'grown up' embryos (with shells) and 'new' embryos (without shells) were counted. The occurrence of egg cells in the oviduct and the maturity of the ovary were noted, as was any mortality in the treatments.

Two weeks' exposure to bisphenol-A concentrations of 30 µg/kg and above resulted in the increased production of unshelled embryos. A similar result was found for the total number of embryos, but not for the number of shelled embryos. At eight weeks, the stimulation of embryo production was significant at all concentrations tested in comparison to the controls. The total number of embryos and the number of shelled embryos varied very little in the controls; the number of unshelled embryos showed a slight but not significant decrease over the eight weeks. (Non-linear regression was used to fit the results and to derive concentrations giving 10% and 50% stimulation. For embryo production at two weeks the values were 0.22 and 24.5 µg/kg, at eight weeks they were 0.001 and 0.004 µg/kg. Note that these latter values are extrapolated by three orders of magnitude below the lowest concentration tested, and so have a very high degree of uncertainty.)

No analysis of the sediment was undertaken because of the reported short half-life of bisphenol-A in sediment. In addition, all of the exposure concentrations were below the reported detection limit for bisphenol-A in sediment of 5 mg/kg. Attempts were made to analyse the soft tissues of the snails to obtain a measure of the levels in the organisms, but insufficient tissue was recovered to allow the analysis to be performed.

The lack of confirmation of exposure concentrations means that these data cannot be used directly in the $PNEC_{sediment}$ derivation. However, given the apparent sensitivity of snail species to aqueous exposures, it is notable that effects were observed, and it should also be recalled that a NOEC of 1 µg/l (nominal) was obtained for stimulation of embryo production with this species via water phase exposure (Jobling *et al*., 2004; discussed in Section 3.2.1.3.1).

##### 3.2.2.1.2 Crustacea

Whale *et al*. (1999) studied the acute toxicity of bisphenol-A to the saltwater benthic amphipod *Corophium volutator*. Artificial sediment was prepared following guidelines in the OECD (1984) earthworm acute toxicity test. Bisphenol-A with 98% purity was added to the sediment by a spiking procedure with and without the presence of acetone as a carrier solvent. Animals were

added to the test system and exposed to bisphenol-A for 10 days. The condition of the organisms was assessed daily as active, immobilised or dead. The resultant $LC_{50}$ (based on mortality) and $EC_{50}$ (based on total adverse effects) values were calculated using probit analysis. The concentration of bisphenol-A in sediment was measured using solvent extraction and liquid chromatography. The pore-water concentration of bisphenol-A was estimated from the sediment concentration using the equilibrium partitioning model approach. The 10-day $LC_{50}$ values calculated for acetone and direct spiked tests based on bulk sediment concentrations were 46 and 60 mg/kg dry weight, respectively. The corresponding 10-day $EC_{50}$ values were 31 and 36 mg/kg dry weight for acetone and direct spiked tests, respectively. The endpoints of the toxicity tests based upon interstitial water concentrations were also determined; the 10-day $LC_{50}$ values were 1.4 and 1.6 mg/l for acetone and direct spiked tests, respectively and the 10-day $EC_{50}$ values were 1.1 and 1.3 mg/l for acetone and direct spiked tests, respectively.

#### 3.2.2.1.3 Insects

Watts *et al*. (2001b) studied the effect of bisphenol-A on development and reproduction in the freshwater midge *Chironomus riparius*. Larvae were exposed to a range of sediment concentrations and raised until the adults emerged. The time to emergence, sex ratio, number of adults, egg production and egg viability were all measured. The sediments in the experiment were spiked with stock solutions of bisphenol-A, and the concentrations of bisphenol-A in the stock solution were confirmed by analysis. The sediment was artificial, containing 15% organic matter; the resultant bisphenol-A concentrations were not measured in the sediment or the exposure water. The authors found that emergence of male and female adults were significantly delayed in the second generation of adults at bisphenol-A concentrations of 78 ng/l to 0.75 mg/l (these are stock solution concentrations and not the actual exposure concentrations in sediment). There was no observable effect on the first generation adults, and no effect on sex ratio or total number of adults produced in either generation. The authors noted that although time of emergence of adults was affected, the results in general do not suggest that the criteria examined, although validated as indicators of general sediment toxicity, could be used to detect oestrogenic effects. In this experiment it is not possible to estimate the actual level of exposure in the test system which may be substantially different from the stock solution concentrations due to adsorption and degradation of bisphenol-A. This study is not considered valid for further use in the risk assessment.

### 3.2.2.2 PNEC derivation for sediment

For bisphenol-A there are limited data on the toxic effects of bisphenol-A to benthic organisms. Based upon a 10-day $EC_{50}$ for *Corophium volutator* of 36 mg/kg dry weight (lowest value for direct spiked tests) and using an assessment factor of 1,000 a $PNEC_{sediment}$ of 36 µg/kg dry weight is calculated. It should be noted that this result is from a test on a saltwater organism carried out in a saltwater sediment medium. As the data set is very limited a $PNEC_{sediment}$ derived from the PNECwater using the equilibrium partitioning method has also been calculated for comparison. The calculated $PNEC_{sediment}$ value is 24 µg/kg wet weight (63 µg/kg dry weight) using the $PNEC_{water}$ of 1.5 µg/l.

The PNECs derived by the two methods are reasonably similar. The equilibrium partitioning approach should be suitable for a substance such as bisphenol-A. The database for aquatic organisms is much more extensive than that for sediment organisms, and so more confidence can be placed in the result. In addition, the sediment study also derived acute toxicity values based

on the measured interstitial water concentrations in the test. The resulting $L(E)C_{50}$ values (1.1-1.4 mg/l) are the same as the lower end of the values for aquatic invertebrates. There are indications from one study that snails may also be more sensitive when exposed to bisphenol-A in sediment. This also supports the importance of developing a result or results for molluscs that can be used with confidence. Whether the snail data are confirmed or not, taking all the evidence together the assessment for aquatic organisms can be considered to be protective for the sediment compartment.

For the marine compartment, there are no additional specific data to that used above, so the equilibrium partition method is used on the marine aquatic PNEC of 0.15 µg/l, giving a $PNEC_{marine\ sediment}$ of 2.4 µg/kg wet weight (6.3 µg/kg dry weight).

### 3.2.3 Terrestrial compartment

#### 3.2.3.1 Terrestrial toxicity data

There were no terrestrial toxicity results available at the time the original risk assessment was developed, and so the PNEC for the terrestrial compartment was derived using the equilibrium partition method. A testing programme for the terrestrial compartment was developed following the publication of the original risk assessment. The degradability of bisphenol-A leads to difficulties in maintaining a constant concentration in all media, but especially in soils where renewal of the soil is both difficult and unrealistic. It was agreed by the Technical Committee for New and Existing Substances that these tests should be performed with a single addition of bisphenol-A to the soil at the start of the exposures. This approach would mimic the only likely route of exposure for soil, which is through the application of sewage sludge containing the substance. Deposition from air is estimated to be negligible in comparison. Effect concentrations would be expressed in terms of the initially added concentration.

##### 3.2.3.1.1 Springtails

The toxicity of bisphenol-A to the collembolan *Folsomia candida* in a test according to ISO 11267 has been reported (ECT, 2007a)[22]. The test was conducted using an artificial soil, composition based on the OECD Guideline 207 (10% sphagnum peat, 20% kaolin clay, 68-69% quartz sand, 1% calcium carbonate). A mixture of radiolabelled ($^{14}C$ ring-labelled) and non-labelled bisphenol-A was used. Solutions of bisphenol-A in acetone were applied to portions of the quartz sand and the solvent allowed to evaporate; the treated sand was then incorporated into the rest of the artificial soil. The soil was wetted to 40-60% of its maximum water holding capacity at the start; the weight was checked once per week, and water added if the weight loss was greater than 2% of the water content. Samples of the treated soil were taken for analysis before the organisms were added. The recovery of the radiolabel from the initially treated soils (expressed as dpm in soil/dpm in dosage solution, where dpm is disintegrations per minute) ranged from 101-109%, so the actual concentrations at the start corresponded to the nominal concentrations.

[22] The rapporteur originally proposed a test on *Folsomia fimetaria* as this is a sexually reproducing species of collembolan. Information from the literature on the toxicity of nonylphenol to *F. fimetaria* and *F. candida* shows them to have similar sensitivities in terms of effects following exposure to a weakly estrogenic substance (nonylphenol). It is therefore considered that the test on *F. candida* is appropriate for the purpose of the risk assessment.

Five exposure concentrations were used, with solvent and deionised water controls, with five replicate vessels for each treatment and control. Collembolans were introduced to the treated soil after the soil was added to the test vessels; ten animals were added to each vessel. The animals were 10-12 days old (juveniles), from a synchronised culture. They were fed with ~30 mg of granulated dry yeast at the start of the exposures, and again after 14 days. The exposures lasted for 28 days.

At the end of the exposures, the soil from each vessel was mixed with water and the collembolans floated to the surface. The appearance and behaviour of the adults was observed, and the number of adults counted directly. Digital photos of the test vessels were taken, and the number of juveniles on these images was counted.

Mortality among the adults in the solvent and water controls was 12%, that in the exposures was 2-12%, so there was no effect on survival at any exposure level. (The test guidelines performance criterion for survival is less that 20% mortality in the controls.) The number of juveniles was reduced at the highest exposure level of 1,000 mg/kg dw, down to 61% of the number in the solvent control. The NOEC for this endpoint is therefore 500 mg/kg dw.

#### 3.2.3.1.2 Earthworms

*a) Eisenia andrei*

As part of a project to investigate endocrine disruption in key invertebrate taxonomic groups, Johnson *et al*. (2005) carried out tests on the earthworm *Eisenia andrei* exposed to a number of substances (individually), including bisphenol-A. Both short-term (14-day) screening tests and longer-term (56-day) reproduction studies were conducted. For both types of test a stock solution of bisphenol-A was prepared in acetone, and the appropriate amount added to OECD earthworm soil. After spiking with the substance, 0.5 kg amounts of soil were added to replicate test vessels, which were left to stand overnight to allow the acetone to evaporate. Ten animals were added to each replicate and allowed to burrow; dried ground rabbit droppings (5 g) were placed on the surface for the worms to feed on. The weight of the test vessels was recorded at this stage; twice a week distilled water was added to restore the weight to the starting value to compensate for water lost by evaporation. The control and solvent controls contained twenty animals each. All worms used in the study were sexually mature with clitella. The environmental conditions were 25±2°C and a photoperiod of 16 hours light and eight hours dark. The test procedures are not described in detail in the report, but for the most part there appear to be only minor variations from the OECD guideline, and these would not be expected to affect the test. A possible exception is the feeding of the worms; the test report indicates this was done once at the start of the exposures, whereas the OECD guideline indicates weekly additions of food.

The nominal concentrations used in the short-term test were 1.0, 3.2, 10, 32, 100, 320, 1,000, 3,200 and 10,000 mg/kg, with two replicates. After 14 days, the live and dead worms were removed from the test vessels by sieving the soil. The numbers of live and dead worms were recorded and the live worms were snap frozen in liquid nitrogen and stored at -80°C for analysis[23]. Concentration-dependent mortality was observed in the study; the responses were 10% at 10 mg/kg, 20% at 32 mg/kg, 90% at 100 mg/kg, 40% at 320 mg/kg, and 100% at 1,000 mg/kg and above. Given the 10% mortality observed in the solvent control (which is within the validity criteria for the OECD guideline), a NOEC of 32 mg/kg and a LOEC of 100 mg/kg are

[23] The report comments that analysis was carried out on samples where significant effects on toxicity indices were recorded, but no analytical results are included in the report

presented in the report. A probit analysis of the data for this paper gives an $LC_{50}$ of 61 mg/kg. No comment is given on the high mortality at the 100 mg/kg dose level, but this may just reflect the natural variation in such tests; it does mean the result will be more uncertain.

The long-term test used nominal concentrations of 1.0, 3.2, 10, 32 and 100 mg/kg, with four replicates at each concentration. Exposures were started in the same way as for the short-term studies; after 28 days the soil was sieved and the adult worms were removed, snap frozen in liquid nitrogen and stored at -80°C. The sieved soil containing cocoons was returned to the test vessels and left for a further 28 days to allow the cocoons to hatch. The number of juvenile worms in each vessel was determined at 56 days after wet sieving the soil. The report notes that soil samples were taken for analysis at the start of the test and at 28 days (when the soil was sieved) and stored at -20°C. Analyses were to be carried out on those samples from vessels where significant effects on toxicity indices or biomarkers were seen. No statistically significant effects were seen on the numbers of hatched cocoons, unhatched cocoons or live worms at any of the exposure levels. In the absence of any significant effects, no soil analyses were conducted. The number of worms in the controls was below the value of 30 set as a validity criterion in the OECD test guideline. Similar low numbers of worms were recorded for three of the other substances. For the other two substances tested the control responses met the validity criteria. The report notes that the production of cocoons varied in a seasonal manner, and that two of the experiments had to be repeated due to the low numbers of cocoons in the original tests. These repeats were the two tests that met the OECD criterion. It is not clear whether the limited addition of food in this study would have an influence on cocoon production. These observations are not considered to affect the overall conclusion of the study.

The study also investigated possible biomarkers for endocrine effects. A robust assay was developed for the gene expression of annetocin, a protein involved in the release of cocoons. No significant effects on the expression of this protein were observed in either the short- or long-term exposures with bisphenol-A. Long-term experiments under the same conditions with oestradiol, ethinylestradiol, testosterone, nonylphenol and propoxur also showed no effect on the gene expression. All but propoxur had no effect on the numbers of cocoons or live young worms; the effects caused by propoxur were not considered to be endocrine related.

The report concludes that earthworms may not be the most appropriate terrestrial species with which to assess the effects of endocrine disrupting chemicals. Earthworms are hermaphroditic, and they appear to have inherent homeostatic mechanisms to compensate for internal fluctuations in the levels of oestrogen and androgen that may result from exposure to chemicals.

*Discussion*

Although earthworms may not be suitable to demonstrate effects arising from endocrine disruption, they are still susceptible to “classical” toxicity, and effects on reproduction were seen with one of the test substances. No effects were seen with bisphenol-A at the highest concentration tested of 100 mg/kg in the long-term study. However, in the short-term study lethality was observed, beginning at a lower concentration than this, with significant lethality being seen at 100 mg/kg.

This apparent discrepancy may be due to degradation of bisphenol-A in the soil during the course of the exposures. Bisphenol-A is considered to be readily biodegradable in aquatic tests (the corresponding half-life in soil from the Technical Guidance Document is 30 days, although it should be noted that this is only a very approximate guide for modelling purposes). It is therefore likely that some degradation occurred over the 14-day study. However, as the soils were dosed in the same way for both the short- and longer-term studies, the extent of degradation

would be expected to be similar at the same times, and hence similar effects would be expected at the same time points. Since no concentrations were measured there is no information to indicate whether the test substance degraded at different rates in the two studies.

It should also be noted that the results obtained with nonylphenol in the same study follow a similar pattern to those with bisphenol-A, in that effects were seen at 14 days in the 100 mg/kg exposure, but not in the long-term study at the same level. The short-term effects for nonylphenol agree fairly well with other results available for that substance (Enviroment Agency, 2005). However, the long-term result for nonylphenol is not consistent with other data, which suggests that there may have been a problem with the longer test.

*b) Enchytraeus crypticus*

As a consequence of the unclear results with *Eisenia andrei*, a study on the effects of bisphenol-A on the enchytraeid species *Enchytraeus crypticus* has been conducted following OECD Guideline 220 (ECT, 2007b). The same artificial soil was used as in the collembolan study above, and the test soil samples were prepared in the same way. Samples were again taken for analysis at the start of the exposures. The recovery (as dpm in soil/dpm in dosage solution) ranged from 110 to 148% of the nominal levels. These were considered to be in reasonable agreement with the nominal levels, and the results are presented in terms of the nominal values.

Six concentrations of bisphenol-A were used, together with a solvent and a deionised water control. Four replicates were used for each treatment level and for the water control, with eight replicates for the solvent control. Ten adult enchytraeids were added to each test vessel. The animals were fed ~50 mg of ground oats at the start of the exposures, and once a week for the 28-day duration.

At the end of the exposures each soil sample was transferred to a shallow plastic tray and ethanol added to fix the juveniles. Water and Bengal red stain were added, the components mixed and left for 12 hours, after which the worms were stained red and lying on the surface where they were counted.

The mortality in the water control was 5% and in the solvent control 7.5% (the test guideline specifies a maximum mortality for validity of 20%). Mortality in the bisphenol-A treatments was 5-12.5%, hence there was no effect on survival. There were no significant differences between the numbers of juveniles in the controls and any of the bisphenol-A exposures (the controls met the validity criterion of >50 per vessel). Hence the NOEC for the study is ≥100 mg/kg dw (the top dose).

#### 3.2.3.1.3 Plants

The effect of bisphenol-A on the emergence and growth of six species of plant has been determined using a protocol meeting the requirements of OECD Test Guideline 208 (Springborn Smithers, 2007). The plant species tested were three monocotyledons: corn (Zea mays); oats (Avena sativa); and wheat (Triticum aestivum); and three dicotyledons: cabbage (Brassica oleracea); soybean (Glycine max); and tomato (Lycopersicum esculentum).

The sandy loam used for the test came from Fairhaven, Massachusetts, and contained 85% sand, 12% silt and 3% clay, with an organic carbon content of 1.1% (1.9% organic matter). The soil was heat sterilised before use.

A master stock solution of bisphenol-A was prepared in acetone, and a series of dilutions was prepared from this, also in acetone. The appropriate volume of each dilution was applied to silica sand and the acetone allowed to evaporate. Once dried, the sand was mixed with soil (0.5 kg sand to 11.5 kg soil for all except wheat, where 6 kg of soil were used). Different exposure levels were used for each plant species based on range finding tests. Solvent controls were prepared in the same way without addition of bisphenol-A to the acetone; controls without the addition of acetone were also used.

Approximately 1.2 kg of treated soil was placed in each pot. Seeds were planted in each pot at the start of the test. The number of seeds per pot was based on the seed and expected plant size (see table headings). Pots were placed on saucers, and well water or nutrient solution was added to the saucer at regular intervals. The tests were conducted in a greenhouse, with a 16-hour light period (sunlight augmented by sodium vapour lights as necessary). The temperature was monitored and ranged from 24 to 42°C; the relative humidity range was 18-100%. Although these exceed the recommended ranges in OECD 208, the same conditions have been used by the laboratory in the past with no negative impact on plants.

The control pots were observed daily until 50% emergence or greater was seen. At 7, 14 and 21 days after this, the number of emerged plants, mortalities and morphological abnormalities (e.g. chlorosis of leaves) were recorded. After 21 days from 50% control emergence, all exposures were terminated, and the above ground portions of living plants were removed and dried to determine dry shoot weights.

Each dosing solution was analysed prior to application to sand. An earlier range finding study using radiolabelled bisphenol-A added to soil in the same way as above demonstrated that the concentration after application ranged from 78-152% of nominal. This range was considered to be within the expected range for mixing a solid substance (sand) into soil, and therefore the nominal concentrations are taken as representative of the initial concentration in soil.

The results for each species are presented in Table 3.25 to Table 3.30. The derived effect levels are summarised in Table 3.32 and Table 3.31.

Table 3.25 Cabbage (10 replicates, 4 seeds per replicate)

| Concentration (mg/kg dw) | 21 day shoot dry weight (g) | SD | Percent emergence at 21 days |
|---|---|---|---|
| Control | 0.2964 | 0.0862 | 59 |
| 20 | 0.2165[a] | 0.0915 | 70 |
| 50 | 0.3058 | 0.0457 | 88 |
| 130 | 0.1622[b] | 0.0570 | 50 |
| 320 | 0.0251[c] | NA[c] | 2.5[b] |
| 800 | NA[c] | NA[c] | 0[b] |

a) Significantly reduced compared to control, but not considered treatment related as next concentration is not reduced

b) Significantly reduced compared to control

c) Statistics not calculated due to lack of emerged plants.

Table 3.26 Corn (10 replicates, 2 seeds per replicate)

| Concentration (mg/kg dw) | 21 day shoot dry weight (g) | SD | Percent emergence at 21 days |
|---|---|---|---|
| Control | 2.2619 | 1.0197 | 80 |
| 3.8 | 1.6899 | 0.4695 | 90 |
| 10 | 1.7635 | 0.1831 | 95 |
| 20 | 1.9959 | 0.7395 | 80 |
| 50 | 1.8348 | 0.4213 | 90 |
| 130 | 1.1461 | 1.0883 | 65 |
| 320 | 0.7472[a] | 0.1563 | 80 |

a) Significantly reduced compared to control

Table 3.27 Oat (10 replicates, 8 seeds per replicate)

| Concentration (mg/kg dw) | 21 day shoot dry weight (g) | SD | Percent emergence at 21 days |
|---|---|---|---|
| Control | 0.2889 | 0.0513 | 76 |
| 9.4 | 0.2802 | 0.0247 | 86 |
| 19 | 0.3133 | 0.0269 | 98 |
| 47 | 0.2736 | 0.0532 | 68 |
| 120 | 0.0894[a] | 0.0775 | 18[b] |
| 300 | 0.0530[a] | 0.0230 | 84 |
| 800 | 0.0100[a] | 0.0026 | 64 |

a) Significantly reduced compared to control

b) Significantly reduced compared to control, but not considered treatment related as next two concentrations are not reduced.

Table 3.28 Soybean (10 replicates, 2 seeds per replicate)

| Concentration (mg/kg dw) | 21 day shoot dry weight (g) | SD | Percent emergence at 21 days |
|---|---|---|---|
| Control | 2.1009 | 0.6438 | 100 |
| 20 | 1.4529 | 0.7335 | 100 |
| 50 | 2.0287 | 0.4238 | 100 |
| 130 | 1.7787 | 0.7694 | 90 |
| 320 | 1.4084 | 0.3400 | 90 |
| 800 | 0.1869[a] | 0.1250 | 75 |

a) Significantly reduced compared to control

Table 3.29 Tomato (10 replicates, 2 seeds per replicate)

| Concentration (mg/kg dw) | 21 day shoot dry weight (g) | SD | Percent emergence at 21 days |
|---|---|---|---|
| Control | 1.1308 | 0.2914 | 85 |
| 4.0 | 1.0774 | 0.3001 | 85 |
| 10 | 0.9528 | 0.0994 | 85 |
| 20 | 0.8137 | 0.1208 | 95 |
| 50 | 0.6790[a] | 0.1390 | 90 |
| 130 | 0.1568[a] | 0.0753 | 90 |
| 320 | 0.0206[a] | 0.0288 | 25[a] |

a) Significantly reduced compared to control

Table 3.30 Wheat (5 replicates, 8 seeds per replicate)

| Concentration (mg/kg dw) | 21 day shoot dry weight (g) | SD | Percent emergence at 21 days |
|---|---|---|---|
| Control | 0.1609 | 0.0178 | 99 |
| 3.8 | 0.1685 | 0.0206 | 98 |
| 9.4 | 0.1541 | 0.0046 | 100 |
| 20 | 0.1858 | 0.0085 | 98 |
| 47 | 0.1678 | 0.0161 | 100 |
| 120 | 0.1230[a] | 0.0176 | 98 |
| 300 | 0.0297[a] | 0.0101 | 98 |

a) Significantly reduced compared to control

Table 3.31 Results based on dry shoot weight (mg/kg nominal)

| Species | EC25[a] | EC50[a] | LOEC | NOEC |
|---|---|---|---|---|
| Cabbage | 82<br>(52-120) | >130<br>NA[b] | 130 | 50 |
| Corn | 83<br>(14-180) | 160<br>(80-280) | 320 | 130 |
| Oat | 69<br>(57-81) | 100<br>(87-130) | 120 | 47 |
| Soybean | 220<br>(72-360) | 460<br>(370-520) | 800 | 320 |
| Tomato | 19<br>(9.8-32) | 67<br>(52-79) | 50 | 20 |
| Wheat | 120<br>(98-140) | 200<br>(180-210) | 120 | 47 |

a) 95% confidence limits in parentheses

b) NA = not applicable; EC25 and EC50 values were estimated empirically, so 95% confidence limits could not be calculated.

Table 3.32 Results based on percent emergence (mg/kg nominal)

| Species | EC25[a] | EC50[a] | LOEC | NOEC |
|---|---|---|---|---|
| Cabbage | 130<br>(83-180) | 190<br>(120-230) | 320 | 130 |
| Corn | >320<br>NA[b] | >320<br>NA[b] | >320 | 320 |
| Oat | >800<br>NA[b] | >800<br>NA[b] | >800 | 800 |
| Soybean | 650<br>(370-800) | >800<br>NA[b] | >800 | 800 |
| Tomato | 190<br>(160-210) | 260<br>(230-300) | 320 | 130 |
| Wheat | >300<br>NA[b] | >300<br>NA[b] | >300 | 300 |

a) 95% confidence limits in parentheses

b) NA = not applicable; EC25 and EC50 values were estimated empirically, so 95% confidence limits could not be calculated.

The lowest $EC_{25}$ value from the study is 19 mg/kg dw, for dry shoot weight in tomato plants. This endpoint also has a NOEC value of 20 mg/kg dw. The value of 20 mg/kg will be used in the derivation of the PNEC.

Ferrera *et al.* (2006) exposed seeds and seedlings of four plant species (broad beans, *Vicia faba* L., var. maior; tomato, *Lycopersicum esculentum* Mill.; lettuce, *Lactuca sativa* L.; and durum wheat, *Triticum durum* Desf.) to bisphenol-A in solution (not in soils). Seeds were exposed on filter paper in Petri dishes, and germination and early growth were evaluated. Seedlings from these exposures were inserted into holes in aluminium lids on glass jars filled with nutrient medium containing bisphenol-A or medium alone for 21 days. The length and weight (wet and dry) of the roots and shoots of the seedlings were measured. The exposure concentrations were 10 and 50 mg/l.

Germination of seeds and root and shoot lengths of seedlings up to six days (Petri dish exposures) were not affected by bisphenol-A, with the exception of the root length of tomato seedlings which was reduced by over 50% at 50 mg/l. The root and shoot lengths and weights (wet and dry) were reduced at both bisphenol-A levels in the 21-day growth tests for tomato, durum wheat and lettuce, but not for broad bean. The bisphenol-A concentration reduced in the nutrient medium over the 21-day exposure by ~90% at the lower concentration and by between 80% and 96% at the higher concentration. Solutions stored under the same conditions with no seedlings showed only limited decreases. Analysis of broad been and tomato seedlings for bisphenol-A was carried out. The tomato seedlings contained measurable levels in both shoots and roots; broad bean seedlings had lower levels that the tomatoes in the roots, and bisphenol-A was not detected in the shoots.

These exposures are through water only, and no NOEC can be determined, so they are not suitable for use in the assessment.

#### 3.2.3.2 Terrestrial PNEC

As discussed in Section 3.2.1.3.1, aquatic snail species might be sensitive to bisphenol-A, and so terrestrial molluscs could be an important group to protect. However, no relevant data are available, and a standardised reproductive toxicity test method is not available either. Unlike the aquatic environment, terrestrial exposures are intermittent, and since bisphenol-A is readily biodegradable, there is no potential for continuous exposure. It is therefore recommended that the standard soil assessment scheme is followed, which is consistent with the approach taken for other endocrine active chemicals, e.g. nonylphenol (EC, 2002).

The results of long-term tests with earthworms, springtails and plants are available, with NOEC values of >100, 500 and 20 mg/kg dw respectively. The first two values were obtained in soils with an organic matter content of 10%. Normalising these values to the standard TGD soil organic matter content of 3.4% gives NOEC values of >34 and 170 mg/kg dw. The value for plants was obtained from a soil with 1.82% organic matter[24]. Normalising the value to the standard TGD soil organic matter content gives a NOEC value of 37 mg/kg dw.

As three NOEC values are available covering a suitable range of organisms[25], an assessment factor of 10 is appropriate, giving a $PNEC_{soil}$ of 3.7 mg/kg dw. For comparison with the calculated concentrations in soil, which are presented on a wet weight basis, this corresponds to a value of 3.2 mg/kg wet weight using the standard TGD. A NOEC of 32 mg/kg has also been reported for mortality in *Eisenia* in a short-term test. As no effects were seen with the same species in a longer-term test with the same test conditions, this short-term result is not considered to have a high reliability. As the $PNEC_{soil}$ derived here is well below the reported value, it is considered to be suitably protective.

### 3.2.4 Secondary poisoning

The $PNEC_{oral}$ was based on the mammalian data reviewed in the human health risk assessment. A NOAEL of 50 mg/kg bw/day was used (related to reduction in litter size in a three-generation feeding study with rats).

#### 3.2.4.1 New information

The effects of bisphenol-A on fertility and reproductive performance in CD-1 mice have been investigated in a two-generation study, conducted in response to the published risk assessment conclusions (Tyl *et al*, 2007). This study has been reviewed for the human health assessment. Overall, the study NOAEL for both general and reproductive toxicity is 50 mg/kg bw/day.

No avian toxicity data were previously available. Male White Leghorn *Gallus domesticus* chicks were administered bisphenol-A orally from two weeks of age to 25 weeks (Furuya *et al*, 2006). The doses used were 2 µg/kg bw to 200 mg/kg bw with administration every two days. The weights of the comb, wattle and testes were examined; cell counts on testes sections were used to monitor spermatogenesis.

[24] The OM content of the test soil as collected was 1.9%. The test medium as used was made up by mixing 11.5 kg of soil with 0.5 kg of sand, hence the final OM content was 1.82%.

[25] Although no data are available for soil micro-organisms, this is considered to be acceptable since bisphenol-A is readily biodegradable and possible endocrine effects are of more importance.

There were no differences in the body weights of birds between the control animals and those exposed to bisphenol-A. No pathological lesions were observed in the liver or kidneys of exposed birds. Decreases in the weight of the comb and wattle were seen in birds exposed to 2 µg/kg bw at ten weeks, but not at other times. At 20 µg/kg bw, similar effects were seen at ten weeks, and at 15 weeks reduced weights in the combs and testes were observed. These had recovered to control levels at 20 and 25 weeks. Higher concentrations tended to show greater effects, although only the 200 mg/kg bw exposure did not recover back to levels not statistically significantly different from the controls after 15 weeks.

The counts of spermatogonia per lumen were reduced in birds exposed to 20 µg/kg bw and above at ten weeks and longer exposures. Spermatocytes per lumen were reduced after 15 weeks and longer at 20 µg/kg and above, and the counts of spermatids per lumen were reduced from ten weeks on at 20 µg/kg bw and above.

The variation in effects over time makes the interpretation of the results difficult. There appears to be a delaying effect on the development of the comb, wattle and testes at most of the exposure levels, but this is temporary in all but the highest exposure. Spermatogenesis was affected at all but the lowest exposure level, but the effect of this on ability to reproduce was not investigated in the study and is not clear. If the highest dose was considered as a LOAEL then the NOAEL for the effects on the comb, wattle and testes weights would be 20 mg/kg bw. As this appears to have been given every two days, the daily dose should be taken as 10 mg/kg bw.

#### 3.2.4.2 PNEC for secondary poisoning

The $PNEC_{oral}$ derived in the published risk assessment was 33 mg/kg food, based on a NOAEL of 50 mg/kg bw/day from a three-generation rat study with a conversion factor of 20 and an assessment factor of 30.

The new two-generation study on mice also has a NOAEL of 50 mg/kg bw/day. However, the conversion factor for mice is 8.3, giving a NOEC of 415 mg/kg; applying the same assessment factor of 30 gives a $PNEC_{oral}$ of 13.8 mg/kg food.

The NOAEL from the study on chickens is 10 mg/kg bw/day. The conversion factor is 8, giving a NOEC of 80 mg/kg; applying an assessment factor of 30 gives a $PNEC_{oral}$ of 2.67 mg/kg food.

The lowest $PNEC_{oral}$ value of 2.67 mg/kg food will be used in the risk characterisation.

## 3.3 RISK CHARACTERISATION

### 3.3.1 Aquatic compartment

#### 3.3.1.1 Surface water

The PNEC for surface water derived in Section 3.2.1.5 is 1.5 µg/l. The PEC/PNEC ratios obtained using this value are presented in Table 3.33 and a) This scenario is included for completeness, but see the main text for further discussion

Table 3.34. Values above 1 are highlighted in bold.

Table 3.33 Risk characterisation ratios for freshwater and marine water – part 1

| | Freshwater | | Marine | |
|---|---|---|---|---|
| | $PEC_{water}$ (µg/l) | PEC/PNEC | $PEC_{marine\ water}$ (µg/l) | PEC/PNEC |
| Site specific | | | | |
| BPA 1 | | | 0.01 | 0.07 |
| BPA 2 | 0.032 | 0.02 | | |
| BPA 3 | | | 0.008 | 0.05 |
| BPA 4 | | | 0.007 | 0.05 |
| BPA 5 | | | 0.003 | 0.02 |
| BPA 6 | | | 0.10 | 0.67 |
| ER 1 | 0.033 | 0.02 | | |
| ER 2, ER 3, ER 6 | 0.032 | 0.02 | | |
| ER 4 | 0.99 | 0.66 | | |
| ER 5 | 0.062 | 0.04 | | |
| PAPER 1 | 0.31 | 0.2 | | |
| PAPER 2 | 0.14 | 0.09 | | |
| PAPER 3 | 0.10 | 0.07 | | |
| PAPER 4 | 1.03 | 0.67 | | |
| PAPER 5 | 1.03 | 0.67 | | |
| PAPER 6 | 0.97 | 0.65 | | |
| PAPER 7 | 0.07 | 0.05 | | |
| Generic scenarios | | | | |
| Polycarbonate bottle washing | 0.032 | 0.02 | 0.003 | 0.02 |
| Phenoplast cast resin processing | 1.47 | 0.98 | *1.2*[a] | ***7.74***[a] |
| PVC – Anti-oxidant during processing | 0.19 | 0.12 | 0.13 | 0.87 |
| PVC – Plasticiser use | 0.14 | 0.09 | 0.09 | 0.61 |

a) This scenario is included for completeness, but see the main text for further discussion

Table 3.34 Risk characterisation ratios for freshwater and marine water – part 2

| | Freshwater | | Marine | |
|---|---|---|---|---|
| | $PEC_{water}$ (µg/l) | PEC/PNEC | $PEC_{marine\ water}$ (µg/l) | PEC/PNEC |
| *PVC additive package* | | | | |
| Site A1 | | | 0.023 | 0.15 |
| Site A2 | 0.036 | 0.02 | | |
| Site A3 | 0.11 | 0.07 | | |
| Site A4 | 0.044 | 0.03 | | |
| Site A5 | 0.045 | 0.03 | | |
| Site A6 | | | 0.013 | 0.08 |
| Site A7 | | | 0.011 | 0.07 |
| Site A8 | 0.054 | 0.04 | | |
| Site A9 | 0.27 | 0.18 | | |
| Site A10 | 0.032 | 0.02 | | |
| Site A11 | 0.033 | 0.02 | | |
| Site A12 | 0.097 | 0.06 | | |
| Site A13 | | | 0.009 | 0.06 |
| *Anti-oxidant use in plasticiser production* | | | | |
| Specific site | | | 0.005 | 0.03 |
| Generic site | 0.39 | 0.26 | | |
| *Thermal paper recycling* | | | | |
| With deinking | 0.033 | 0.02 | 0.003 | 0.02 |
| Without deinking | 0.033 | 0.02 | 0.003 | 0.02 |

No PEC/PNEC ratio is above one for the freshwater compartment for any life cycle stage. The $PNEC_{water}$ of 1.5 µg/l is also above the 95%ile value of 0.35 µg/l from the whole freshwater monitoring data set as presented in Section 3.1.4.6.3.

Nevertheless, there remains a possibility that the $PNEC_{water}$ does not take full account of the potential effects of bisphenol-A on snails. The UK Government funded some additional research with native European[26] gastropod mollusc species in 2006 (the pulmonate snail *Planorbarius corneus* and the prosobranch snails *Bithynia tentaculata* and *Viviparus viviparus*). Much of this work has involved method development, since the selected species are not typically cultured in laboratories (and *V. viviparus* could not be cultured successfully). Initial results (unpublished) are as follows:

[26] The original work on snails involved a tropical species – it was decided early in the development of the conclusion (i) programme that the same species should be tested since:
- there was little experience in testing European freshwater snails at the time, and
- if a test with a different species failed to show any effect, there would still have been an open question about the original findings.

- Adult *P. corneus* were exposed to estradiol over an 8-week period in a semi-static system. At exposure concentrations of 1, 10 and 100 ng/l there was evidence of an increase in egg production relative to the controls at 15°C, whilst at 20°C there appeared to be a small decrease.
- A preliminary experiment exposed adult *P. corneus* to bisphenol-A at concentrations of 0.2, 2 and 20 µg/l at 15°C. Compared to the estradiol study, a much lower egg production rate was obtained for both exposed and control snails, which might have been caused by operational problems. The results were inconclusive as to whether the bisphenol-A exposure resulted in a change in egg production rate, although the mean egg productivity of the control groups was below all the bisphenol-A exposed groups.

There is therefore a residual concern that the $PNEC_{water}$ might be too high, despite the thorough testing conducted under the conclusion (i) programme. The following conclusion is therefore drawn for the freshwater compartment:

**Conclusion (i)** There is a need for further information and/or testing.

The rapporteur has commissioned an additional study that will expose adult *P. corneus* over a 6-month period using a more robust test design than that used for the original trial. If an effect is indeed apparent, further work will need to be considered (such as a life-cycle test). The implications for other priority substances will need to be considered at the same time.

#### 3.3.1.2 Marine water

The $PNEC_{marine\ water}$ derived in Section 3.2.1.5 is 0.15 µg/l, although this should also be considered provisional for the same reasons as for freshwater (it is noted that effects of bisphenol-A on marine molluscs have been recorded).

The resulting risk characterisation ratios are presented in Table 3.33 and a)This scenario is included for completeness, but see the main text for further discussion

Table 3.34. The generic scenario for phenoplast resins is the only scenario to give a potential risk for marine discharges; however, consultation with the European Phenolic Resins Association has confirmed that the sites previously identified as having marine discharges no longer use bisphenol-A for this purpose. Hence this scenario is not relevant for the marine environment.

The marine PNEC is above the 95%ile value from the measured levels in marine waters reviewed in Section 3.1.4.6.3.

The considerations with regard to toxicity to snails described in the freshwater assessment are also relevant for the marine assessment. Therefore the conclusion is:

**Conclusion (i)** There is a need for further information and/or testing.

No scenarios pose a potential risk using the current $PNEC_{marine\ water}$, but this should be reconsidered once the results of further toxicity testing with freshwater snails are available.

### 3.3.1.3 Sediment

The sediment PNEC and the sediment PEC values are obtained through the equilibrium partition method, and so the risk characterisation ratios are the same as for the freshwater and marine compartments and the same conclusions apply.

There are also additional scenarios related to the possible degradation of TBBPA in anaerobic sediments to give bisphenol-A. The PEC values estimated for the relevant freshwater TBBPA scenarios and the risk characterisation ratios (using a PNEC of 24 µg/kg wwt) are provided in Table 3.35 (marine sediment concentrations are expected to be around one order of magnitude lower). All ratios are below 1.

Table 3.35 Risk characterisation ratios for sediment (scenarios for TBBPA degradation)

| Scenario | | | PEC (mg/kg wwt) | PEC/PNEC |
|---|---|---|---|---|
| Reactive flame retardant use | Manufacture of epoxy and/or polycarbonate resins | | $(1.42\text{-}1.95)\times10^{-4}$ | <0.01 |
| | Processing of epoxy resins | | $(1.23\text{-}1.7)\times10^{-6}$ | <0.01 |
| Additive flame retardant use | ABS | Compounding | $(5.75\text{-}7.9)\times10^{-3}$ | 0.24-0.32 |
| | | Conversion | $(2.6\text{-}3.6)\times10^{-4}$ | 0.01-0.02 |

### 3.3.2 Terrestrial compartment

The PNEC for the terrestrial compartment is 3.2 mg/kg wwt. This is derived from the initial concentrations of bisphenol-A applied to the soils as described in Section 3.2.3.1. The concentrations in soil for the comparison therefore also need to be on the same basis. The values presented in Section 3.1.4.7 are on the standard TGD basis at a time 30 days after application. From the calculation method in the TGD, the ratio between the initial concentration and the 30-day value is 1.39:1, and so the calculated concentrations have been increased by a factor of 1.39. These revised concentrations and the resulting risk characterisation ratios are in Table 3.36 for bisphenol-A uses and Table 3.37 for possible formation of bisphenol-A through the degradation of TBBPA during sludge digestion. All of the ratios are below one.

**Conclusion (ii)** There is at present no need for further information and/or testing and no need for risk reduction measures beyond those which are being applied already.

There are no risks for the terrestrial compartment from the current production and use of bisphenol-A, nor from the possible degradation of TBBPA to bisphenol-A during sludge digestion.

Table 3.36 Risk characterisation ratios for soil from bisphenol-A uses

| | PEC (µg/kg wwt) | Revised PEC | PEC/PNEC |
|---|---|---|---|
| *Site specific* | | | |
| Epoxy resin ER4 | 13.3 | 18.5 | <0.01 |
| PVC additive package: A2 | 1.43 | 2.0 | <0.01 |
| A3 | 0.86 | 1.2 | <0.01 |
| A4 | 1.38 | 1.9 | <0.01 |
| A6 | 3.46 | 4.8 | <0.01 |
| A8 | 0.77 | 1.1 | <0.01 |
| A13 | 0.07 | 0.1 | <0.01 |
| *Generic scenarios* | | | |
| Phenoplast cast resin processing | 20 | 28 | 0.01 |
| PVC – anti-oxidant during processing | 2.2 | 3.1 | <0.01 |
| PVC – plasticiser use | 1.6 | 2.2 | <0.01 |
| Anti-oxidant in plasticiser production | 5.0 | 7.0 | <0.01 |
| Thermal paper recycling with deinking | 633 (p); 1.5 (b); 534 (c) | 880 (p); 2.1 (b); 742 (c) | 0.28 (p); <0.01 (b); 0.23 (c) |
| Thermal paper recycling without deinking | 35 (p); 1.8 (b); 29 (c) | 49 (p); 2.5 (b); 40 (c) | 0.02 (p); <0.01 (b); 0.01 (c) |

p Paper sludge;

b Biological sludge;

c Combined paper and biological sludges (in ratio produced)

Table 3.37 Risk characterisation ratios for soil from TBBPA uses

| Scenario | | | PEC | PEC/PNEC |
|---|---|---|---|---|
| Reactive flame retardant use | Manufacture of epoxy and/or polycarbonate resins | | 0.013 | <0.01 |
| | Processing of epoxy resins | | $2.5\times10^{-5}$ | <0.01 |
| Additive flame retardant use | ABS | Compounding | 0.54 | <0.01 |
| | | Conversion | 0.025 | <0.01 |

### 3.3.3 Secondary poisoning

The PNEC for secondary poisoning is 2.67 mg/kg food based on a non-standard test with birds (Section 3.2.4.2). The resulting risk characterisation ratios for freshwater and terrestrial predators are in Table 3.38 and for marine predators are in Table 3.39. All of the ratios are below one, the majority below 0.01. This would be the case even if the slightly higher BCF for clams were used for the aquatic food chain.

Table 3.38 Risk characterisation ratios for secondary poisoning – freshwater and soil

| | PEC fish (µg/kg) | PEC/PNEC | PEC worms (µg/kg) | PEC/PNEC |
|---|---|---|---|---|
| *Site specific* | | | | |
| Bisphenol-A production (BPA 2) | 2.2 | <0.01 | - | |
| Epoxy resin (ER 4) | 29 | <0.01 | 5.3 | <0.01 |
| Thermal paper production (PAPER 6) | 28 | <0.01 | - | |
| PVC additive package (A6) | 21 | <0.01 | 1.6 | <0.01 |
| *Generic scenarios* | | | | |
| Polycarbonate bottle washing | 2.3 | <0.01 | - | |
| Phenoplast cast resin processing | 36 | <0.01 | 7.8 | <0.01 |
| PVC – anti-oxidant during processing | 5.8 | <0.01 | 1.2 | <0.01 |
| PVC – plasticiser use | 4.8 | <0.01 | 0.92 | <0.01 |
| Anti-oxidant use in plasticiser production | 11 | <0.01 | 2.2 | <0.01 |
| Thermal paper recycling with deinking | 2.3 | <0.01 | 237 (p); 0.84 (b); 200 (c) | 0.09 (p); <0.01 (b); 0.07 (c) |
| Thermal paper recycling without deinking | 2.3 | <0.01 | 13 (p); 0.98 (b); 12 (c) | <0.01 (p); <0.01 (b); <0.01 (c) |

p Paper sludge;

b Biological sludge;

c Combined paper and biological sludges (in ratio produced)

Information on avian reproductive toxicity is important for endocrine disrupting chemicals, since mammalian toxicity data are of limited predictive value (birds are fundamentally different in certain aspects of their physiology, e.g. the control of sexual differentiation, egg laying, etc.). In this case a standard test guideline study is not available. However, it is not considered appropriate to request a further multi-generational study with birds because:

- bisphenol-A is readily biodegradable and has a low bioaccumulation potential,
- the existing study addressed several relevant end points, and
- the PEC/PNEC ratios are all significantly below 1.

Table 3.39 Risk characterisation ratios for secondary poisoning - marine

| | PECpredators (µg/kg) | PEC/PNEC | PEC top predators (µg/kg) | PEC/PNEC |
|---|---|---|---|---|
| *Site specific* | | | | |
| Bisphenol-A production (BPA 6) | 3.5 | <0.01 | 0.85 | <0.01 |
| PVC additive package (A1) | 0.73 | <0.01 | 0.3 | <0.01 |
| *Generic scenarios* | | | | |
| Polycarbonate bottle washing | 0.2 | <0.01 | 0.2 | <0.01 |
| Phenoplast cast resin processing | 28 | <0.01 | 5.8 | <0.01 |
| PVC – anti-oxidant during processing | 3.2 | <0.01 | 0.78 | <0.01 |
| PVC – plasticiser use | 2.3 | <0.01 | 0.61 | <0.01 |
| Anti-oxidant use in plasticiser production | 7.1 | <0.01 | 1.6 | <0.01 |
| Thermal paper recycling with deinking | 0.2 | <0.01 | 0.2 | <0.01 |
| Thermal paper recycling without deinking | 0.2 | <0.01 | 0.2 | <0.01 |

**Conclusion (ii)** There is at present no need for further information and/or testing and no need for risk reduction measures beyond those which are being applied already.

There are no risks for secondary poisoning from the current production and uses of bisphenol-A

### 3.3.4 PBT assessment

*Persistence*: Bisphenol-A is readily biodegradable, and so does not meet the P criterion.

*Bioaccumulation*: The measured BCF values in fish for bisphenol-A are in the range 30-75, with slightly higher values for other aquatic organisms (tadpoles, clams). These values are well below the threshold, and so bisphenol-A does not meet the B criterion.

*Toxicity*: There are no reliable chronic NOEC values below 0.01 mg/l, although there are some less reliable values and indications of possible effects at this level. Bisphenol-A has been shown to have effects on the endocrine systems of a number of organisms. It is therefore considered to meet the T criterion.

*Conclusion*: Bisphenol-A is not a PBT or vPvB substance; it meets the T criterion but not the P or B criteria.

### 3.3.5 Uncertainties

The exposure assessment is based on data provided by Industry, much of which is based on site-specific considerations. It is possible that some suppliers or users exist outside of the main trade associations, particularly in those Member States that joined the EU in recent years. For example, the rapporteur has been informed that there is a producer in Poland that is not part of the Industry consortium (no data have been supplied from this site). Competent Authorities may therefore need to check that the scenarios presented in this report are appropriate for their national situation.

As discussed in Section 3.2.1.5, the $PNEC_{water}$ can be derived in several ways, depending on how the *Marisa cornuarietis* data are viewed. The conclusion (i) study is reliable, and has not confirmed the original findings of Oehlmann and co-workers. Nevertheless, there are certainly strain differences in the snail stocks used in the different laboratories, and it is possible that the role of seasonality was not sufficiently investigated. Differences in exposure regimes might also have an influence if metabolites are more potent than the parent substance (though there is no evidence for this).

It is also apparent that reproductive effects have been observed at apparently low concentrations in more than one aquatic snail species (*Nucella lapillus* and *Potamopyrgus antipodarum*), although the available data are not sufficiently robust for direct use in the PNEC derivation. Whilst some of these effects might be an artefact of the experimental design, histopathological changes are difficult to dismiss in this way (although these are not necessarily directly related to effects that could influence population growth).

There therefore remains a possibility that the $PNEC_{water}$ does not take full account of the potential effects of bisphenol-A on snails. Further work being conducted by the UK Government should be taken into account when results are available in 2008. The implications for other endocrine active compounds will also need to be considered at the same time.

The PNEC for the marine compartment should also be considered as provisional for the same reasons as for freshwater; it is noted that effects of bisphenol-A on marine molluscs have been recorded.

If the aquatic PNEC is revised, then the sediment ratios would also change.

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# ABBREVIATIONS

| | |
|---|---|
| ADI | Acceptable Daily Intake |
| AF | Assessment Factor |
| ASTM | American Society for Testing and Materials |
| ATP | Adaptation to Technical Progress |
| AUC | Area Under The Curve |
| B | Bioaccumulation |
| BBA | Biologische Bundesanstalt für Land- und Forstwirtschaft |
| BCF | Bioconcentration Factor |
| BMC | Benchmark Concentration |
| BMD | Benchmark Dose |
| BMF | Biomagnification Factor |
| BOD | Biochemical Oxygen Demand |
| bw | body weight / *Bw*, *bw* |
| C | Corrosive (Symbols and indications of danger for dangerous substances and preparations according to Annex II of Directive 67/548/EEC) |
| CA | Chromosome Aberration |
| CA | Competent Authority |
| CAS | Chemical Abstract Services |
| CEC | Commission of the European Communities |
| CEN | European Standards Organisation / European Committee for Normalisation |
| CEPE | European Committee for Paints and Inks |
| CMR | Carcinogenic, Mutagenic and toxic to Reproduction |
| CNS | Central Nervous System |
| COD | Chemical Oxygen Demand |
| CSTEE | Scientific Committee for Toxicity, Ecotoxicity and the Environment (DG SANCO) |
| $CT_{50}$ | Clearance Time, elimination or depuration expressed as half-life |
| d.wt | dry weight / dw |
| dfi | daily food intake |
| DG | Directorate General |
| DIN | Deutsche Industrie Norm (German norm) |
| DNA | DeoxyriboNucleic Acid |
| DOC | Dissolved Organic Carbon |
| DT50 | Degradation half-life or period required for 50 percent dissipation / degradation |
| DT90 | Period required for 90 percent dissipation / degradation |
| E | Explosive (Symbols and indications of danger for dangerous substances and preparations according to Annex II of Directive 67/548/EEC) |
| EASE | Estimation and Assessment of Substance Exposure Physico-chemical properties [Model] |

| | |
|---|---|
| EbC50 | Effect Concentration measured as 50% reduction in biomass growth in algae tests |
| EC | European Communities |
| EC10 | Effect Concentration measured as 10% effect |
| EC50 | median Effect Concentration |
| ECB | European Chemicals Bureau |
| ECDIN | Environmental Chemicals Data and Information Network |
| ECETOC | European Centre for Ecotoxicology and Toxicology of Chemicals |
| ECVAM | European Centre for the Validation of Alternative Methods |
| EDC | Endocrine Disrupting Chemical |
| EEC | European Economic Communities |
| EINECS | European Inventory of Existing Commercial Chemical Substances |
| ELINCS | European List of New Chemical Substances |
| EN | European Norm |
| EPA | Environmental Protection Agency (USA) |
| ErC50 | Effect Concentration measured as 50% reduction in growth rate in algae tests |
| ESD | Emission Scenario Document |
| EU | European Union |
| EUSES | European Union System for the Evaluation of Substances [software tool in support of the Technical Guidance Document on risk assessment] |
| F(+) | (Highly) flammable (Symbols and indications of danger for dangerous substances and preparations according to Annex II of Directive 67/548/EEC) |
| FAO | Food and Agriculture Organisation of the United Nations |
| FELS | Fish Early Life Stage |
| foc | Organic carbon factor (compartment depending) |
| GLP | Good Laboratory Practice |
| HEDSET | EC/OECD Harmonised Electronic Data Set (for data collection of existing substances) |
| HELCOM | Helsinki Commission -Baltic Marine Environment Protection Commission |
| HPLC | High Pressure Liquid Chromatography |
| HPVC | High Production Volume Chemical (> 1000 tonnes/annum) |
| IARC | International Agency for Research on Cancer |
| IC | Industrial Category |
| IC50 | median Immobilisation Concentration or median Inhibitory Concentration |
| ILO | International Labour Organisation |
| IPCS | International Programme on Chemical Safety |
| ISO | International Organisation for Standardisation |
| IUCLID | International Uniform Chemical Information Database (existing substances) |
| IUPAC | International Union for Pure and Applied Chemistry |
| JEFCA | Joint FAO/WHO Expert Committee on Food Additives |

| | |
|---|---|
| JMPR | Joint FAO/WHO Meeting on Pesticide Residues |
| Koc | organic carbon normalised distribution coefficient |
| Kow | octanol/water partition coefficient |
| Kp | solids-water partition coefficient |
| L(E)C50 | median Lethal (Effect) Concentration |
| LAEL | Lowest Adverse Effect Level |
| LC50 | median Lethal Concentration |
| LD50 | median Lethal Dose |
| LEV | Local Exhaust Ventilation |
| LLNA | Local Lymph Node Assay |
| LOAEL | Lowest Observed Adverse Effect Level |
| LOEC | Lowest Observed Effect Concentration |
| LOED | Lowest Observed Effect Dose |
| LOEL | Lowest Observed Effect Level |
| MAC | Maximum Allowable Concentration |
| MATC | Maximum Acceptable Toxic Concentration |
| MC | Main Category |
| MITI | Ministry of International Trade and Industry, Japan |
| MOE | Margin of Exposure |
| MOS | Margin of Safety |
| MW | Molecular Weight |
| N | Dangerous for the environment (Symbols and indications of danger for dangerous substances and preparations according to Annex II of Directive 67/548/EEC |
| NAEL | No Adverse Effect Level |
| NOAEL | No Observed Adverse Effect Level |
| NOEL | No Observed Effect Level |
| NOEC | No Observed Effect Concentration |
| NTP | National Toxicology Program (USA) |
| o/oo | Parts per thousand |
| O | Oxidising (Symbols and indications of danger for dangerous substances and preparations according to Annex II of Directive 67/548/EEC) |
| OC | Organic Carbon content |
| OECD | Organisation for Economic Cooperation and Development |
| OEL | Occupational Exposure Limit |
| OJ | Official Journal |
| OSPAR | Oslo and Paris Convention for the protection of the marine environment of the Northeast Atlantic |
| P | Persistent |

| | |
|---|---|
| PAH | Polycyclic aromatic hydrocarbons |
| PBT | Persistent, Bioaccumulative and Toxic |
| PBPK | Physiologically Based PharmacoKinetic modelling |
| PBTK | Physiologically Based ToxicoKinetic modelling |
| PEC | Predicted Environmental Concentration |
| pH | logarithm (to the base 10) (of the hydrogen ion concentration $\{H^+\}$ |
| pKa | logarithm (to the base 10) of the acid dissociation constant |
| pKb | logarithm (to the base 10) of the base dissociation constant |
| PNEC | Predicted No Effect Concentration |
| POP | Persistent Organic Pollutant |
| PPE | Personal Protective Equipment |
| QSAR | (Quantitative) Structure-Activity Relationship |
| R phrases | Risk phrases according to Annex III of Directive 67/548/EEC |
| RAR | Risk Assessment Report |
| RC | Risk Characterisation |
| RfC | Reference Concentration |
| RfD | Reference Dose |
| RNA | RiboNucleic Acid |
| RPE | Respiratory Protective Equipment |
| RWC | Reasonable Worst-Case |
| S phrases | Safety phrases according to Annex IV of Directive 67/548/EEC |
| SAR | Structure-Activity Relationships |
| SBR | Standardised birth ratio |
| SCE | Sister Chromatic Exchange |
| SCHER | Scientific Committee on Health and Environmental Risks |
| SDS | Safety Data Sheet |
| SETAC | Society of Environmental Toxicology And Chemistry |
| SNIF | Summary Notification Interchange Format (new substances) |
| SSD | Species Sensitivity Distribution |
| STP | Sewage Treatment Plant |
| T(+) | (Very) Toxic (Symbols and indications of danger for dangerous substances and preparations according to Annex II of Directive 67/548/EEC) |
| TDI | Tolerable Daily Intake |
| TG | Test Guideline |
| TGD | Technical Guidance Document |
| TNsG | Technical Notes for Guidance (for Biocides) |
| TNO | The Netherlands Organisation for Applied Scientific Research |
| ThOD | Theoritical Oxygen Demand |

| | |
|---|---|
| UC | Use Category |
| UDS | Unscheduled DNA Synthesis |
| UN | United Nations |
| UNEP | United Nations Environment Programme |
| US EPA | Environmental Protection Agency, USA |
| UV | Ultraviolet Region of Spectrum |
| UVCB | Unknown or Variable composition, Complex reaction products of Biological material |
| vB | very Bioaccumulative |
| VOC | Volatile Organic Compound |
| vP | very Persistent |
| vPvB | very Persistent and very Bioaccumulative |
| v/v | volume per volume ratio |
| w/w | weight per weight ratio |
| WHO | World Health Organisation |
| WWTP | Waste Water Treatment Plant |
| Xn | Harmful (Symbols and indications of danger for dangerous substances and preparations according to Annex II of Directive 67/548/EEC) |
| Xi | Irritant (Symbols and indications of danger for dangerous substances and preparations according to Annex II of Directive 67/548/EEC) |

## Appendix 1 Non-summarised references

The following table lists all references retrieved from the literature search that were considered to be of low relevance for the environment update report based on the abstract. A brief reason for this decision is given in the final column. Some of these may be relevant for the human health assessment, and a few, indicated in bold highlighting, may need to be reviewed in future.

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| 2007 | Fernandez, M. P., Ikonomou, M. G., and Buchanan, I. | An assessment of estrogenic organic contaminants in Canadian wastewaters. | Science of the Total Environment. 373(1):250-269. | Waste water and contamination. |
| 2007 | Fu, K.-Y., Chen, C.-Y., and Chang, W. | Application of a yeast estrogen screen in non-biomarker species *Varicorhinus barbatulus* fish with two estrogen receptor subtypes to assess xenoestrogens. | Toxicolgy In Vitro. In Press. | Yeast assay, screening study. |

| Year | Authors | Title | Reference | Notes |
|---|---|---|---|---|
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European Commission

**EUR 24588 EN – Joint Research Centre – Institute for Health and Consumer Protection**
Title: European Union Risk Assessment Report - Environment Addendum of April 2008 - 4,4'-ISOPROPYLIDENEDIPHENOL (BISPHENOL-A) - Part 1 Environment
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**Abstract**
A risk assessment of 4,4'-isopropylidenediphenol (Bisphenol-A, BPA) produced in accordance with Council Regulation (EEC) 793/93[27] was published in 2003[28]. This Addendum (2008) has been prepared by the UK in the frame of Council Regulation (EEC) No. 793/93 on the evaluation and control of the risks of existing substances, following the principles for assessment of the risks to man and the environment, laid down in Commission Regulation (EC) No. 1488/94. The evaluation considers the emissions and the resulting exposure to the environment and the human populations in all life cycle steps. Following the exposure assessment, the environmental risk characterisation for each protection goal in the aquatic, terrestrial and atmospheric compartment has been determined.

This Addendum of environmental risk assessment for bisphenol-A, concludes that there is concern to the freshwater and marine aquatic compartments (including sediment, since the equilibrium partitioning approach has been used). Although no risks are indicated using the freshwater and marine PNEC for any scenario, there are still some uncertainties over the potential effects of bisphenol-A on snails, despite the thorough testing undertaken as part of the conclusion (i) programme.

The human health risk assessment for bisphenol-A is reported in Part II.

The format of the report is broadly in line with that of the original (2003) risk assessment. Significant new information is summarised in this updated (2008) risk assessment and a comment is added to indicate how this affects the findings from the original risk assessment.

27 O.J. No. L 084, 05/04/1993 p. 0001 - 0075
28 European Union Risk Assessment Report: 4,4'-isopropylidenediphenol (BPA) – 3rd Priority List, Volume 37. European Commission Joint Research Centre, EUR 20843 EN.

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