Recommendation from the Scientific Committee on Occupational Exposure Limits for Bisphenol-A

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Employment, Social Affairs and Inclusion

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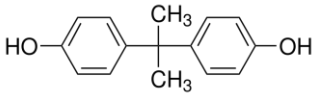
8-hour TWA:	2 mg/m^3 (as inhalable dust)
STEL (15-min):	-
BLV:	-
BGV:	7 µg/l (urinary total bisphenol-A)
Additional categorisation:	-
Notation:	-

This Recommendation is based on the compilations by EFSA (2010 and 2014), EC (2003 and 2008) and WHO (2011). This was further supplemented by a literature search conducted by SCOEL in February 2014 covering the data published since the adoption of the previous evaluation of bisphenol-A by SCOEL in 2004.

1. Substance identification, physico-chemical properties

Chemical name: Bisphenol-A
Synonyms (selected): 4,4'-Isopropylidenediphenol; 4,4'-dihydroxydiphenyl propane
IUPAC name: 2,2-bis(4-hydroxyphenyl)propane
Structural formula:



CAS No.:	80-05-7
EC No.:	201-245-8
Molecular formula:	$C_{15}H_{16}O_2$
Molecular weight:	228.29
Physical state at normal temperature and pressure:	White solid flakes or powder (depends upon manufacturing process
Melting point:	155–157 °C (depends upon manufacturing process)
Boiling point:	360 °C at 101.3 kPa (decomposition is also likely)
Relative density at 25 °C:	ca. 1.1–1.2 kg/m^3
Vapour pressure at 25 °C:	5.3 × 10^{-9} kPa
Solubility in water:	300 mg/l
Partition coefficient:	Log K_{ow} ca. 3.3–3.5
Flash point:	ca. 207 °C
Autoflammability:	ca. 532 °C
Explosive limits (in air):	Minimum explosive concentration 0.012 g/l with O_2 > 5 %
Oxidising properties:	Not an oxidising agent

EU harmonised classification:

Skin sens. 1	H317	May cause an allergic skin reaction
Eye dam. 1	H318	Causes serious eye damage
STOT SE 3	H335	May cause respiratory irritation
Repr. 2	H361	Suspected of damaging fertility

The ECHA Risk Assessment Committee (RAC) recently proposed to strengthen the reproductive toxicity classification of bisphenol-A (BPA) to a category 1B (H360 May

damage fertility) reproductive toxicant regarding the adverse effects on sexual function and fertility.

2. Occurrence/use and occupational exposure

Four companies within the EU manufacture BPA. There are a total of six production sites based in Germany, the Netherlands, Belgium and Spain. The total amount of BPA manufactured within the EU was 1 438 kilotonnes in 2008. Global BPA consumption has increased at an average rate of almost 10 % per year from 2003 to 2006. However, since then the growth has slowed down and in Europe it is expected to be flat (Chemical Weekly 2009).

BPA is manufactured from phenol and acetone by an acid or alkaline catalysed condensation reaction. Its main use is in the production of polycarbonate plastics followed by use for manufacture of epoxy resins. These account for more than 95 % of the uses of BPA. Other uses include for example flame retardants, unsaturated polyester resins and polyacrylate, polyetherimide and polysulphone resins (EC 2008).

There are validated methods for the analysis of BPA from air samples (OSHA 2013, Bruhn 2012). Sampling is performed using sampling pumps and collection to glass fibre filters. After extraction (e.g. acetonitrile), samples are analysed using e.g. high or ultrahigh performance liquid chromatography.

BPA can be measured in urine or blood in the form of free, conjugated or total (free and conjugated) BPA. Usually, total BPA is measured from spot urinary samples. The most commonly used analytical methods include gas chromatography and liquid chromatography coupled with mass spectrometry (MS) or tandem MS (MS/MS). Also an ELISA assay is available for the detection of BPA from biological materials but the main disadvantage of this method is its reduced accuracy at low analyte concentrations due to cross-reactivity with other structurally related compounds (Fukata *et al* 2006).

3. Health significance

3.1. Toxicokinetics

3.1.1. Absorption

The toxicokinetics of BPA after oral and parenteral administration has been well studied in rats and mice both *in vivo* and *in vitro*, and has been investigated to a lesser extent also in cynomolgus monkeys and humans (EC 2003, EFSA 2014, NTP 2008, WHO 2011). In the species studied, the available evidence shows that following oral administration, BPA is rapidly and extensively (about 85–100 % of the administered dose) absorbed from the gastrointestinal tract.

Dermal absorption has been studied *in vivo* or in *ex vivo* skin models. Morck *et al* (2010) reported 13 % absorption via the human skin. This study was performed according to OECD test guideline 428 but with an extended exposure period up to 48 hours. This result is rather well in accordance with a study by Demierre *et al* (2012), in which a penetration of 8.6 % with a maximum penetration rate of 0.022 $\mu g/cm^2$/hour was measured in a test performed according to OECD guideline 428 and under GLP (good laboratory practise). Of the applied dose, 0.6 % was recovered from the remaining skin resulting in a total amount of bioavailable BPA of 9.3 %. This was calculated to mean that with an external exposure of 100 µg/day e.g. from thermal paper, an internal exposure of 9.3 µg may be reached (Demierre *et al* 2012). In a

third *ex-vivo* dermal penetration study (Kaddar *et al* 2008) percutaneous penetration of 4.1 % via pig skin was reported. In contrast to these studies, Zalko *et al* (2011) observed an absorption of 46 % via the human skin in a 72-hour culture system using human skin explants. The methodology applied differed, however, from the standard methodology for skin penetration testing.

Marquet *et al* (2011) measured an *in vivo* percutaneous absorption flux of 0.4 µg/cm^2/hour in rats. According to their *ex vivo* studies on frozen human and rat skin, the permeability of human skin was 12-fold lower than that of rat skin. However, a 10-fold inter- and intraindividual variation was observed. Based on their results, it was calculated that a 1-hour occupational exposure over 2 000 cm^2 may lead to absorption of 4 µg/kg/day.

There were no data on the toxicokinetics of BPA following inhalation exposure, but it is assumed that appreciable absorption would occur.

3.1.2. Metabolism

After oral dosing, BPA is removed rapidly from the blood by first pass metabolism in the liver. In controlled oral dosing studies in humans using labelled BPA, free (unconjugated) BPA represented only 0.2–1.2 % of the total AUC (area under the curve) of BPA in blood or < 2 % of the total maximum concentration (C_{max}) (Taylor *et al* 2011, Volkel *et al* 2005 and 2011). However, the route of exposure is of paramount importance as there are marked differences in free BPA concentrations after oral as compared to parenteral administration of an equivalent dose (EC 2003). The bioavailability of free BPA can be 6–240-fold higher after intraperitoneal or subcutaneous dosing than after oral dosing (Pottenger *et al* 1997a,b). These differences may explain some effects seen after parenteral dosing but not after oral dosing.

Doerge *et al* (2010a,b, 2011b) have studied comparative kinetics of BPA in adult mice, rats and monkeys. According to their data, the levels of free (unconjugated) BPA in serum after single oral 100-µg/kg bw exposures are very low in all species: the AUC being 0.1 nMh in mice (0.2 % of the dose), 2.6 nMh in rats (2.8 %) and 1.5 nMh (0.9 %) in monkeys. This is well in accordance with the human data presented above. No comparative data on the levels of free BPA after inhalation exposure were available. It should be noted that a significant portion of inhaled BPA aerosols may actually become ingested.

There are contradictory data on the ability of the viable skin to metabolise BPA (Zalko *et al* 2011, Marquet *et al* 2011). According to *in vitro* studies, first-pass metabolism of BPA does not occur in lungs (Mazur *et al* 2010, Trdan Lusin *et al* 2012).

The major metabolic pathway in all species studied involves conjugation of BPA with glucuronic acid. In addition to the glucuronidation pathway, *in vivo* and *in vitro* studies suggest that BPA may be subject to limited oxidation to bisphenol *O*-quinone by cytochrome P450, and also to conjugation with sulphate.

3.1.3. Excretion

The major route of excretion in the rat and mouse is via faeces. The available data indicate that the percentage of the administered dose recovered in the faeces is in the range of 50–83 %. Urinary excretion is of secondary importance in the rat, with 13–42 % of the administered dose being recovered in the urine. Over 7 days post-dosing, 70–80 % of the administered dose was excreted in the faeces in rats. Elimination was rapid; the majority of the dose was excreted by 72 hours post-dosing. A sex difference

was also observed in rats in urinary excretion, with females excreting approximately twice as much radioactivity (24–28 %) as males (14–16 %). In addition, a strain difference was observed, with female F344 rats excreting approximately twice as much radioactivity in the urine as female CD rats (EC 2008). Data from a number of studies suggest limited excretion of BPA in the milk. Doerge *et al* (2010c) evaluated the lactational transfer of BPA after repeated oral dosing in rats and noted that even when free BPA was detected in all dam serum and milk samples, levels in pup serum were below the detection limits, and calculated doses delivered to pups lactationally were 300-fold lower than the dose administered to the dams. In rats and monkeys, free BPA has been shown to cross the placenta following oral administration, but the foetal levels have been in the same range or lower than those in maternal tissues (Doerge *et al* 2011a, Patterson *et al* 2013). *Ex vivo* studies using human placentas suggest a transplacental transfer rate of 1 (Mose *et al* 2012, Balakrishnan *et al* 2010).

In contrast to the findings in rodents, 84–97 % of a BPA dose administered to humans is excreted as glucuronide or sulphate conjugates in urine within a few hours (5–7 hours) after the administration. Within 24 hours, recovery from the urine is increased up to 100 % (Volkel *et al* 2002 and 2005). Free urinary BPA is only rarely detected in the general population (Volkel *et al* 2008). These interspecies differences in the main route of excretion of BPA have been explained by the differences in the thresholds for biliary elimination; the molecular weight of BPA-glucuronide is above the threshold in rats (approximately 350 Daltons) but below the threshold in humans (about 550 Daltons). Enterohepatic circulation in rodents accounts for the longer elimination half-life in rodents as compared to humans.

3.1.4. Biological monitoring

BPA has been a subject for several biomonitoring studies among the general population.

Results of several population studies measuring BPA levels in the general population were recently reviewed by e.g. Vandenberg *et al* 2010. Measurable levels of total BPA is usually present in the urine of most subjects among the general population. The levels measured in general, mostly adult, populations in USA, Canada, Germany and Finland are presented in Table 1.

The German Federal Environment Agency recently set a reference value of 7 µg/l for 20–29-year old adults (UBA 2012). This is based on the 95th percentile of total urinary BPA in a reference population of 600 20–29-year old adults. Children usually have higher BPA levels than adolescents who in turn have higher levels than adults (Calafat *et al* 2008).

Limited data is available on the BPA biomarker levels in occupationally exposed populations. Hanaoka *et al* (2002) reported urinary BPA (total BPA) levels in epoxy resin sprayers. Median levels were 1.06 (range ND–11.2 µmol/mol creatinine, n = 42), whereas the median in the control group in this study was 0.52 (range ND–11.0 µmol/mol creatinine, n = 42). Regardless of the statistically significant difference between the sprayers and the control group, the range of measured values was similar in both groups. He *et al* (2009) studied BPA exposure in Chinese workers in epoxy resin and BPA manufacturing facilities by air monitoring and by measuring urinary BPA levels. BPA was detected in 96 % of the air samples and the median concentration was 6.67 µg/m^3. Measurable levels were detected both at epoxy resin manufacturing and BPA manufacturing (median 7.89 and 4.72 µg/m^3, respectively). Pre-shift and post-shift urinary samples were collected. In resin manufacturing, median pre- and post-shift levels were 80.2 and 108 µg/g creatinine, respectively (n = 178 and 191),

Table 1. Total urinary BPA levels (after hydrolysis) in the general population.

Study (country)	Study population and sample size	BPA level (µg/l) GM	95th percentile
Calafat *et al* 2005 (NHANES 1988–94, USA)	184 males, 210 females	1.33	5.18
Calafat *et al* 2008 (NHANES 2003–04, USA)	9– < 60 year-old males and females (n = 2 517)	2.6	15.9
	20–59 year-old males and females (n = 951)	2.6	15.9
CDC 2012 (NHANES 2005–06, USA)	> 20 years (n = 1 490)	1.75	10.7
CDC 2012 (NHANES 2007–08, USA)	> 20 years (n = 1 814)	1.99	13.3
CDC 2012 (NHANES 2009–10, USA)	> 20 years (n = 1 914)	1.79	9.60
Koch *et al* 2012 (Germany)	20–29 years (n = 600)	1.55	7.37
Health Canada 2010 (Canada)	20–39 years (n = 1 165)	1.33	7.30
	40–59 years (n = 1 219)	1.04	6.58
Porras *et al* 2014 (Finland)	22–67 years (n = 121)	2.6	8.1

and in BPA manufacturing 170 and 233 µg/g creatinine (n = 8 and 7). Correlation analysis of 131 workers who contributed urine samples both pre- and post-shift showed that there was a significant correlation between levels of personal airborne BPA and urinary BPA pre-/post-shift levels. The main pollution sources were said to be crushing, feeding and packing workstations. Although not discussed in the report, skin (including skin to mount) exposure may have contributed to urinary levels. In addition, there were some discrepancies in the reported air and urinary levels in the report. In non-occupationally exposed Chinese males (n = 419), median urinary BPA levels of 1.43 µg/g creatinine were reported by the same research group. The 75th percentile was 14.18 µg/g creatinine (He *et al* 2009).

Wang *et al* (2012b) reported average urinary BPA concentrations of 55.73 ± 5.48 ng/ml (range 5.56–1 934.85 ng/ml) among 28 Chinese workers exposed to BPA in epoxy resin manufacturing. Brill (2013) measured levels up to 2 062 µg/l among workers in a BPA processing plant in Germany. In a Finnish study, levels up to 1 500 µg/l were seen in thermal paper manufacturing (Porras *et al* 2014).

Krishnan *et al* (2010) estimated the concentration of BPA in urine corresponding to the tolerable daily intake set by EFSA in 2006 (0.05 mg/kg) on the basis of available data on BPA toxicokinetics after oral exposure. This is called a biomonitoring equivalent. Taking into account that BPA is almost completely eliminated from the blood into urine after oral exposure, a biomonitoring equivalent of 2.0 mg/l (2.6 mg/g creatinine) was calculated using the following formula: $C_v = D \times BW \times F_{UE} / V$, where C_V is the average urinary BPA concentration on a volume basis, D is a unit dose of BPA at the tolerable daily intake (TDI) level, BW is the body weight for the group, F_{UE} is the urinary excretion fraction (= 1 for BPA), i.e. the fraction of the applied dose excreted in the urine, and V is the 24-hour average urinary volume.

In Germany, a biological limit value (BLV) for occupational exposure of 80 mg/l has been set for total BPA in urine (DFG 2013).

3.2. Acute toxicity

No useful information was available on the acute toxicity of BPA in humans. Oral LD_{50} values beyond 2 000 mg/kg are indicated in the rat and mouse, and dermal LD_{50} values above 2 000 mg/kg are evident in the rabbit (Hazleton Laboratories 1985, Mellon Institute 1948 and 1965, NTP 1982). For inhalation, a 6-hour exposure to 170 mg/m^3 (the highest attainable concentration) produced no deaths in rats; slight and transient nasal tract epithelial damage was observed (Nitschke *et al* 1985b). These data indicate that BPA is of low acute toxicity by all routes of exposure relevant to human health.

3.3. Irritancy

Limited human anecdotal information of uncertain reliability is available from written industry correspondence suggesting that workers handling BPA in the past experienced skin, eye and respiratory tract irritation (Dow Chemical 1957, Du Pont 1962). It cannot be determined whether the reported skin reactions were related to skin sensitisation (see Section 3.4) or irritation. However, a well conducted animal study clearly showed that BPA is not a skin irritant (Leuschner 2000b). The same research group also showed in a well conducted animal study that BPA is an eye irritant; effects persisted until the end of the study (day 28 post-instillation) in 1 of 3 rabbits (Leuschner 2000a). Overall, taking into account the animal and human evidence, BPA has the potential to cause serious damage to the eyes.

Slight and transient nasal tract epithelial damage was observed in rats exposed to BPA dust at 170 mg/m^3 (the highest attainable concentration) for 6 hours (Nitschke *et al* 1985b). These data suggest that BPA appears to have a limited respiratory irritation potential.

3.4. Sensitisation

With respect to skin sensitisation in humans, there are several reports of patients with dermatitis responding to BPA in patch tests (EC 2003). However, it is unclear whether BPA or related epoxy resins were the underlying cause of the hypersensitive state. Anecdotal information indicates skin inflammation in workers handling BPA although, given the uncertain reliability of this information, no conclusions can be drawn from it. In animals, a skin sensitisation test performed according to current regulatory standards is not available. The available studies are negative, but the test reports lack detail and no reliable justifications were given for the choice of concentrations used (Thorgeirsson and Fregert 1977, Procter and Gamble Co. 1969). It is possible that the concentrations used in all the available studies were not maximised and a greater response might have been obtained with higher induction and challenge concentrations. Based on the findings from the most robust study, BPA may possess a skin sensitisation potential, albeit a limited one. BPA in the presence of UV light can also elicit skin responses in humans, and reproducible positive results for photosensitisation have been obtained in the mouse ear swelling test (Allen and Kaidbey 1979, Gerberick and Ryan 1990, Maguire 1988). Therefore, examination of the available human and experimental animal studies leaves the picture somewhat unclear as to whether one or more of the following are properties of BPA; (1) orthodox skin sensitisation (2) photosensitisation (3) BPA eliciting a response in people previously skin sensitised to another substance (e.g. epoxy resins). Thus, the precise nature of the hazardous properties of BPA on the skin is unclear, but clearly skin reactions can be a potential consequence of repeated skin exposure in humans. Overall, taking all of the available data into account, BPA is considered capable of

producing skin sensitisation responses in humans. There are no data from which to evaluate the potential of BPA to be a respiratory sensitiser.

3.5. Endocrine modulating activity of BPA

BPA has been shown to have endocrine modulating activity in a number of *in vitro* and *in vivo* screening assays (EC 2003). The potency of this activity in these assays generally ranged from 3–5 orders of magnitude less than that of oestradiol. Regardless of the low activity compared to oestradiol, these endocrine-modulating effects of BPA have been the main concern and subject for BPA related research during the past few years. These effects have been suggested to occur at very low dose levels and exhibit so-called non-monotonic dose-response curves (NMDRCs), defined as a nonlinear relationship between dose and response where the slope of the curve changes sign somewhere within the range of doses examined (Vandenberg *et al* 2012). The scientific validity of the non-monotonic dose-response relationship has been questioned. However, non-monotonic dose-response has been observed at un-physiological conditions, which are not relevant for risk assessment. Toxic effects suggested to be related to the endocrine modulating activity of BPA are discussed below under the respective chapters: repeated dose toxicity (metabolic effects), carcinogenicity (hormonal cancers) and reproductive toxicity.

3.6. Repeated dose toxicity

3.6.1. Human data

There are some recent cross-sectional studies on the general population reporting associations between urinary BPA levels and diabetes, obesity or cardiovascular diseases (Carwile and Michels 2011, Eng *et al* 2013, Melzer *et al* 2012a,b, Shankar *et al* 2011, Shankar *et al* 2012a,b,c, Silver *et al* 2011, Trasande *et al* 2012, Wang *et al* 2012a, all reviewed in EFSA 2014). Because of the cross-sectional nature of these studies and possible confounding by diet (which is also the main source of BPA) or other concurrent exposures, no conclusions on the association can be made based on these studies. In addition, an association was not supported by the re-analysis of the NHANES (National Health and Nutrition Examination Survey) based data sets with control of all relevant confounders (Lakind *et al* 2012). The authors of this study emphasised the inappropriateness of using cross-sectional datasets like NHANES to draw conclusions about the causal associations between short-lived environmental chemicals like BPA and chronic complex diseases.

Wang *et al* (2012b) reported a cross-sectional analysis of the relationship between urinary BPA concentrations and blood or urinary markers of liver function, glucose homeostasis, thyroid function and cardiovascular diseases among 28 Chinese workers exposed to BPA in epoxy resin manufacturing. The average urinary BPA concentration was 55.73 ± 5.48 ng/ml (range 5.56–1934.85 ng/ml). Higher urinary BPA concentrations were associated with a significant increase in FT3 (free triiodothyronine) levels in this group of workers. A possible effect of other, confounding exposures cannot be ruled out. No conclusions can be made on the basis of this single, small study.

3.6.2. Animal data

In animals, there were no data relating to repeated dermal exposure. Repeat inhalation studies were available in the rat (Nitschke *et al* 1985a and 1988). The principal effect was the same as that observed following a single exposure - slight upper respiratory tract epithelium inflammation. Very slight to slight inflammation and

hyperplasia of the olfactory epithelium were observed following exposure to 50 and 150 mg/m^3 [6 hours/day, 5 days/week for 2 or 13 weeks; 150 mg/m^3 is close to the highest attainable concentration; the particle mass median aerodynamic diameter (MMAD) was 2–6 µm], and a NOAEC of 10 mg/m^3 was identified in rats in this 13-week study.

In early 90-days studies in rats, a decrease in body weight gain and minor changes in organ weights at 100 mg/kg/day and above were seen after dietary administration (NTP 1982, Til *et al* 1978). Dietary studies in mice indicated that the liver is a target organ in this species with changes being observed in the size and nucleation state of hepatocytes in 2-year and 90-day studies (Furukawa *et al* 1994, NTP 1982). The incidence and severity of these treatment-related multinuclear giant hepatocytes were markedly greater in males than in females. It was not possible to identify a no-effect level for males, the effect being observed at all dose levels used from the lowest dose tested of 120 mg/kg/day (2-year study). Even at this lowest dose level, a large proportion (84 %) of the animals examined showed signs of this effect. In females, a no-effect level of 650 mg/kg/day was identified for these cellular changes in the 2-year study.

The studies providing relevant dose-response data on repeated dose toxicity after oral exposure include also the multigeneration and 2-generation studies by Tyl *et al* (2002 and 2008) in rats and mice. Tyl *et al* (2002) studied the effects of dietary levels of 0, 0.015, 0.3, 4.5, 75, 750 and 7 500 mg/kg feed (corresponding to an intake of 0.001, 0.02, 0.3, 5, 50 and 500 mg/kg bw/day of BPA) in Sprague-Dawley rats over three offspring generations. Adult systemic toxicity was evident at the two highest doses of 50 and 500 mg/kg bw/day in all generations. The effects included reductions in body weights and weight gains, which were evident in males already at 50 mg/kg/day. At necropsy, F0, F1, and F2 parental and F3 retained adult absolute non-reproductive organ weights were almost uniformly reduced for liver, kidneys, adrenal glands, spleen, pituitary and brain at 500 mg/kg bw. Slight to mild renal tubular degeneration and chronic hepatic inflammation were observed at a higher incidence in F0, F1 and F2 females at 500 mg/kg bw. No effects on food consumption were seen and no treatment or dose-related effects were seen in clinical observations. There were no toxicologically significant effects on these parameters at 5 mg/kg bw/day (NOAEL).

In a 2-generation study in mice (Tyl *et al* 2008) at dietary doses of 0, 0.018, 0.18, 1.8, 30, 300 or 3 500 mg/kg feed (corresponding to an intake of 0, 0.003, 0.03, 0.3, 5, 50 or 600 mg BPA/kg bw/day), effects on liver were observed in F0/F1 adult males in the two highest dose groups. The effects included increased weights of the liver at 600 mg/kg bw/day and increased incidence of liver centrilobular hepatocyte hypertrophy at 50 mg/kg bw (minimal severity) and at 600 mg/kg bw (minimal to mild severity). Also renal nephropathy with minimal severity was seen at the highest dose. Absolute kidney weights were increased in both F0 and F1 males at the two highest dose levels and a small (statistically significant) increase was seen also at the dose levels of 0.3 and 5 mg/kg in F1 males only (not in F0 or in retained F1 males). Reduced body weights were seen in males at the highest dose without any effects on food consumption. In females, increased absolute and/or relative weight of the liver and kidneys and centrilobular hepatocyte hypertrophy of minimal severity were seen at the highest dose level. The authors suggested a NOAEL of 5 mg/kg bw based on liver effects. Effects on kidney weights in male mice at the dose levels of 0.3–50 mg/kg bw were not considered relevant by the authors because of the lack of accompanied histological changes, lack of clear dose-response relationships or lack of clear effects in F0 or retained F1 male mice. EFSA (2014) calculated the benchmark dose level corresponding to 10 % extra risk for liver and kidney effects ($BMDL_{10}$) based on this study. $BMDL_{10}$ for hepatocyte hypertrophy was 3 460 µg/kg bw and for increased kidney weights 3 633 µg/kg bw (right kidney) and 3 887 µg/kg bw (left

kidney). Kidney weight changes were considered more relevant than possibly adaptive hepatocyte hypertrophy. It should be noted, however, that in rats (Tyl *et al* 2002), a reduction rather than an increase in kidney weights were seen. Altogether, these data show that liver and kidneys are the main target organs of BPA after high oral daily doses > 5 mg/kg bw.

In dogs, a 90-day dietary study showed a no-effect level of approximately 80 mg/kg bw/day, with increases in relative liver weight observed at approximately 270 mg/kg bw/day (General Electric 1976).

In addition, there are several animal studies using lower doses of BPA (< 5 mg/kg bw) claiming that BPA has an effect on lipogenesis (causing obesity), and glucose or insulin regulation (resulting in diabetes). These studies were reviewed by EFSA (2014). Many of these employed prenatal exposure, but some studies were performed also in animals exposed postnatally. Results from these studies are, however, inconsistent, and even if some changes in glucose and insulin regulation or pancreas have been seen in short-term studies, these are not supported by the findings related to diabetes or obesity in long-term term animal studies (EFSA 2014).

3.7. Genotoxicity

3.7.1. Genotoxicity in vitro

BPA appears to have demonstrated aneugenic potential *in vitro*, positive results being observed without metabolic activation in a micronucleus test in Chinese hamster V79 cells and in a non-conventional aneuploidy assay in cultured Syrian hamster embryo cells (Pfeiffer *et al* 1997, Tsutsui *et a*l 1998). Additionally, in cell-free and cellular systems, there is information showing that BPA disrupts microtubule formation and spindle apparatus, which may result in aneuploidy (EC 2003, NTP 2008). However, these effects have not been unequivocally demonstrated *in vivo* (NTP 2008). BPA produced adduct spots in one post-labelling assay with isolated DNA and a peroxidase activation system, but it does not appear to produce either gene mutations or structural chromosome aberrations in bacteria, fungi or mammalian cells *in vitro* (EC 2003, NTP 2008).

3.7.2. Genotoxicity in vivo

No human data regarding genotoxicity were available. The standard mouse bone marrow micronucleus test gave negative result (Shell Oil Company 1999). Pacchiorotti *et al* (2008) found no increase in chromosomal aberrations in germ cells or in bone marrow cells of rats after acute, sub-chronic or chronic *in vivo* exposure. Female mice were orally treated with BPA, either a single dose with 7 daily administrations or for 7 weeks to BPA in drinking water. No significant induction of hyperploidy or polyploidy was observed in oocytes and zygotes at any treatment condition. With male mice, no delay of meiotic divisions was found in the BrdU assay after 6 daily oral doses of BPA and no induction of hyperploidy and polyploidy in epididymal sperm was seen after 6 daily oral BPA doses. Finally, 2 daily oral BPA doses did not induce any increase in micronucleus frequencies in polychromatic erythrocytes of mouse bone marrow. The doses used were up to 20 mg/kg bw in the single dose study, and 0.002–0.2 mg/kg bw per day in the repeated dose studies. Doses were selected on the basis of the Hunt *et al* (2003) study showing aneuploidy in mice oocytes *in vivo*.

Lack of clastogenic effects were supported also by e.g. Naik *et al* (2009) who did not see any increases in chromosomal aberrations or micronuclei in mice bone marrow cells after oral exposure. However, increased incidences of c-mitosis were seen at dose levels of 50 and 100 mg/kg suggesting an effect on the mitotic spindle

apparatus. This effect is supported by *in vitro* studies by Johnson and Parry (2008) and Tayama *et al* (2008) showing increased incidences in binucleate-micronucleate cells and c-mitosis *in vitro*, respectively, at dose levels not causing cytotoxicity. An effect on microtubules can be considered, however, to have a dose threshold. Considering all of the available genotoxicity data and the absence of significant tumour findings in animal carcinogenicity studies (see Section 3.8), it does not appear that BPA has significant mutagenic or genotoxic potential *in vivo*.

3.8. Carcinogenicity

3.8.1. Human data

There were no human data contributing to the assessment of whether or not BPA is carcinogenic.

3.8.2. Animal data

In animals, a dietary carcinogenicity study in two species, F344 rats and B6C3F_1 mice, was available (NTP 1982). A small increased incidence of leukaemias was seen in male and female F344 rats along with increases in the frequency of mammary gland fibroadenomas in male rats. These increases were not statistically significant, were slight and in a strain prone to these tumours. An increased incidence in benign Leydig cell tumours seen in male rats was within historical control limits. In mice, a small increased incidence in lymphomas was observed in males, but was not statistically significant and there was no dose-related trend. No increased incidence in any tumour type was observed in female mice. Overall, all of these tumour findings in rats and mice were considered not toxicologically significant. Consequently, it was concluded that BPA was not carcinogenic in this study in either species.

No inhalation or dermal carcinogenicity studies were available, although in repeat exposure inhalation toxicity studies, BPA did not exhibit properties that raise concern for potential carcinogenicity. Only minimal inflammation was seen in the upper respiratory tract at 50 mg/m^3 in a 13-week study, and the severity did not increase up to concentrations close to 150 mg/m^3, the maximum attainable concentration in the experimental system used. Taking into account all of the animal data available, the evidence suggests that BPA does not have carcinogenic potential.

Recently, concerns have been raised for the possible contribution of BPA on prostate and mammary gland development rendering these organs more susceptible to neoplasia especially when exposed during neonatal age (Acevedo *et al* 2013, Betancourt *et al* 2010, Jenkins *et al* 2009 and 2011, Lamartiniere *et al* 2011, Moral *et al* 2008, Prins *et al* 2011, Tharp *et al* 2012, Timms *et al* 2005, Vandenberg *et al* 2013, Weber Lozada and Keri 2011). These studies were performed in the "low dose range" i.e. at levels well below 5 mg/kg bw. Most of these studies did not study the effect on tumour incidence but rather on tissue/cell proliferation. Some of these suggest normal monotonic dose-response relationships for these carcinogenic or proliferative effects while in other studies a non-monotonic dose-response curve is claimed. The studies evaluating the effects on cancer incidence include the study by Jenkins *et al* (2009) in which rats were exposed lactationally to low doses (25 and 250 µg/kg) of BPA and a single oral dose of the tumour inducer dimethylbenzanthracene (DMBA). A dose-related increase in the number of tumours was seen, which was statistically significant at the highest dose. A decrease in tumour latency was also reported. Similar results were reported also by Betancourt *et al* (2010) with both prenatal and postnatal exposure to BPA. However, in a subsequent study by Jenkins *et al* (2011), in which adult transgenic mice were exposed to 0.5, 5, 50 or 500 µg/kg of BPA from week 8 to week 36 of age, an increase in the number of tumours per mouse and in the number

of mice with metastases were observed only at the 1–2 lowest dose levels without any clear dose-response relationship. No data on the exact number of mice with tumours were given. Acevedo *et al* (2013) studied the effect of subcutaneous prenatal or both pre- and postnatal exposure to BPA on mammary gland cell proliferation and neoplasia at the dose levels of 0.25, 2.5 or 250 µg/kg. Some preneoplastic lesions and single cancers (0–1 cancers per 23–33 animals) were detected in the treated groups without any significant increase or dose-response relationship. The highest dose level resulted in measurable serum levels of free BPA in pups exposed via lactation. Lower dose levels were estimated to result in such low serum levels that they would not have been detected with current analytical methods (and would not have been distinguishable from background levels measured in untreated animals). All these studies, however, suffer from deficiencies in design or execution, which have been discussed in detail in EFSA 2014. The US Food and Drug Administration/National Center for Toxicological Research (FDA/NCTR) is currently conducting a long-term study in rats in order to evaluate the potential carcinogenicity of BPA after pre- and postnatal exposure. Related to this long-term study, a shorter duration reproductive study was performed, in which rats were exposed from gestation day 6 to postnatal day 90 to a wide-range of oral doses (0.0025–300 mg/kg) of BPA (Delclos *et al* 2014). At postnatal days 21 and 90, an increase in mammary gland duct hyperplasia was seen in the three highest dose groups (2.7, 100 and 300 mg/kg) and in females only. Variability in incidence across the dose range was seen. The severity of hyperplasia was minimal. It should be noted that pups were dosed directly by gavage from postnatal day 1 instead of being exposed via dam's milk. Thus, the postnatal exposure was higher than in many other studies involving postnatal exposure via dam's milk. Ethinyl oestradiol at the doses of 0.5 and 5 µg/kg, in contrast, induced mammary gland duct hyperplasia especially in males, which is in accordance with earlier studies on the effects of oestrogenic agents.

Thus, there is currently no convincing evidence of carcinogenicity of BPA when administered either during the adulthood or perinatally. However, as concluded by EFSA (2014), there are some data (including the data by Delclos *et al* 2014) that raise some concern for BPA effects on mammary gland cell proliferation after pre- and perinatal exposure. Whether this is linked to increased cancer incidence in later life or not remains to be shown.

3.9. Reproductive toxicity

3.9.1. Human data

In a study conducted in China, Li *et al* (2010b) examined the effect of occupational BPA exposure on male reproductive function. Workers (n = 164) were exposed to mean air levels of 0.006 mg/m^3 of BPA, the highest levels being in packaging operations (geometric mean 0.016 mg/m^3), and their sexual function was evaluated using a standardised male sexual function inventory. BPA exposed workers reported higher levels of reduced sexual desire (OR 3.9), erectile or ejaculation difficulty (ORs 4.5 and 7.1, respectively), and reduced satisfaction with their sex life (OR 3.9). A dose-response relationship with cumulative BPA exposure was seen. When sexual function among these workers was correlated with urinary BPA levels (based on two spot samples, before and after the work shift), a significant correlation between urinary BPA levels and self-reported sexual dysfunction was seen. The median urinary BPA level was 53.7 µg/g creatinine (with an interquartile range of 8.6–558.9 µg/g creatinine) among the exposed workers (Li *et al* 2010a). In their third study, Li *et al* (2011) reported a statistically significant association between increasing urinary BPA levels and decreasing sperm concentration, total sperm count, sperm vitality and motility among 218 men working in the same factories. Compared to those men who

had no detectable urinary BPA, those with detectable urinary BPA had an OR of 3.4 for lower sperm concentration, an OR of 3.3 for lower sperm vitality, an OR of 4.1 for lower sperm count and an OR of 2.3 for lower sperm motility. Among the highest tertile of BPA exposure, higher ORs for these effects were detected. An inverse correlation between urinary BPA levels and sperm concentration and sperm count was noted also among environmentally exposed persons (n = 88). Although some confounders had been taken into account in these occupational studies, it is not possible to exclude an effect of other occupational exposures on the studied parameters. Also a selection bias cannot be excluded since only 58 % of the invited men participated in the study. The latest cross-sectional study from China among petrochemical industry workers (n = 137) reported decreased androstenedione and free testosterone levels, decreased free androgen index and increased sex-hormone binding globulin levels when compared to the control group. Inhibin, follicle-stimulating hormone (FSH), prolactin, oestradiol and total testosterone levels were unchanged. The exposed group had a median serum BPA level of 3.198 compared to 0.276 µg/l in controls (Zhou *et al* 2013).

Cha *et al* (2008), on the other hand, reported decreased testosterone levels and increased luteinising hormone (LH) and FSH levels among 25 epoxy resin painters with increased urinary BPA levels (2.61 µg/g creatinine vs. 1.38 µg/g creatinine in controls). This contrasts with the findings of Hanaoka *et al* 2002 who showed decreased FSH levels among 42 epoxy resin sprayers with slightly elevated urinary BPA levels. It should be noted that the difference in BPA levels between exposed and non-exposed was very small.

Regarding developmental effects, Miao *et al* (2011a,b) reported decreased birth weight and shortened anogenital distance (in boys) in the offspring of occupationally BPA exposed mothers. Characterisation of the exposure was limited and potential confounding by diet or other exposures cannot be excluded. There are also other, mainly cross-sectional studies which have suggested a linkage between maternal BPA exposure from environmental sources and pregnancy outcome (foetal growth etc.). However, the effect of diet or other concurrent exposures on pregnancy outcome cannot be ruled out. Thus, no firm conclusions on causal association can be drawn from these studies (EFSA 2014).

Braun *et al* (2009 and 2011) examined the relationship between gestational BPA exposure (measured as serial urinary BPA samples) and neurobehavioral effects in infants in a prospective study. An association between BPA levels and externalising behaviours (aggression, hyperactivity) among 2-year old girls was noted. At the age of 3, the girls showed a more anxious and depressed behaviour and poorer emotional control and inhibition. However, another prospective study observed an association with aggressive behaviour and emotional reactivity only in boys (Perera *et al* 2012), whereas in some other studies no association with child behaviour was seen (Miodovnik *et al* 2011, Yolton *et al* 2011). Thus, no conclusions on the possible association between pre- or early postnatal exposure to BPA and behaviour can be made based on the human data.

3.9.2. Animal data

The effects of BPA on fertility and reproductive performance have been investigated in three good quality 3-generation and 2-generation studies in rats or mice, and one older continuous breeding study in mice. Since there is an ongoing discussion on possible low-dose effects and non-monotonic dose-response curves, three of these studies employed also low dose ranges.

The oldest one of these reproductive toxicity studies is a continuous breeding study in mice, which provides some evidence that BPA can cause adverse effects on fertility at high dose levels (NTP 1985a). In the F0 generation, no effects on fertility were seen at 300 mg/kg bw/day, but at dose levels of approximately 600 mg/kg bw/day and above, reductions in the numbers of litters produced, litter size and numbers of live pups per litter were observed in each of the 4–5 litters produced. These effects were observed in the absence of significant parental toxicity. In contrast, no adverse effects on fertility were observed in the single litter tested at each dose level from the F1 generation. A small but statistically significant and dose related decrease in epididymal weight was seen at all doses in the F1 generation, but the significance of this finding is uncertain because a comparable effect was not seen in F0 mice. In spite of the uncertainty, the epididymis is associated with sperm transport and storage, and any reduction in the weight of this organ would be of concern.

In the 3-generation study, an effect on fertility (reduction in litter size) was seen in all three generations at the top dose of 500 mg/kg bw (Tyl *et al* 2002). Although this effect was seen only at a dose level causing parental toxicity (a reduction in body weight gain of > 13 %) in both sexes and renal tubule degeneration in females, it is not clear whether or not the finding could be a secondary consequence of parental toxicity, or a direct effect of BPA. Reductions in body weights and weight gains were seen in males already at 50 mg/kg bw. No effects on fertility were seen at 50 mg/kg or at lower dosages (0.001–5 mg/kg bw/day). Regarding developmental effects, a statistically significant decrease in mean pup body weight gain with concomitant delays in the acquisition of developmental landmarks (vaginal patency and preputial separation) was observed at 500 mg/kg bw on postnatal days 7–21 in males and females of all generations (F1–F3) (Tyl *et al* 2002). These decreases in pup body weight gain and delays in development were seen in the presence of maternal toxicity. No treatment-related effects were reported in the offspring of animals exposed to 50 mg/kg bw. The NOAEL for reproductive and developmental endpoints was 50 mg/kg bw/day and for systemic toxicity 5 mg/kg bw/day.

In a 2-generation study in mice, no effects on adult mating, fertility or gestational indices, ovarian primordial follicle counts, oestrous cyclicity, precoital interval, sperm parameters or reproductive organ weights or histopathology (including the testes and prostate) were seen in the dose range of 0.003–600 mg/kg bw (Tyl *et al* 2008). Signs of systemic toxicity (e.g. liver centrilobular hepatocyte hypertrophy) were seen at the doses of 50 mg/kg bw and higher (see Section 3.6). However, reduced F1/F2 weanling body weight, reduced weanling spleen and testes weights (with seminiferous tubule hypoplasia), slightly delayed preputial separation (PPS), and an increased incidence of undescended testes in weanlings were seen at the highest dose level of 600 mg/kg bw/day. The latter finding was considered as a developmental delay in the normal process of testes descent since it did not result in impaired reproductive performance later in life (Tyl *et al* 2008). Offspring sex ratios or postnatal survival was unaffected. The NOAEL for developmental effects was 50 mg/kg bw/day and for systemic toxicity 5 mg/kg bw/day. No effects were seen in the low dose range of 0.003–5 mg/kg bw/day.

Also in a 2-generation rat study employing low doses of 0.2–200 µg/kg bw/day by gavage with endocrine-sensitive and neurobehavioural end-points, no effects on any reproductive or developmental parameters were seen at any dose level (Ema *et al* 2001).

In a repeated dose study by FDA/NCTR (Delclos *et al* 2014), rats were exposed from gestation day 6 to postnatal day 90 to a wide-range of oral doses (0.0025–300 mg/kg bw) of BPA. Body weights of high-dose males and females, and of the second highest-dose (100 mg/kg) females were decreased when compared to the controls. No effect

on male sperm production, reproductive organ weights or histopathology was seen on postnatal day 90. A 1–2 days delay in testicular descent was seen in the 0.26- and 300-mg/kg dose groups but not in others (including 2.6 or 100 mg/kg). In females, higher rates of abnormal cyclicity, decreased ovarian weights and depletion of corpora lutea and antral follicles were detected at the highest dose level (300 mg/kg). Increased serum oestradiol and prolactin and decreased progesterone levels were seen in females at postnatal day 80. No treatment related effects were seen in markers of sexual developmental in either sex. Ethinyl oestradiol at the dose levels of 0.5 and 5 µg/kg induced several changes in the above mentioned parameters. BPA did not affect obesity or glucose metabolism parameters (fat pad weights, serum glucose, insulin) either.

Regarding standard developmental endpoints, no effects were seen in old standard developmental studies in rats and mice. In rats, a maternal LOAEL and a foetal NOAEL of 160 and 640 mg/kg bw/day, respectively, were identified (Morrisey *et al* 1987, NTP 1985c). In mice, maternal and foetal NOAELs were 250 and 1 000 mg/kg bw/day, respectively (NTP 1985b).

In contrast to these guideline based studies described above, there are several other studies on the effects of low BPA doses (< 5 mg/kg bw/day) on the reproductive parameters. Some of these claim a non-monotonic dose-response curve, whereas in others, a monotonic dose-response relationship has been seen.

In early studies in mice, adverse effects on male reproductive tract development (an increase in prostate weight in two studies and a reduction in epididymis weight in one study) were reported after gestational exposure at daily dose levels in the range of 2–50 µg/kg (Nagel *et al* 1997, vom Saal *et al* 1998, Gupta 2000). However, these results were not reproducible in two other studies, one of which included additional dose levels, and using larger group sizes compared with those used in either of the two studies showing effects (Cagen *et al* 1999, Ashby *et al* 1999).

Rubin *et al* (2001), on the other hand, reported a statistically significant and dose-dependent increase in the number of females with irregular cycles after gestational and lactational exposure to BPA at dose levels of 0.1 mg/kg bw and 1.2 mg/kg bw. Also increased body weights in males and females were seen. This effect was more pronounced at the lower dose level and in females. Salian *et al* (2009) performed a 3-generation study in Holzman strain rats and reported a significant increase in post implantation loss, decrease in litter size and decrease in sperm count and motility in the offspring of female rats dosed daily at 1.2 and 2.4 µg/kg bw of BPA by gavage. The effects were more pronounced with the positive control diethylstilbestrol (DES) at dose levels of 10 µg/kg bw. Both of these studies used, however, a limited number of parental animals and did not, for example, describe whether the litter effect was taken into account in the analysis of the results or not.

Ryan *et al* (2010) studied the effects of *in utero* and lactational exposure (from gestation day 7 to postnatal day 18) to gavaged BPA doses of 2, 20 or 200 µg/kg bw/day on sexually dimorphic behaviour, age of puberty and reproductive function of female offspring of treated rats. The results on the effects of the same BPA treatment on male offspring were published by Howdeshell *et al* 2008. No effects on female anogenital distance, pups body weights, age at vaginal opening, F1 fertility, F2 litter sizes, reproductive organ malformations, female saccharin preference and lordosis behaviour were observed. Also in males, no effects on male anogenital distance, pups body weights, androgen dependent tissue weights and epididymal sperm counts were seen.

Concerns have been raised also regarding the developmental neurotoxicity and neurobehavioural effects of BPA. Xu *et al* (2010) reported effects on memory and learning in mice exposed from gestational day 7 to postnatal day 21 to oral doses of 0.5–50 mg/kg bw. Effect were also reported e.g. by Kim *et al* (2011, postnatal exposure) at a dose level of 20 mg/kg. In some other studies, effects were seen at even lower dose levels (Miyagawa *et al* 2007, Jasarevic *et al* 2013), whereas in some other studies, no effects were observed (Jones and Watson 2012, Ferguson *et al* 2012). Stump and co-workers (2010) performed a developmental neurotoxicity study in rats according to OECD guideline 426 to address these uncertainties regarding potential neurodevelopmental effects of BPA. BPA was administered daily in the diet at concentrations of 0, 0.15, 1.5, 75, 750 and 2 250 mg/kg feed to female Sprague-Dawley rats from gestational day 0 to postnatal day 21. Estimated intakes were 0, 0.01, 0.12, 5.85, 56.4 and 164 mg/kg bw/day during gestation and 0, 0.03, 0.25, 13.1, 129 and 410 mg/kg bw/day during lactation. The offspring were evaluated for detailed clinical observations, auditory startle, motor activity, learning and memory using the Biel water maze, brain and nervous system neuropathology and brain morphometry. No treatment related neurobehavioral effects were seen, nor was there evidence of neuropathology or effects on brain morphometry (Stump *et al* 2010). Lower body weight and body weight gain in adults and neonates were seen at the two highest dose groups resulting in a NOAEL for systemic effects of 5.85 mg/kg bw/day during pregnancy. The NOAEL for neurodevelopmental effects was the highest dose level tested. However, EFSA concluded in its evaluation 2010 (EFSA 2010) that data on Biel water maze test as performed by Stump *et al* (2010) suffer from censoring and concluded that this test on learning and memory was inconclusive and only of limited value in the risk assessment of BPA. Thus, there is still some uncertainty regarding developmental effects.

Increased or decreased anxiety (contradictory findings between the studies) has also been reported in several studies in rodents (see EFSA 2014 for a review). Because of the inconsistent findings it is not possible to conclude on these effects (EFSA 2014). Loss of sexual differences after gestational exposure has also been suggested by some studies (Carr *et al* 2003, Fujimoto *et al* 2006, Jones and Watson 2012). There are, however, a number of weaknesses in these studies including a limited number of doses and animals evaluated.

Overall, in standard reproductive and developmental studies in rodents, effects on reproduction have been seen only at high doses showing also other toxic effects. Even though several non-guideline studies suggest effects on reproductive and developmental parameters at lower dose levels (< 5 mg/kg bw), the data are contradictory and are not supported by the recent FDA/NTCR study with a wide-dose range (Delclos *et al* 2014). In humans, based on Chinese epidemiological studies, there is some concern for impaired sperm quality but, for example, the effect of other concurrent exposures cannot be excluded. In addition, there are some concerns on the potential developmental neurotoxicity of BPA based on animal studies suggesting effects on memory and learning and anxiety-like behaviour. However, since the data are very inconsistent it is difficult to conclude on the relevance of these findings.

4. Recommendation

Key data

To establish a recommended occupational exposure limit (OEL), SCOEL began by considering the available data relating to inhalation exposure. In rats exposed daily to airborne BPA for 13 weeks there was a NOAEC of 10 mg/m^3, with mild olfactory

epithelium inflammation at 50 and 150 mg/m^3. There was no evidence of systemic toxicity in this study (Nitschke 1988).

If one considers the other toxicological evidence, most of which arises from oral studies in rodents, there were no findings that preclude the recommendation of a health-based OEL. In repeated oral dosing studies, a NOAEL of 5 mg/kg bw/day have been found for liver effects in rats and mice, with mild liver hypertrophy, increased liver weights and reductions in weight gain seen at 50 mg/kg bw/day (Stump *et al* 2010, Tyl *et al* 2002 and 2008). Also effects on kidney weight were reported in mice by Tyl *et al* (2008) at these dose levels. EFSA (2014) calculated $BMDL_{10}$s for liver and kidney effects in mice, which were ~3.5 mg/kg bw/day for liver effects and 3.6 mg/kg bw/day and 3.9 mg/kg bw/day for weight changes in right and left kidney, respectively. If 100 % absorption is assumed for both exposure routes, a $BMDL_{10}$ of ~3.5 mg/kg bw and a NOAEL of 5 mg/kg bw at continuous subchronic exposure correspond to 34 and 49 mg/m^3, respectively, at occupational inhalation exposure (8 hours/day, 5 days/week) in humans. It should be noted that these liver and kidney effects observed in oral rodent studies were very mild; even at the highest dose levels (50 and 500/600 mg/kg) only mild effects in histopathology were seen. In addition, kidney weight changes in mice at the dose levels ≤ 50 mg/kg were not accompanied by any histological changes and were not seen in rats (Tyl *et al* 2002 and 2008). The liver effects (mild hypertrophy) seen in mice, on the other hand, may have been adaptive in nature.

Extrapolation issues and uncertainties in hazard assessment

There are some species differences in the metabolism of BPA. Enterohepatic circulation in rats results in a longer half-life of BPA in rats as compared to that in humans. On the other hand, the glucuronidation rate in rats is higher than in humans. Regardless of these apparent differences in BPA toxicokinetics, levels of unconjugated BPA have been shown to remain at a very low level after oral exposure in all species (0.2–2.8 % of the total AUC, see Section 3.1).

When considering route-to route extrapolation, following oral dosing there is extensive first-pass metabolism of BPA transported directly to the liver. Following inhalation exposure, this first pass effect is missed, which may result in higher levels of free BPA after inhalation than after oral dosing. On the other hand, the maximum BPA concentration (C_{max}) in the liver (one of the main target organs) is likely to be lower after inhalation or dermal exposure than after oral exposure. However, after inhalation of BPA it is likely that a significant part of the inhaled material becomes ingested resulting in combined oral and inhalation exposure.

There are some uncertainties related to the so-called "low-dose effects". Main concerns are related to the developmental neurotoxicity (anxiety and loss of sexual differences in behaviour) as well as possible mammary gland effects (mammary gland hyperplasia after pre- and perinatal exposure). However, there is currently no concluding evidence showing that these effects at these low levels are real, and in the latter case, relevant for human susceptibility to breast cancer. Also reports on male reproductive dysfunction in occupationally exposed persons need to be confirmed by other studies before any final conclusions can be made on the effects of BPA on human reproductive function.

Overall assessment

The inhalation NOAEC of 10 mg/m^3 is taken as the starting point for recommending an OEL. The critical effect in this study was respiratory tract irritation. This value of 10 is divided by an assessment factor of 3 to cover the uncertainties related to the inter-species extrapolation in these local effects resulting in a recommended OEL of 3

mg/m^3. Using the preferred value approach, 3 mg/m^3 is rounded to 2 mg/m^3. There are also some concerns about long-term systemic effects (liver and kidney effects), which may not have been fully addressed in this subchronic inhalation study. There is a 17–25-fold safety margin to the inhalation exposure levels of 34 and 49 mg/m^3, which correspond to the $BMDL_{10}$ of ~3.5 mg/kg bw (EFSA 2014) and to the NOAEL of 5 mg/kg bw observed for kidney and liver effects in oral studies. Because liver and kidney effects observed in oral long-term rodent studies were very mild even at the highest dose levels (50 mg/kg bw and 500/600 mg/kg bw, Tyl *et al* 2002 and 2008), this margin of safety is considered sufficient to cover extrapolation to long-term exposure, and also to cover possible remaining inter- and intra-species differences in toxicokinetics and toxicodynamics.

Even though there are some concerns related to the long-term effects of BPA at exposure levels lower than 5 mg/kg bw after exposure during the foetal and early postnatal period, the results of these studies are controversial and there is no clear support for these effects at low dose levels from good quality animal studies (including the recent study by Delclos *et al* 2014). Therefore, at present SCOEL did not consider them relevant for deriving the recommended OEL.

There is no toxicological basis for recommending an additional specific short-term exposure limit (STEL).

Biomonitoring

Measurement of total urinary BPA has been used for biomonitoring of BPA exposure. In the general population, urinary BPA levels are usually below 7 µg/l (95th percentile based on German and Canadian studies). Limited data were available for recommending a BLV. Using the same formula and assumptions as used in Krishnan *et al* (2010, page 7), the recommended OEL of 2 mg/m^3 (meaning a daily intake of 0.29 mg/kg bw) can be calculated to correspond to a urinary level of 11.8 mg/l (13.3 mg/g creatinine) in a 70-kg male. There are, however, several uncertainties related to this calculation, the main uncertainty being related to the short half-life of BPA resulting in variation in the urinary excretion over the course of the day. In addition, the data on the toxicokinetics of BPA after inhalation or dermal exposure is limited, the majority of toxicokinetic data coming from oral exposure. Thus, no BLV can be proposed, but a biological guidance value (BGV) of 7 µg/l is recommended for the identification of potentially occupationally exposed from the occupationally non-exposed.

Other assignments

A "Sen" notation is considered not appropriate. A recent OECD guideline based study showed that skin absorption may have only a minor contribution to systemic BPA levels at the recommended OEL. Thus, no skin notation is recommended.

Measurement and analysis

Appropriate methods are available to measure airborne and urinary BPA in relation to the recommended OEL (OSHA 2013) and BGV (Fukata *et al* 2006).

This Recommendation reflects the present knowledge on the toxicity of BPA. It will be revisited and revised when new relevant data (e.g. the results from the FDA/NCTR long-term toxicity studies) become available.

The present Recommendation was adopted by SCOEL on 11 June 2014.

5. References

Acevedo N, Davis B, Schaeberle CM, Sonnenschein C, Soto AM (2013). Perinatally administered bisphenol A acts as a mammary gland carcinogen in rats. Environ Health Perspect 121:1040-1046.

Allen H, Kaidbey K (1979). Persistent photosensitivity following occupational exposure to epoxy resins. Arch Dermatol 115:1307-1310.

Ashby J, Tinwell H, Haseman J (1999). Lack of effects for low dose levels of bisphenol-A and diethylstilbestrol on the prostate gland of CF1 mice exposed in utero. Regul Toxicol Pharmacol 30:156-166.

Balakrishnan B, Henare K, Thorstensen EB, Ponnampalam AP, Mitchell MD (2010). Transfer of bisphenol A across the human placenta. Am J Obstet Gynecol 202:393.e1–e7.

Betancourt AM, Eltoum IA, Desmond RA, Russo J, Lamartiniere CA (2010). In utero exposure to bisphenol A shifts the window of susceptibility for mammary carcinogenesis in the rat. Environ Health Perspect 118:1614-1619.

Braun JM, Yolto K, Dietrich KN, Hornung R, Ye X, Calafat AM, Lanphear BP (2009). Prenatal bisphenol A exposure and early childhood behavior. Environ Health Perspect 117(12):1945-1952.

Braun JM, Kalkbrenner AE, Calafat AM, Yolton K, Ye X, Dietrich KN, Lanphear BP (2011). Impact of early-life bisphenol A exposure on behavior and executive function in children. Pediatrics 128(5):873-882.

Brill (2013). Biomonitoring of employees occupationally exposed to bisphenol A - a comparison with environmental and occupational assessment values. The 9th International Symposium on Biological Monitoring in Occupational and Environmental Health, 9th–11th September 2013, Manchester, UK.

Bruhm C (2012). Method for the determination of bisphenol A. MAK Collection for Occupational Health and Safety. Air monitoring methods, 2012. http://onlinelibrary.wiley.com/doi/10.1002/3527600418.am8005e0013/full.

Cagen SZ, Waechter JM, Dimond SS, Breslin WJ, Butala JH, Jekat FW, Joiner RL, Shiotsuka RN, Veenstra GE, Harris LR (1999). Normal reproductive organ development in CF-1 mice following prenatal exposure to bisphenol-A. Toxicol Sci 50:36-44.

Calafat AM, Kuklenyik Z, Reidy JA, Caudill SP, Ekong J, Needham LL (2005). Urinary concentrations of bisphenol A and 4-nonylphenol in a human reference population. Environ Health Perspect 113(4):391-395.

Calafat AM, Ye X, Wong LY, Reidy JA, Needham LL (2008). Exposure of the U.S. population to bisphenol A and 4-tertiary-octylphenol: 2003-2004. Environ Health Perspect 116(1):39-44.

Carr R, Bertasi F, Betancourt A, Bowers S, Gandy BS, Ryan P, Willard S (2003). Effect of neonatal rat bisphenol A exposure on performance in the Morris water maze. J Toxicol Environ Health Part A 66(21):2077-2088.

Carwile JL, Michels KB (2011). Urinary bisphenol A and obesity: NHANES 2003-2006. Environ Res 111:825-830.

CDC, Centers of Disease Control and Prevention (2012). Fourth national report on human exposure to environmental chemicals, updated tables, February 2012. http://www.cdc.gov/exposurereport/.

Cha BS, Koh SB, Park JH, Eom A, Lee KM, Choi HS (2008). Influence of occupational exposure to bisphenol A on the sex hormones of male epoxy resin painters. Mol Cell Toxicol 4(3):230-234.

Chemical Weekly (2009). Bisphenol-A: a techno-commercial profile. September 1, 205-211.

Delclos KP, Camacho L, Lewis SM, Vanlandingham MM, Latendresse JR, Olson GR, Davis KJ, Patton RE, da Costa GG, Woodling KA, Bryant MS, Chidambaram M, Trbojevich R, Juliar BE, Felton RP, Thorn BT (2014). Toxicity evaluation of bisphenol A administered by gavage to Sprague Dawley rats from gestation day 6 through postnatal day 90. Toxicol Sci 139:174-197.

Demierre AL, Peter R, Oberli A, Bourqui-Pittet M (2012). Dermal penetration of bisphenol A in human skin contributes marginally to total exposure. Toxicol Lett 213(3):305-308.

DFG, Deutsche Forschungsgemeinschaft (2013). MAK- und BAT-Werte-Liste 2013. Senatskommission zur Prüfung Gesundheitsschädlicher Arbeitsstoffe. Wiley-VCH Verlag GmbH & Co. KgaA, Weinheim.

Doerge DR, Twaddle NC, Vanlandingham M, Fisher JW (2010a). Pharmacokinetics of bisphenol A in neonatal and adult Sprague-Dawley rats. Toxicol Appl Pharmacol 247(2):158-165.

Doerge DR, Twaddle NC, Woodling KA, Fisher JW (2010b). Pharmacokinetics of bisphenol A in neonatal and adult rhesus monkeys. Toxicol Appl Pharmacol 248(1):1-11.

Doerge DR, Vanlandingham M, Twaddle NC, Delclos KB (2010c). Lactational transfer of bisphenol A in Sprague-Dawley rats. Toxicol Lett 199:372-376.

Doerge DR, Twaddle NC, Vanlandingham M, Brown RP, Fisher JW (2011a). Distribution of bisphenol A into tissues of adult, neonatal, and fetal Sprague-Dawley rats. Toxicol Appl Pharmacol 255:261-270.

Doerge DR, Twaddle NC, Vanlandingham M, Fisher JW (2011b). Pharmacokinetics of bisphenol A in neonatal and adult CD-1 mice: inter-species comparisons with Sprague-Dawley rats and rhesus monkeys. Toxicol Lett 207:298-305.

Dow Chemical Company (1957). Results of the range finding toxicological tests on bisphenol-A - regular grade and bisphenol-A - E.R. grade, unpublished report.

Du Pont (1962). Summary of toxicological tests on bisphenol-A. Letter from Rowe VK, Dow Chemical Company to Clayton JW, Du Pont dated 2/05/1962. EPA/OTS Document #878214650. Order No. 206607 (NTIS), p. 1-3.

EC, European Commission (2003). European Commission EUR 20843 EN. European Union Risk Assessment Report. 4,4'-Isopropylidenediphenol (bisphenol-A). Environment and quality of life series, Volume 37. Office for Official Publications of the European Communities, Luxembourg.

EC, European Commission (2008). European Union Risk Assessment Report. 4,4'-Isopropylidenediphenol (bisphenol-A). Human health addendum of April 2008.

http://publications.jrc.ec.europa.eu/repository/bitstream/111111111/15069/1/lbna24589enn.pdf.

EFSA, European Food Safety Authority (2006). Opinion of the Scientific panel on food additives, flavourings, processing aids and materials in contact with food on a request from the Commission related to 2,2-bis(4-hydroxyphenyl)propane (Bisphenol A). EFSA Journal 428:1-75.

EFSA, European Food Safety Authority (2010). Scientific Opinion on bisphenol A: evaluation of a study investigating its neurodevelopmental toxicity, review of recent scientific literature on its toxicity and advice on the Danish risk assessment of bisphenol A of the EFSA Panel on food contact materials, enzymes, flavourings and processing aids (CEF) on request from the European Commission, Questions No. 2010. EFSA-Q-2009-00864, EFSA-Q-2010-01023 and EFSA-Q-2010-00709, adopted on 23rd September 2010. EFSA Journal 8:1829, p 1-116. http://www.efsa.europa.eu/en/scdocs/scdoc/1829.htm.

EFSA, European Food Safety Authority (2014). Draft Scientific Opinion on the risks to public health related to the presence of bisphenol A (BPA) in foodstuffs, 314 pp., Parma, Italy.

Eng DS, Gebremariam A, Meeker JD, Peterson K, Padmanabhan V, Lee JM (2013). Bisphenol A and chronic disease risk factors in US children. Pediatrics 132:e637-e645.

Ema M, Fujii S, Furukawa M, Kiguchi M, Ikka T, Harazono A (2001). Rat two-generation reproductive toxicity study of bisphenol A. Reprod Toxicol 15:505–523.

Ferguson SA, Law CD, Abshire JS (2012). Developmental treatment with bisphenol A causes few alterations on measures of postweaning activity and learning. Neurotoxicol Teratol 34:598-606.

Fujimoto T, Kubo K, Aou S (2006). Prenatal exposure to bisphenol A impairs sexual differentiation of exploratory behavior and increases depression-like behavior in rats. Brain Res 1068(1):49-55.

Fukata H, Miyagawa H, Yamazaki N, Mori (2006). Comparison of Elisa- and LC-MS-based methodologies for the exposure assessment of bisphenol A. Toxicol Mech Methods 16(8):427-430.

Furukawa F, Nishikawa A, Mitsui M, Sato M, Suzuki J, Imazawa T, Takahashi M (1994). A 13-week subchronic toxicity study of bisphenol-A in B6C3F1 mice. Eisei Shikensho Hokoku 112:89-96.

General Electric (1976). Reproductive and ninety day oral toxicity study in rats. IRDC study 313-078, unpublished report.

Gerberick GF, Ryan CA (1990). A predictive mouse-ear swelling model for investigating topical photoallergy. Food Chem Toxicol 28:361-368.

Gupta C (2000). Reproductive malformation of the male offspring following maternal exposure to estrogenic chemicals. Proc Soc Exp Biol Med 224:61-68.

Hanaoka T, Kawamura N, Hara K, Tsugane S (2002). Urinary bisphenol A and plasma hormone concentrations in male workers exposed to bisphenol A diglycidyl ether and mixed organic solvents. Occup Environ Med 59(9):625-628.

He Y, Miao M, Wu C, Yuan W, Gao E, Zhou Z, Li DK (2009). Occupational exposure levels of bisphenol A among Chinese workers. J Occup Health 51(5):432-436.

Health Canada (2010). Report on human biomonitoring of environmental chemicals in Canada. Results of the Canadian Health Measures Survey Cycle 1 (2007–2009). Ottawa, Ontario.

Hazleton Laboratories (1985). Bisphenol-A: acute oral toxicity study in the rat. Hazleton Laboratories Europe Limited. Dow Chemical Company, unpublished report.

Howdeshell KL, Furr J, Lambright CR, Wilson VS, Ryan BC, Gra, LE, Jr (2008). Gestational and lactational exposure to ethinyl estradiol, but not bisphenol A, decreases androgen-dependent reproductive organ weights and epididymal sperm abundance in the male long evans hooded rat. Toxicol Sci 102(2):371-382.

Hunt PA, Koehler KE, Susiarjo M, Hodges CA, Ilagan A, Voigt RC, Thomas S, Thomas BF, Hassold TJ (2003). Bisphenol A exposure causes meiotic aneuploidy in the female mouse. Curr Biol 13(7):546-553.

Jasarevic E, Williams SA, Vandas GM, Ellersieck MR, Liao C, Kannan K, Roberts RM, Geary DC, Rosenfeld CS (2013). Sex and dose-dependent effects of developmental exposure to bisphenol A on anxiety and spatial learning in deer mice (Peromyscus maniculatus bairdii) offspring. Horm Behav 63:180-189.

Jenkins S, Raghuraman N, Eltoum I, Carpenter M, Russo J, Lamartiniere CA (2009). Oral exposure to bisphenol A increases dimethylbenzanthracene-induced mammary cancer in rats. Environ Health Perspect 117(6):910-915.

Jenkins S, Wang J, Eltoum I, Desmond R, Lamartiniere CA (2011). Chronic oral exposure to bisphenol A results in a nonmonotonic dose response in mammary carcinogenesis and metastasis in MMTV-erbB2 mice. Environ Health Perspect 119(11):1604-1609.

Johnson GE, Parry EM (2008). Mechanistic investigations of low dose exposures to the genotoxic compounds bisphenol-A and rotenone. Mutat Res 651:56-63.

Jones BA, Watson NV (2012). Perinatal BPA exposure demasculinizes males in measures of affect but has no effect on water maze learning in adulthood. Horm Behav 61(4):605-610.

Kaddar N, Harthe C, Dechaud H, Mappus E, Pugeat M (2008). Cutaneous penetration of bisphenol A in pig skin. J Toxicol Environ Health A 71:471-473.

Kim ME, Park HR, Gong EJ, Choi SY, Kim HS, Lee J (2011). Exposure to bisphenol A appears to impair hippocampal neurogenesis and spatial learning and memory. Food Chem Toxicol 49:3383-3389.

Koch HM, Kolossa-Gehring M, Schroter-Kermani C, Angerer J, Bruning T (2012). Bisphenol A in 24 h urine and plasma samples of the German Environmental Specimen Bank from 1995 to 2009: a retrospective exposure evaluation. J Expo Sci Environ Epidemiol 22(6):610-616.

Krishnan K, Gagne M, Nong A, Aylward LL, Hays SM (2010). Biomonitoring equivalents for bisphenol A (BPA). Regul Toxicol Pharmacol 58(1):18-24.

Lakind JS, Levesque J, Dumas P, Bryan S, Clarke J, Naiman DQ (2012). Comparing United States and Canadian population exposures from national biomonitoring

surveys: bisphenol A intake as a case study. J Expo Anal Environ Epidemiol 22(3): 219–226.

Lamartiniere CA, Jenkins S, Betancourt AM, Wang J, Russo J (2011). Exposure to the endocrine disruptor bisphenol A alters susceptibility for mammary cancer. Horm Mol Biol Clin Investig 5(2):45-52.

Leuschner J (2000a). Acute eye irritation study of bisphenol-A by instillation into the conjunctival sac of rabbits. Laboratory of Pharmacology and Toxicology KG, unpublished test report no. 12665.

Leuschner J (2000b). Acute skin irritation test (patch test) of bisphenol-A in rabbits. Laboratory of Pharmacology and Toxicology KG, unpublished test report no. 12664/99.

Li DK, Zhou Z, Miao M, He Y, Qing D, Wu T, Wang J, Weng X, Ferber J, Herrinton LJ, Zhu Q, Gao E, Yuan W (2010a). Relationship between urine bisphenol-A level and declining male sexual function. J Androl 31(5):500-506.

Li D, Zhou Z, Qing D, He Y, Wu T, Miao M, Wang J, Weng X, Ferber JR, Herrinton LJ, Zhu Q, Gao E, Checkoway H, Yuan W (2010b). Occupational exposure to bisphenol-A (BPA) and the risk of self-reported male sexual dysfunction. Hum Reprod 25(2):519-527.

Li DK, Zhou, Z, Miao, M, He Y, Wang J, Ferber J, Herrinton LJ, Gao E, Yuan W (2011). Urine bisphenol-A (BPA) level in relation to semen quality. Fertil Steril 95(2):625-630.

Maguire HC (1988). Experimental photoallergic contact dermatitis to bisphenol-A. Acta Derm Venereol 68:408-412.

Marquet F, Payan JP, Beydon D, Wathier L, Grandclaude MC, Ferrari E (2011). In vivo and ex vivo percutaneous absorption of [14C]-bisphenol A in rats: a possible extrapolation to human absorption? Arch Toxicol 85(9):1035-1043.

Mazur CS, Kenneke JF, Hess-Wilson JK, Lipscomb JC (2010). Differences between human and rat intestinal and hepatic bisphenol A glucuronidation and the influence of alamethicin on in vitro kinetic measurements. Drug Metab Dispos 38:2232-2238.

Mellon Institute of Industrial Research (1948). The acute and subacute toxicity of diphenylol propane. Study no. 11-13. Union Carbide Corporation, unpublished report.

Mellon Institute of Industrial Research (1965). Range finding tests on bisphenol-A. Study no. 28-49. Union Carbide Corporation, unpublished report.

Melzer D, Gates P, Osborn NJ, Henley WE, Cipelli R, Young A, Money C, McCormack P, Schofield P, Mosedale D, Grainger D, Galloway TS (2012a). Urinary bisphenol A concentration and angiography-defined coronary artery stenosis. PLoS One 7(8):e43378.

Melzer D, Osborne NJ, Henley WE, Cipelli R, Young A, Money C, McCormack P, Luben R, Khaw KT, Wareham NJ, Galloway TS (2012b). Urinary bisphenol A concentration and risk of future coronary artery disease in apparently healthy men and women. Circulation 125(12):1482-1490.

Miao M, Yuan W, He Y, Zhou Z, Wang J, Gao E, Li G, Li DK (2011a). In utero exposure to bisphenol-A and anogenital distance of male offspring. Birth Defects Res A Clin Mol Teratol 91:867-872.

Miao M, Yuan W, Zhu G, He X, Li DK (2011b). In utero exposure to bisphenol-A and its effect on birth weight of offspring. Reprod Toxicol 32:64-68.

Miodovnik A, Engel SM, Zhu C, Ye X, Soorya LV, Silva MJ, Calafat AM, Wolff MS (2011). Endocrine disruptors and childhood social impairment. Neurotoxicol 32:261-267.

Miyagawa K, Narita, M, Akama H, Suzuki T (2007). Memory impairment associated with a dysfunction of the hippocampal cholinergic system induced by prenatal and neonatal exposures to bisphenol-A. Neurosci Lett 418(3):236-241.

Moral R, Wang, R, Russo IH, Lamartiniere CA, Pereira J, Russo J (2008). Effect of prenatal exposure to the endocrine disruptor bisphenol A on mammary gland morphology and gene expression signature. J Endocrinol 196(1):101-112.

Morck TJ, Sorda G, Bechi N, Rasmussen BS, Nielsen JB, Ietta F, Rytting E, Mathiesen L, Paulesu L, Knudsen LE (2010). Placental transport and in vitro effects of Bisphenol A. Reprod Toxicol 30(1):131-137.

Morrissey RE, George JD, Price CJ, Tyl RW, Marr MC, Kimmel CA (1987). The developmental toxicity of bisphenol-A in rats and mice. Fundam Appl Toxicol 8:571-582.

Mose T, Mathiesen L, Karttunen V, Nielsen JK, Sieppi E, Kummu M, Morck TA, Myohanen K, Partanen H, Vahakangas K, Knudsen LE, Myllynen P (2012). Meta-analysis of data from human ex vivo placental perfusion studies on genotoxic and immunotoxic agents within the integrated European project NewGeneris. Placenta 33:433-439.

Nagel SC, vom Saal FS, Thayer KA, Dhar MG, Boechler M, Welshons WV (1997). Relative binding affinity-serum modified access (RBA-SMA) assay predicts the relative in vivo bioactivity of the xenoestrogens bisphenol A and octylphenol. Environ Health Perspect 105(1):70-76.

Naik P, Vijayaaxmi KK (2009). Cytogenetic evaluation for genotoxicity of bisphenol-A in bone marrow cells of Swiss albino mice. Mutat Res 676:106-112.

Nitschke KD, Quast JF, Schuetz DJ, Wolfe EL (1985a). Bisphenol-A: 2 week aerosol toxicity study with Fischer 344 rats. Dow Chemical Company, unpublished report.

Nitschke KD, Quast JF, Wolfe EL (1985b). Bisphenol-A: acute aerosol toxicity study with Fischer 344 rats. Dow Chemical Company, unpublished report.

Nitschke KD, Lomax LG, Schuetz DJ, Hopkins PJ, Weiss SW (1988). Bisphenol-A: 13 week aerosol toxicity study with Fischer 344 rats. Dow Chemical Company, unpublished report.

NTP, National Toxicology Program (1982). Carcinogenesis bioassay of bisphenol-A (CAS No. 80-05-7) in F344 rats B6C3F1 mice (feed study). Technical Report No. 215, Order No. PB82-184060 (NTIS), 116 pp. U.S. Department of Health and Human Services.

NTP, National Toxicology Program (1985a). Bisphenol-A: Reproduction and fertility assessment in CD-1 mice when administered in the feed. Report NTP-85-192,

Order No. PB86-103207 (NTIS), 346 pp. U.S. Department of Health and Human Services.

NTP, National Toxicology Program (1985b). Teratologic evaluation of bisphenol-A (CAS No. 80-05-7) administered to CD-1 mice on gestational days 6 through 15. Report NTP-85-088, Order No. PB85-205102 (NTIS). National Institute of Environmental Health Sciences.

NTP, National Toxicology Program (1985c). Teratologic evaluation of bisphenol-A (CAS No. 80-05-7) administered to CD(R) rats on gestation days 6 through 15. Report NTP-85-089, Order No. PB85-205112 (NTIS). National Institute of Environmental Health Sciences.

NTP, National Toxicology Program (2008). NTP-CERHR monograph on the potential human reproductive and developmental effects of bisphenol A, p. 10–64. Research Triangle Park, NC, U.S. Department of Health and Human Services. http://ntp.niehs.nih.gov/ntp/ohat/bisphenol/bisphenol.pdf.

OSHA, Occupational Safety and Health Administration (2013). Bisphenol A and diglycidyl ether of bisphenol A. OSHA method 1081, December 2013. U.S. Department of Labor, Occupational Safety and Health Administration. https://www.osha.gov/dts/sltc/methods/validated/1018/1018.html.

Pacchierotti F, Ranaldi R, Eichenlaub-Ritter U, Attia S, Adler ID (2008). Evaluation of aneugenic effects of bisphenol A in somatic and germ cells of the mouse. Mutat Res 651(1-2):64-70.

Patterson TA, Twaddle NC, Roegge CS, Callicott RJ, Fisher JW, Doerge DR (2013). Concurrent determination of bisphenol A pharmacokinetics in maternal and fetal rhesus monkeys. Toxicol Appl Pharmacol 267:41-48.

Perera F, Vishnevetsky J, Herbstman JB, Calafat AM, Xiong W, Rauh V, Wang S (2012). Prenatal bisphenol A exposure and child behavior in an inner-city cohort. Environ Health Perspect 120:1190-1194.

Pfeiffer E, Rosenburg B, Deuschel S, Mezler M (1997). Interference with microtubules and induction of micronuclei in vitro by various bisphenols. Mutat Res 390:21-31.

Porras S, Heinälä M, Ylinen K, Tuomi T, Liukkonen T, Santonen T (2014). Bisfenoli A – altistuminen suomalaisilla työpaikoilla. [Occupational exposure to Bisphenol A in Finland], Työterveyslaitos, Helsinki, 2014. http://www.tsr.fi/tutkimustietoa/tata-tutkitaan/hanke/?h=112106&n=aineisto.

Pottenger LH, Domoradzki JY, Markham DA, Hansen SC (1997a). Bioavailability of 14C-bisphenol-A in Fischer rats following oral, subcutaneous or intraperitoneal administration (Part A). Dow Chemical Company, unpublished report K-001304-12A.

Pottenger LH, Domoradzki JY, Markham DA, Hansen SC (1997b). Bioavailability of 14C-bisphenol-A in Fischer rats following oral, subcutaneous or intraperitoneal administration (Part B). Dow Chemical Company, unpublished report K-001304-12B.

Prins GS, Ye SH, Birch L, Ho SM, Kannan K (2011). Serum bisphenol A pharmaco-kinetics and prostate neoplastic responses following oral and subcutaneous exposures in neonatal Sprague-Dawley rats. Reprod Toxicol 31(1):1-9.

Procter & Gamble Company (1969). Guinea pig closed patch test. Unpublished data. NTIS/OTSO206621, Doc. I.D. 878214688/9.

Rubin BS, Murray MK, Damassa DA, King JC, Soto AM (2001). Perinatal exposure to low doses of bisphenol A affects body weight, patterns of estrous cyclicity, and plasma LH levels. Environ Health Perspect 109:675-680.

Ryan BC, Hotchkiss AK, Crofton KM, Gray LE (2010). In utero and lactational exposure to bisphenol A, in contrast to ethinyl estradiol, does not alter sexually dimorphic behavior, puberty, fertility, and anatomy of female LE rats. Toxicol Sci 114:133-148.

Salian S, Doshi T, Vanage G (2009). Perinatal exposure of rats to bisphenol A affects the fertility of male offspring. Life Sci 85(21-22):742-752.

Shankar A, Teppala S (2011). Relationship between urinary bisphenol A levels and diabetes mellitus. J Clin Endocrinol Metab 96:3822-3826.

Shankar A, Teppala S (2012a). Urinary bisphenol A and hypertension in a multiethnic sample of US adults. J Environ Public Health, Article ID 481641, 5 pp.

Shankar A, Teppala S, Sabanayagam C (2012b). Bisphenol A and peripheral arterial disease: Results from the NHANES. Environ Health Perspect 120(9):1297-1300.

Shankar A, Teppala S, Sabanayagam C (2012c). Urinary bisphenol A levels and measures of obesity: results from the national health and nutrition examination survey 2003-2008. ISRN Endocrinol, Article ID 965243, 6 pp.

Shell Oil Company (1999). Mammalian erythrocyte micronucleus test. Unpublished test report BPA 99-01.

Silver MK, O'Neill MS, Sowers MR, Park SK (2011). Urinary bisphenol A and type-2 diabetes in U.S. adults: data from NHANES 2003-2008. PLoS One 6(10):e26868.

Stump DG, Beck MJ, Radovsky A, Garman RH, Freshwater LL, Sheets LP, Marty MS, Waechter JM Jr, Dimond SS, Van Miller JP, Shiotsuka RN, Beyer D, Chappelle AH, Hentges SG (2010). Developmental neurotoxicity study of dietary bisphenol A in Sprague-Dawley rats. Toxicol Sci 115(1):167-182.

Tayama S, Nakagawa Y, Tayama K (2008). Genotoxic effects of environmental estrogen-like compounds in CHO-K1 cells. Mutat Res 649:114-125.

Taylor JA, vom Saal FS, Welshons WV, Drury B, Rottinghaus G, Hunt PA, Toutain PL, Laffont CM, VandeVoort CA (2011). Similarity of bisphenol A pharmacokinetics in rhesus monkeys and mice: relevance for human exposure. Environ Health Perspect 119(4):422-430.

Tharp AP, Maffini MV, Hunt PA, VandeVoort CA, Sonnenschein C, Soto AM (2012). Bisphenol A alters the development of the rhesus monkey mammary gland. Proc Natl Acad Sci U S A 109:8190-8195.

Thorgeirsson A, Fregert S (1977). Allergenicity of epoxy resins in the guinea pig. Acta Derm Venereol 57:253-256.

Til HP, Roverts WG, Beems RB (1978). Sub-chronic (90 day) oral toxicity study with diphenylpropane (DPP) in rats. Unpublished report (No. R 6229) of TNO, the Netherlands.

Timms BG, Howdeshell KL, Barton L, Bradley S, Richter CA, vom Saal FS (2005). Estrogenic chemicals in plastic and oral contraceptives disrupt development of the fetal mouse prostate and urethra. Proc Natl Acad Sci U S A 102(19):7014-7019.

Trasande L, Attina TM, Blustein J (2012). Association between urinary bisphenol A concentration and obesity prevalence in children and adolescents. JAMA 308:1113-1121.

Trdan Lusin T, Roskar R, Mrhar A (2012). Evaluation of bisphenol A glucuronidation according to UGT1A1*28 polymorphism by a new LC-MS/MS assay. Toxicology 292:33-41.

Tsutsui T, Tamura Y, Yagi E, Hasegawa K, Takahashi M, Maizumi N, Yamaguchi F, Barrett C (1998). Bisphenol-A induces cellular transformation, aneuploidy and DNA adduct formation in cultured Syrian hamster embryo cells. Int J Cancer 75:290-294.

Tyl RW, Myers CB, Marr MC, Thomas BF, Keimowitz AR, Brine DR, Veselica MM, Fail PA, Chang TY, Seely JC, Joiner RL, Butala JH, Dimond SS, Cagen SZ, Shiotsuka RN, Stropp GD, Waechter JM (2002). Three-generation reproductive toxicity study of dietary bisphenol A in CD Sprague-Dawley rats. Toxicol Sci 68:121-146.

Tyl RW, Myers CB, Marr MC, Sloan CS, Castillo NP, Veselica MM, Seely JC, Dimond SS, Van Miller JP, Shiotsuka RN, Beyer D, Hentges SG, Waechter JM, Jr (2008). Two-generation reproductive toxicity study of dietary bisphenol A in CD-1 (Swiss) mice. Toxicol Sci 104(2):362-384.

UBA, Umweltbundesamt (2012). Stoffmonographie Bisphenol A (BPA) - Referenz- und Human-Biomonitoring-(HBM)-Werte für BPA im Urin. Bundesgesundheitsblatt 55:1215-1231. http://www.umweltbundesamt.de/sites/default/files/medien/pdfs/stoffmonographie_bisphenol_a.pdf.

Vandenberg LN, Chahoud I, Heindel JJ, Padmanabhan V, Paumgartten FJ, Schoenfelder G (2010). Urinary, circulating, and tissue biomonitoring studies indicate widespread exposure to bisphenol A. Environ Health Perspect 118(8): 1055-1070.

Vandenberg LN, Colborn T, Hayes TB, Heindel JJ, Jacobs DR, Lee D-H, Shioda T, Soto AM, vom Saal FS, Welshons WV, Zoeller RT, Myers JP (2012). Hormones and endocrine-disrupting chemicals: low-dose effects and nonmonotonic dose responses. Endocr Rev 33:378-455.

Vandenberg LN, Schaeberle CM, Rubin BS, Sonnenschein C, Soto AM (2013). The male mammary gland: a target for the xenoestrogen bisphenol A. Reprod Toxicol 37:15-23.

Wang T, Li M, Chen B, Xu M, Xu Y, Huang Y, Lu J, Chen Y, Wang W, Li X, Liu Y, Bi Y, Lai S, Ning G (2012a). Urinary bisphenol A (BPA) concentration associates with obesity and insulin resistance. J Clin Endocrinol Metab 97(2):e223-e227.

Wang F, Hua J, Chen M, Xia Y, Zhang Q, Zhao R, Zhou W, Zhang Z, Wang B (2012b). High urinary bisphenol A concentrations in workers and possible laboratory abnormalities. Occup Environ Med 69(9):679-684.

Weber Lozada K, Keri RA (2011). Bisphenol A increases mammary cancer risk in two distinct mouse models of breast cancer. Biol Reprod 85:490-497.

WHO, World Health Organization (2011). Toxicological and health aspects of bisphenol-A. Report of joint FAO/WHO expert meeting, 2-5 November 2010.

Volkel W, Colnot T, Csanady GA, Filser JG, Dekant W (2002). Metabolism and kinetics of bisphenol A in humans at low doses following oral administration. Chem Res Toxicol 15:1281-1287.

Volkel W, Bittner N, Dekant W (2005). Quantitation of bisphenol A and bisphenol A glucuronide in biological samples by high performance liquid chromatography-tandem mass spectrometry. Drug Metab Dispos 33(11):1748-1757.

Volkel W, Kiranoglu M, Fromme H (2008). Determination of free and total bisphenol A in human urine to assess daily uptake as a basis for a valid risk assessment. Toxicol Lett 179(3):155-162.

Volkel W, Kiranoglu M, Fromme H (2011). Determination of free and total bisphenol A in urine of infants. Environ Res 111(1):143-148.

vom Saal FS, Cooke P, Buchanan DL, Palanza P, Thayer KA, Nagel SC, Parmigiani S, Welshons WV (1998). A physiologically based approach to the study of bisphenol-A and other oestrogenic chemicals on the size of reproductive organs, daily sperm production, and behaviour. Toxicol Ind Health 14:239-260.

Xu XH, Zhang J, Wang YM, Ye YP, Luo QQ (2010). Perinatal exposure to bisphenol-A impairs learning-memory by concomitant down-regulation of N-methyl-D-aspartate receptors of hippocampus in male offspring mice. Horm Behav 58:326-333.

Yolton K, Xu Y, Strauss D, Altaye M, Calafat AM, Khoury J (2011). Prenatal exposure to bisphenol A and phthalates and infant neurobehavior. Neurotoxicol Teratol 33:558-566.

Zalko D, Acques C, Duplan H, Bruel S, Perdu E (2011). Viable skin efficiently absorbs and metabolizes bisphenol A. Chemosphere 82(3):424-430.

Zhou Q, Miao M, Ran M, Ding L, Bai L, Wu T, Yuan W, Gao E, Wang J, Li G, Li DK (2013). Serum bisphenol-A concentration and sex hormone levels in men. Fertil Steril 100:478-482.