European Commission

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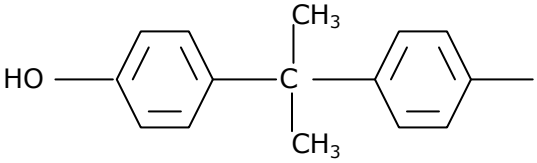
8-hour TWA:	2 mg/m^3 (as inhalable dust)
STEL (15-min):	-
Notation:	-
BLV:	-
BGV:	7 µg/l

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/m3
Vapour pressure	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 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

This document is based on the following criteria documents: WHO 1985, Deutsche Forschungsgemeinschaft 1993 and 1999, IARC 1994 and 2008, Thier and Bolt 2000, EPA 2006, European Commission 2003 (and update 2008), WHO 2011 and EFSA 2010. This was further supplemented by a literature search conducted by SCOEL at

May 2012 covering the data published since the publication of previous evaluation of bisphenol A by SCOEL at May 2004.

2. Occurrence/use and occupational exposure

Four companies within the EU manufacture bisphenol-A (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 resins 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.

3. Health significance

3.1. Toxicokinetics

The toxicokinetics of BPA has been well studied in rats both *in vivo* and *in vitro*, and has been investigated to a lesser extent in mice, cynomolgus monkeys and humans (European Commission, 2002, Domoradski *et al* 2002, Kurebayashi *et al* 2003, Volkel *et al* 2002, NTP 2008, WHO 2011). In the species studied, the available evidence suggests that following oral administration, BPA is rapidly and extensively (about 85–100 % of administered dose) absorbed from the gastrointestinal tract.

Dermal absorption was recently studied in rats *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. 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 calculations, 1 hour of occupational exposure over 2000 cm^2 may lead to absorption of 4 µg/kg/day. Zalko *et al* (2010), on the other hand, observed an absorption of 46 % via the human skin. This value is higher than that reported in other studies. A penetration of 8.6 % with a maximum penetration rate of 0.022 µg/cm^2/hour was measured in a test performed according to OECD 428 and under GLP (Demierre *et al* 2012). Of the applied dose, 0.6 % was recovered from the remaining skin resulting in a total amount of bioavailable BPA of 9.3 %. This means that with an external exposure of 100 µg/day e.g. from thermal paper, an internal exposure of 9.3 µg is reached (Demierre *et al* 2012). There were no data on the toxicokinetics of BPA following inhalation exposure but it is assumed that appreciable absorption would occur.

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 isotopically labelled BPA, free (unconjugated) BPA has 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 (European Commission 2003). The bioavailability of free BPA can be 6–240-fold higher after

intraperitoneal or subcutaneous dosing than after oral dosing (Pottenger *et al* 2000). These differences may explain some effects seen after parenteral dosing but not after oral dosing. No comparative data on the levels of free BPA after inhalation exposure were available.

There are contradictory data on the ability of the viable skin to metabolise BPA (Zalko *et al* 2011, Marquet *et al* 2011).

The major metabolic pathway in all species studied involves conjugation of BPA to 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 to sulphate.

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 for 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 than female CD rats. Data from a number of studies suggest limited excretion of BPA in the milk. However, the data do not allow a reliable quantitative determination to be made. In rats, free BPA have shown a limited distribution to the placenta and embryo/foetus following oral administration, the foetal levels being in the same range as those in other maternal tissues (EC 2008, WHO 2010).

In contrast to the findings in rodents, 84–97 % of a BPA dose administered to humans is absorbed and excreted as glucoronide 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.

3.1.1. Biological monitoring

BPA has been a subject for several biomonitoring studies among the general population. Most of the studies have, however, involved only a limited number of subjects. Large-scale studies have been published only from the USA (NHANES).

BPA can be measured either from urine or blood in the form of free, conjugated or total (free and conjugated) BPA. Most commonly, 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).

Results of several population studies measuring BPA levels in normal population have

Table 1. Urinary BPA levels.

Study (country)	Study population and sample size	BPA level (mean or median) µg/l	95th percentiles or range*
Calafat *et al* 2005 (NHANES 1988-94, USA)	184 males, 210 females	1.3 (median)	5.18
Calafat *et al* 2008 (NHANES 2003-2004, USA)	Total population of age 9– >60 years (n = 2 517)	2.6	15.9
	20–59 year-old males and females (n = 951)	2.6	15.9
Völkel *et al* 2008 (Germany)	83 subjects	1.2 (median)	<0.3–9.3*
Koch *et al* 2012 (Germany)	20–29 years old adults (n = 600)	1.55	7.37
Health Canada 2010 (Canada)	1 165 adults 20–39 years	1.33	7.30
	1 219 adults 40–59 years	1.04	6.58

been recently reviewed by e.g. Vandenberg *et al* 2010. Measurable levels of total BPA is usually present in the urine of most of the subjects among the normal population.

The levels measured in normal adult population in USA, Canada and Germany are presented in Table 1.

The German Federal Environment Agency has 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 increased urinary BPA (total BPA) levels in epoxy resin sprayers (median 1.06, range ND–11.2 µmol/mol creatinine, n = 42) when compared to controls (median 0.52, range ND–11.0 µmol/mol creatinine, n = 42). No data on air levels were available. 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), 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. Main pollution sources were said to be crushing, feeding and packing workstations. Although not discussed in the report, skin (including skin-mount) exposure may have significantly contributed to urinary levels. In addition, there were some discrepancies in the reported air and urinary levels within the report. In non-occupationally exposed Chinese males (n = 419), median urinary BPA levels of 1.43 µg/g creatinine have been reported by the same research group. The 75th percentile was 14.18 µg/g creatinine (He *et al* 2009).

Krishnan *et al* (2010) have estimated the concentration of BPA in urine corresponding

to the tolerable daily intake set by EFSA (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 TDI level, BW is the body weight for the group, F_{UE} is the urinary excretion fraction (=1 for BPA), i.e., fraction of the applied dose excreted in the urine and V is the 24-hour average urinary volume.

3.2. Effects of single exposure

No useful information was available on the effects of single exposure to 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, NTP 1982, Mellon Institute 1948 and 1965). For inhalation, a 6-hour exposure to 170 mg/m^3 (the highest attainable concentration) produced no deaths in rats; slight and transient slight nasal tract epithelial damage was observed (Nitschke *et al* 1985a). 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 have 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 below) or irritation. However, a well conducted animal study clearly shows that BPA is not a skin irritant (Leuschner 2000a). A well conducted animal study shows that BPA is an eye irritant; effects persisted until the end of the study (day 28 post-instillation) in 1 of 3 rabbits (Leuschner 2000b). 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*, 1985a). These data suggest 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 (European Commission 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, Maguire 1988, Gerberick and Ryan 1990). 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 data available 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. Effects of repeated exposure

There are some recent cross-sectional studies on the general population reporting associations between urinary BPA levels and diabetes, obesity or cardiovascular diseases (e.g. Shankar *et al* 2012a,b,c; Melzer *et al* 2012a,b; Wang *et al* 2012a, Silver *et al* 2011). However, no conclusions on the basis of these cross-sectional studies can be made without any confirmation from other, preferably longitudinal studies. 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 concentration was associated with a significant increase in FT3 (free triiodothyronine) levels in this group of workers. No conclusions can, however, be made on the basis of this single, small study.

In animals, there were no data relating to repeated dermal exposure. Repeat inhalation studies were available in the rat (Nitschke *et al* 1985b, 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 MMAD was 2–6 µm), and a NOAEL 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 weight at 100 mg/kg/day and above were seen after dietary administration (Til *et al* 1978, NTP 1982). 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 (NTP 1982, Furukawa *et al* 1994). 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 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 ppm (corresponding to the intake of 0.001, 0.02, 0.3, 5, 50 and 500 mg/kg bw/day of BPA) in Sprague-Dawley 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 the dietary doses of 0, 0.018, 0.18, 1.8, 30, 300 or 3 500 ppm (corresponding to the 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 increased kidney weight and renal nephropathy with minimal severity was seen at the highest dose. 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. A NOAEL of 50 mg/kg bw based on liver effects can be set based on this study.

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).

Based on the data in mice and rats, an oral LOAEL for repeated dose toxicity of 50 mg/kg bw/day and a NOAEL of 5 mg/kg bw/day can be set.

3.6. Mutagenicity

No human data regarding mutagenicity were available. However, 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 (European Commission 2003, NTP 2008). However, these effects have not been unequivocally demonstrated *in vivo* (NTP 2008). BPA has been shown to produce adduct spots in a 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* (European Commission 2003, NTP 2008). The standard mouse bone marrow micronucleus test has given a 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 either a single BPA 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 epydidimal 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 in repeated dose studies. Doses were selected on the basis of Hunt *et al* (2003) study showing aneuploidy in mice oocytes *in vivo*.

Considering all of the available genotoxicity data, and the absence of significant tumour findings in animal carcinogenicity studies (see below), it does not appear that BPA has significant mutagenic potential *in vivo*.

3.7. Carcinogenicity

There were no human data contributing to the assessment of whether or not BPA is carcinogenic. 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 not considered toxicologically significant. Consequently, it was concluded that BPA was not carcinogenic in this study in both 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 the maximum attainable concentration in the experimental system used, 150 mg/m^3. Taking into account all of the animal data available the evidence suggests that BPA does not have carcinogenic potential.

Recently, concerns have been raised on the possible contribution of BPA on prostate and mammary gland rendering these organs more susceptible to neoplasia when exposed during neonatal age (Timms *et al* 2005, Moral *et al*, Jenkins *et al* 2009, Prins *et al* 2011, Lamartiniere *et al* 2011). These studies have been performed at "low dose range" i.e. at levels well below 0.05 mg/kg bw. All these studies, however, suffer from deficiencies in design or execution, including small numbers of animals or dose groups or lack of long-term follow-up to see whether observed effects (suggested to increase cancer susceptibility) really result in cancers. WHO (2011) concluded that these studies, although suggestive of increases in certain tumour types, do not provide convincing evidence of carcinogenicity. Regardless of a couple of new studies published since then, this statement still applies.

3.8. Endocrine modulating activity

BPA has been shown to have endocrine modulating activity in a number of *in vitro* and *in vivo* screening assays (European Commission 2003). The potency of this activity in these assays generally ranged from 3 to 5 orders of magnitude less than that of oestradiol. The available data also indicate that there is a marked strain difference in the response to BPA in rats. However, there were no data to indicate the underlying reasons for such differences.

It should be noted that these studies investigating endocrine modulating activity are essentially screening tests and many of them employ experimental protocols, which have not undergone any international validation. In addition, many of the available *in vivo* studies have used parenteral routes of exposure, the relevance of which are

uncertain with respect to relevant routes of human exposure.

3.9. Effects on reproduction

3.9.1. Human data

Li *et al* (2010a) examined the effect of occupational BPA exposure on male reproductive function. The exposed 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 workshift), a significant correlation between urinary BPA levels and self-reported sexual dysfunction was seen (Li *et al* 2010b). 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. It is likely that skin exposure has contributed to the urinary levels.

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 these 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 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 the effect of other occupational exposures on the studied parameters.

Cha *et al* (2008) reported decreased testosterone levels and increased luteinising hormone (LH) and follicle-stimulating hormone (FSH) levels among the 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 the 42 epoxy resin sprayers with slightly elevated urinary BPA levels.

Regarding developmental effects, Braun *et al* (2009, 2011) examined the relationship between gestational BPA exposure (measured as serial urinary BPA samples) and neurobehavioral effects in infants. 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. An association between BPA exposure and lower birth weight, small for gestational age (SGA) infants and disturbed adipogenesis has been also suggested (Chou *et al* 2011) but also increased birth weight has been observed (Wolff *et al* 2008). No conclusions can be made on the basis of these small, cross sectional studies.

3.9.2. Animal data

The effects of BPA on fertility and reproductive performance have been investigated in three good quality studies: 3-generation and 2-generation studies in mice, and one

older continuous breeding study in rats. Since there is an ongoing discussion on possible non-monotonic dose-response, three of these studies employed also low dose ranges.

The oldest one of these reproductive toxicity studies is a continuous breeding study in the mouse, which provides some evidence that BPA can cause adverse effects on fertility at high dose levels (NTP 1985b). 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 (> 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). The NOAEL for reproductive 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 (Tyl *et al* 2008) at the dose range of 0.003–600 mg/kg bw. Signs of systemic toxicity (e.g. liver centrilobular hepatocyte hypertrophy) were seen at the doses of 50 mg/kg bw and higher (see Section 2.5).

Regarding developmental toxicity, no effects were seen in old standard development studies in rats and mice. In rats, a maternal LOAEL and foetal NOAEL of 160 and 640 mg/kg bw/day, respectively, were identified (NTP 1985c, Morrisey *et al* 1987). In mice, maternal and foetal NOAELs were 250 and 1 000 mg/kg bw/day, respectively (NTP 1985a). However, since then several studies have appeared investigating the potential of BPA to affect male reproductive tract development in rats and mice at a low dose range. Conflicting results have been reported in many studies. For example 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 at dose levels in the range 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).

In a rat multigeneration study, 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 post-natal 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 maternal toxicity and no treatment-related effects

were reported in the offspring of animals exposed to 50 mg bw/kg. The NOAEL for maternal and developmental toxicity in this study was 50 mg/kg bw/day.

In a 2-generation study in mice (Tyl *et al* 2008, see above), 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 were unaffected. The NOAEL for developmental effects was 50 mg/kg bw/day and for systemic toxicity 5 mg/kg/day. No effects were seen at low dose range of 0.003–5 mg/kg bw/day.

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 dams. The results on the effects of the same BPA treatment on male offspring have been 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.

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 contrast, Salian *et al* (2009) reported a significant increase in post implantation loss, decrease in litter size and decrease in sperm count and motility in the offspring of female Holzman strain rats dosed 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. Taken into account negative results from other, well-conducted studies, these findings are very unexpected. In addition, there are some limitations in the conduct and reporting of the study. Also doubts on the representativeness of the control group have been raised (see discussion by EFSA 2010).

Concerns have been raised also on the developmental neurotoxicity and neurobehavioural effects of BPA. For example, Miyagawa *et al* (2007) reported impaired memory in the offspring of dams exposed via the diet to BPA at the estimated doses of 4.5 µg/kg bw/day, and 300 mg/kg bw/day. Increased aggressiveness has been reported in limited studies in rats and mice at the dose levels of 2–40 µg/kg (Farabollini *et al* 2002, Kawai *et al* 2003). Increased or decreased anxiety (contradictory findings between the studies) has also been reported in rodents (Ryan *et al* 2006, Farabollini *et al* 1999). An area which has gained a lot of interest recenty is possible effects of BPA on sexual differences. Loss of sexual differences after gestational exposure has been suggested by some studies (Carr *et al* 2003, Fujimoto *et al* 2006, Jones and Watson 2012). There are, however, number of limitations in all these studies including a limited number of doses and animals evaluated.

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. The 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, and 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 the pregnancy. The NOAEL for neurodevelopmental effects was the highest dose level tested. However, EFSA have concluded in its recent evaluation (EFSA, 2010) that data on Biel 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 left regarding developmental effects.

Overall, in standard developmental studies in rodents, there is no convincing evidence that BPA is a developmental toxicant at doses below those causing maternal toxicity. However, there are some uncertainties on the potential developmental toxicity of BPA related especially to developmental neurotoxicity. A recent evaluation by WHO/FAO concluded that further investigations are needed especially related to the changes in anxiety and convergence of anatomical brain sex differences (WHO 2011). Also a concern on impaired sperm parameters, based on Chinese epidemiological studies, was expressed (WHO 2011).

4. Recommendation

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 NOAEL 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.

If one then considers the other toxicological evidence, most of which arises from oral dosing studies in rodents, there were no findings that preclude the recommendation of a health-based OEL. In repeated oral dosing studies, NOAELs of 5 mg/kg bw/day in rats and mice have been found with mild liver hypertrophy, increased liver weights and reductions in weight gain at 50 mg/kg bw (Tyl *et al* 2002 and 2008, Stump *et al* 2010). This NOAEL has been used as a starting point by EFSA for the setting of an oral reference dose of 0.05 mg/kg bw/day for BPA. If 100 % absorption is assumed for both exposure routes, a NOAEL of 5 mg/kg bw in continuous subchronic exposure corresponds to 49 mg/m^3 at occupational inhalation exposure (8 hours per day, 5 days per week) in humans.

There are some species differences in the metabolism of BPA. Enterohepatic circulation in rats results in a longer half-life of BPA in rats when 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, it has been noted that internal exposures to free BPA are rather similar in rodents and humans reducing the need for allometric scaling (WHO 2011).

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.

There are some uncertainties related to 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 prostate effects (increased susceptibility to prostate cancer). However, there is currently no concluding evidence showing that these effects are real and relevant for humans. Also reports on male reproductive dysfunction in occupationally exposed persons need to be confirmed by other studies before any conclusions can be made on the effects of BPA on human reproductive function.

The inhalation NOAEL of 10 mg/m^3 is taken as the starting point for recommending an OEL. This value is divided by an assessment factor of 3 resulting in an OEL of 3 mg/m^3 to cover the uncertainties related to the inter-species extrapolation. Using the preferred value approach, 3 mg/m^3 is rounded to 2 mg/m^3. This leaves almost a 25-fold safety margin to the systemic liver effects seen in rats at the oral dose levels of > 5 mg/kg bw (NOAEL, corresponding to an inhalation exposure level of 49 mg/m^3). This is considered to suffice since according to toxicokinetic data there is no need for specific adjustment for inter-species differences in toxicokinetics. In addition, C_{max} in the target organ (liver) is likely to be lower after inhalation or dermal exposure than after oral exposure even thought a part of the inhaled BPA is likely to be actually ingested and absorbed from the gastro-intestinal tract.

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 the setting of a BLV. Using the same formula and assumptions as used in Krishnan *et al* (2010, page 6), 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 urinary excretion over the course of the day. In addition, the data on the toxicokinetics of BPA after inhalation exposure is limited, the majority of toxicokinetic data coming from oral exposure. Thus, no BLV can be proposed. A biological guidance value (BGV) of 7 µg/l is proposed for the identification of potentially occupationally exposed from the occupationally non-exposed.

There is no toxicological basis for recommending an additional specific short-term exposure limit (STEL); nor is a "Sen" notation appropriate. A recent OECD guideline based study on skin absorption showed that skin absorption may have only a minor contribution to systemic BPA levels at the proposed OEL. Thus, no "Sk" notation is proposed.

An appropriate method is available to measure airborne BPA in relation to the occupational exposure limit recommended (NIOSH 1980).

The present Recommendation was adopted by SCOEL XX Date Month year.

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