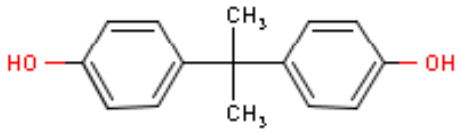
**Bijlage 4 van het advies 29-2009 : Fiche Bisphenol A**

## BISPHENOL A

CAS no. 80-05-7

2,2-(4,4´-dihydroxydiphenyl)propane, 4,4´-isopropyllidenediphenol or 2,2-bis(4-hydroxyphenyl)propane, usually named Bisphenol A (C15H16O6) is a monomer of polycarbonate plastics.

### Chemical form (EFSA, 2006)




### Contamination source, origin, use

Bisphenol A (BPA) is used for manufacturing synthesized polymers including polycarbonates, epoxy resins, phenol resins polyesters and polyacrylates (Staples *et al.,* 1998). Polycarbonate is a type of transparent, rigid plastic (EFSA, 2006), used in a wide variety of common products including digital media (e.g., CDs, DVDs), electrical and electronic equipment, glazing in the building and construction industry, automobiles, sports safety equipment, reusable food and drink containers (Mercea, 2009), toys, water pipes, eyeglass lenses, dental monomers, medical equipment and tubing (Vandenberg *et al*., 2007). Polycarbonate is used to make food containers, such as returnable beverage bottles, infant feeding (baby) bottles, tableware (plates and mugs) and storage containers. Residues of BPA are also present in epoxy resins used to make protective coatings and linings for food and beverage cans and vats (EFSA, 2006). The plastic monomer and plasticizer BPA is one of the highest volume chemicals produced worldwide (Vandenberg *et al.,* 2007).

BPA is permitted for use in food contact materials in the European Union, under Commission Directive 2002/72/EC of 6 August 2002 relating to plastic materials and articles intending to come into contact with foodstuffs. It is also permitted for food contact use in other countries, such as the USA and Japan.

Hydrolysis of polycarbonate (PC) is the dominant mechanism responsible for the release of BPA from the polymer surface into the contacting aqueous liquid (Mercea, 2009). Factors found to be of importance include temperature, pH, and ozone concentration of the liquids, as well as the surface ageing of the PC (Mercea, 2009). Mostly, BPA migration levels obtained from experiments performed under standard conditions as given in the EU legislation and its associated guidance documents were found to be well below the EU specific migration limit of 600 µg/kg food which applies to plastics in contact with foodstuffs (EU Directive 2002/72/EC as amended). Migration is lower in oil than in the aqueous food-simulants water, 3% acetic acid, and 10 or 50% ethanol (Mercea, 2009).
The Government of Canada has banned polycarbonate baby bottles.
The Government of Canada is proposing to reduce bisphenol A exposure in infants and newborns by proposing a number of actions: to ban polycarbonate baby bottles; to develop stringent migration targets for bisphenol A in infant formula cans; to work with industry to develop alternative food packaging and develop a code of practice; and to list bisphenol A under Schedule 1 of the Canadian Environmental Protection Act.

### Mode of action (toxicological data: major biologic effect, active dose)

**Carcinogenic activity**

An expert panel of scientists has discussed the carcinogenic activity of BPA at the forum entitled "Bisphenol A: An Expert Panel Examination of the Relevance of Ecological, *In Vitro* and Laboratory Animal Studies for Assessing Risks to Human Health" in Chapel Hill, NC on 28–30 November 2006.
The consensus report on the role of BPA in carcinogenesis, based on the examination of available evidence in humans and animal models gave the following conclusions (Keri *et al*., 2007).
Based on existing evidence, one is confident that :

- Natural 17 β-estradiol is a carcinogen as classified by the International Agency for Research on Cancer (group 1).
- BPA acts as an endocrine disruptor with some estrogenic properties among other hormonal activities.

Based on existing evidence, it is believed to be *likely* but requiring more evidence:

- BPA may be associated with increased cancers of the hematopoietic system and significant increases in interstitial cell tumors of the testes.
- BPA alters microtubule function and can induce aneuploidy in some cells and tissues.
- Early life exposure to BPA may induce or predispose to preneoplastic lesions of the mammary gland and prostate gland in adult life.
- Pre-natal exposure to diverse and environmentally relevant doses of BPA alters mammary gland development in mice, increasing endpoints that are considered markers of breast cancer risk in humans.

Based on existing evidence, the following are *possible*:

- BPA may induce *in vitro* cellular transformation.
- In advanced prostate cancers with androgen receptor mutations, BPA may promote tumor progression and reduce time to recurrence.

## Endocrine disrupting activity

The estrogenic effect of BPA have been recognized since the early 1900s and these effects are attributed to BPA acting both as an estrogen agonist and to promote the effect of endogenous 17 β-estradiol (Crain *et al.,* 2007).

BPA is considered a weak estrogenic compound both *in vitro* and *in vivo* (SCF, 2002; EFSA, 2006) and an anti-androgenic compound (cited in Scippo *et al*., 2004). When compared to estradiol 100000 times more BPA is required to trigger proliferation of MCF-7 cells. On the other hand, Ca influx and prolactin secretion in pituitary cancer cells does not require higher BPA doses than estradiol (vom Saal *et al.,* 2005).

### - Epidemiological studies

Human studies of possible health effects of BPA exposure are extremely limited (Vandenberg *et al.*, 2007). There are insufficient data to evaluate whether BPA causes male or female reproductive toxicity in humans (Sekizawa, 2008).
Abnormal breast development has been described in men exposed to high doses of BPA (Cooper and Kavlock, 1997) (cited in Desmetz, 2004).

### - *in vivo studies*

BPA showed no androgenic/antiandrogenic effects in rats *in vivo* (Kim *et al.*, 2002) and reduced steroidogenesis only at the lowest of three doses given to rats *in vivo (cited in EFSA, 2006)*.

Although estrogenic activity of BPA was claimed to be fairly low as compared to estradiol (E2), recently, BPA was found to be able to interact with membrane estrogen receptor (ER) α and could cause rapid estrogen-mediated signal-regulated kinase signalling in developing rat cerebellar neurons as a potent nongenomic agonist at $10^{-12}$M concentration as comparable to E2 (Sekizawa, 2008).

BPA is capable to stimulate prolactin secretion (*Wozniak et al., 2005)*, cell proliferation of the uterus and vagina, and uterine c-fos mRNA levels in Fischer 344 rats but not in Sprague-Dawley female

rats (Steinmetz *et al*., 1998), and MCF-7 cell proliferation (Cited in Li and Li, 1998).

Estrogenic activity, using the oral route of exposure, changes to the uteri were observed in Alpk rats at 200 mg/kg BPA and above. No effects were observed at dose levels up to, and including, 100 mg/kg (EU, 2003).

Very low doses of BPA increased expression of genes in fœtal mouse prostate cells that are responsible for directing production of hormone receptors (Richter *et al.,* 2007).

Rodent studies suggest that BPA causes neural and behavioural alterations related to disruptions in normal sex differences in rats and mice at doses of 0.01 – 0.2 mg/kg/day (Sekizawa, 2008).

*In vivo* studies in rodents show that BPA induces estrogenic responses: proliferation of the uterine epithelium at high doses and proliferation of vaginal epithelium associated with overexpression of c-fos at low doses (Ashby and Tinwell 1998; Long *et al.*, 2000; Schonfelder *et al.*, 2002). Furthermore, it increases the expression of genes for prolactin and in some cases, produces anomalies in the reproductive system (Steinmetz *et al.*, 1998).

In addition to effects on survival and growth seen at high dose levels of BPA, a variety of effects related to neural and behaviour alterations, precancerous lesions in the prostate and mammary glands, altered prostate gland and urinary tract development, and early onset of puberty in females have been reported in laboratory rodents exposed during development to much lower doses of BPA (≥ 0.0024 mg/kg bw/day) that are more similar to human exposures (NTP, 2008).

The NTP has *some* concern for BPA exposure in foetuses, infants, and children. The scientific evidence that supports this concern comes from a number of laboratory animal studies reporting that "low" level exposure to BPA during development can cause changes in behaviour and the brain, prostate gland, mammary gland, and the age at which females attain puberty (NTP, 2008).

There is clear evidence of adverse effects of BPA at high dose of developmental toxicity: reduced survival in fœtuses or newborns (≥ 500 mg/kg bw/day), reduced fœtal or birth weight or growth of offspring early in life (≥ 300 mg/kg bw/day) and delayed puberty in female rats (≥ 50 mg/kg bw/day) and male rats and mice (≥ 50 mg/kg bw/day); There is some evidence of adverse effects of reproductive toxicity: decreased fertility in mice (≥ 875 mg/kg bw/day), altered estrous cycling in female rats (≥ 600 mg/kg bw/day), and cellular effects on the testis of male rats (235 mg/kg bw/day). There is limited evidence of adverse effects at 'low' dose of developmental toxicity based on a variety of effects related to neural and behaviour alterations (≥10 µg/kg bw/day), precancerous lesions in the prostates (10 µg/kg bw/day) and mammary glands (0,0025 – 1 mg/kg bw/day), altered prostate gland and urinary tract development (10 µg/kg bw/day), and early onset of puberty (2,4 and 200 µg/kg bw/day) (NTP, 2008).

In contrast to the "high" dose developmental effects of BPA, there is a scientific controversy over the interpretation of the "low" dose findings. When considered together, the results of "low" dose studies of BPA provide *limited evidence* for adverse effects on development in laboratory animals (NTP, 2008).

The lowest dose previously examined for risk assessment purposes was 50 mg/kg per day in studies with rats and mice. The **50 mg/kg** per dose is the currently accepted lowest adverse effect level **(LOAEL)** that was used to calculate the current reference dose (vom Saal *et al.,* 2007).

The **NOAEL**s for uterotrophic effects following oral administration of BPA range from **40 - 400 mg/kg bw/day**, with the exception of a single rat study reporting a low effect level (25% increase in uterine weight) of 10 mg/kg bw/day with a **NOAEL of 1 mg/kg bw/day** (SCF, 2002).

***Effects of BPA on wildlife***

Endocrine-disrupting effects occur at environmentally relevant concentrations (i.e., concentrations found in the environment). The endocrine disrupting effects of BPA that have been identified in wildlife species include: (1) alteration of sex determination from exposure during gonadal organogenesis, (2) alteration of gonadal function from exposure both during and after gonadal

organogenesis, and (3) induction of hepatic vitellogenin production following exposure of fully organized individuals. Thus, like many other endocrine-disrupting contaminants, BPA is a substance that can act both organizationally to permanently alter organ structure (e.g., the gonad) and activationally to cause a change in normally organized systems, e.g., the gonad and liver (Crain *et al.*, 2007).

- ***in vitro* studies**

MtT/E2 cells were transfected with an estrogen inducible reporter gene encoding for the enzyme β-galacosidase, and the transcription activation of BPA was investigated. Transfected cells were cultured with BPA for 24 hours. BPA was observed to stimulate gene expression receptors; a statistically significant increase in enzyme activity was seen at concentrations from $10^{-6}$ M and upwards (EU, 2003).

It is well established that BPA can exert some of its effects by binding at the nuclear steroid receptors ERα and ERβ to induce estrogenic signals that modify estrogen-responsive gene expression (Wetherill *et al.,* 2007). Mechanisms for ER-mediated gene regulation are complex, and depend on the recruitment of tissue-specific co-regulatory factors that differentially affect the interaction of ERs with estrogen-related receptors (ERRs) of different target genes (cited in Wetherill *et al.,* 2007).

BPA has a higher affinity to the ERβ as compared to the ERα. BPA binds both ERα and ERβ with approximately 10-fold higher affinity to ERβ (cited in Vandenberg *et al.,* 2007). The relative binding affinity of BPA to the ERα is 3 to 4 orders of magnitude below that of the reference compound 17 β-estradiol (EU, 2003). The affinity of BPA to ERβ is approximately 40-fold lower than that of 17 β-estradiol (cited in EFSA, 2006).

Recent evidence suggests that BPA also binds strongly to ERRγ, an orphan nuclear receptor belonging to the ERR family of receptor that do not directly bind estradiol (E2) (cited in Hugo *et al*., 2008).

BPA has also been shown to have a weak antagonism to thyroid hormone receptors with affinities four to five orders of magnitude below that of triiodothyronine (Moriyama *et al.*, 2002). BPA also may weakly interfere with different steps of androgen receptor function *in vitro* (Lee and Rhee, 2007).

Kuiper *et al.* (1997) reported a $K_i$ for BPA of 195 and 35 nM at ERα and ERβ, respectively (cited in Wetherill *et al.,* 2007).

For BPA, EC50 values for ERα and ERβ induction of luciferase activity were 6.4 $10^{-7}$ M and 8.9 $10^{-7}$ M, respectively (compared with 1.9 $10^{-9}$ M and 1.0 $10^{-8}$ M for 17 β- estradiol) (EU, 2003).

Satoh *et al.* (2004) showed that BPA could bind to human ERα and reported an IC50 (the concentration of chemical required to reduce specific 17 β -estradiol binding by 50%) of 7.8 µM (cited in Wetherill *et al*., 2007).
Calculated IC50 value for BPA in the presence of $10^{-9}$ mol/L progesterone is 4.3 $10^{-6}$ M (Willemsen *et al.,* 2004).

Binding of BPA to recombinant human estrogen receptor (hERα) is evaluated by its IC50 = 8 µM, relative binding affinity (RBA) = 0.03% and to progesterone receptor (hPR): IC50= 45 µM, RBA = 0,1 %. The RBA is the ratio between IC50 (concentration needed to observe a 50% inhibition of the maximum binding of [$^3$H] ligand) of the tested chemical and that of the natural ligand of the receptor (Scippo *et al*., 2004). BPA displayed a high binding potency to hPR and high affinity for hERα (Scippo *et al*., 2004).

*In vitro*, BPA binds and activates ERα and ERβ and is 3-5 orders of magnitude less potent than 17β-estradiol (MCF-7 cells), BPA glucuronides are devoid of estrogenicity (SCF, 2002).
Estrogenic effect with 160 ng/ml (38% of the maximal activity obtained with 1.4 ng of 17 β-estradiol/ml of medium) was observed (results of 1 test) in human mammary tumor MCF7, stably transformed after 24h exposition. The principle of this test is a competition between BPA and radiolabelled 17 β-estradiol for binding to a human recombinant receptor ERα at a concentration

range of 160 - 20480 ng/mL. Binding of BPA to the recombinant ER was evaluated by measuring an IC50 = 4500 ng/mL. RBA (in comparison with IC50 of 17 β-estradiol) was estimated 2.5 $10^{-4}$ (Ribonnet *et al.,* 2007).

BPA is 1000 to 5000 times less active than 17 β-estradiol. BPA were described as, ligand of receptor IIEBS (Estrogen Binding Site II) whose affinity for estradiol is 10 to 100 times lower than that of ERα and ERβ (Desmetz, 2004).

Bonefeld-Jørgensen *et al.* (2007) investigated the effect *in vitro* of BPA on four key cell mechanisms including transactivation of *a*) the human estrogen receptor (ER), *b*) the human androgen receptor (AR), *c*) aromatase activity, and *d*) the aryl hydrocarbon receptor (AhR). BPA elicited ER-mediated dose–response luciferase activity in the concentration range of $10^{-8}$ to 5 $10^{-5}$ M, with the maximum response being approximately 75% of the natural ligand E2- induced maximum response. The EC50 value was 3.9 μM for BPA (Table 1) (Bonefeld-Jørgensen *et al.*, 2007). BPA elicited a significantly antiandrogenic effect on the R1881-induced AR activity in the range of 0.60 – 20 μM, with IC50 value of 1 μM and a maximum inhibition (MI) of 90% (Table 1) (Bonefeld-Jørgensen *et al.*, 2007). BPA decreased the aromatase activity significantly at $10^{-4}$ M, with MI of 59% (Table 1) (Bonefeld-Jørgensen *et al.*, 2007).

Table 1. ER, AR, aromatase and AhR characteristics of BPA (Bonefeld-Jørgensen *et al.*, 2007).

| Assay | LOEC (M) | MOEC (M) | Maximum[a] (%) | REP | EC50/IC50[b] | Cytotox (M) |
|---|---|---|---|---|---|---|
| ER | $1x10^{-7}$ | $1x10^{-5}$ | / | $1x10^{-4}$ | $3,9 \times 10^{-6}$ | / |
| AR[d] | $0,6x10^{-6}$ | $2x10^{-5}$ | 90 | ND | $1,0x10^{-6}$ | $>4x10^{-5}$ |
| Aromatase[d] | $1x10^{-4}$ | $1x10^{-4}$ | 59 | $1x10^{-5}$ | / | / |
| AhR | $5x10^{-5d}$ | $1x10^{-4d}$ | 54 | / | ND | $<10^{-4}$ |

/: No data, LOEC: lowest observed effect concentration in molar (M), MOEC: Maximum observed effect concentration in molar (M), ND: not determined; REP: relative potency, [a]Maximum down-regulation of the control inducer which was set to 100%, [b]EC50/IC50: molar concentration which exert 50% increase/50 % inhibition compared to the max response of their respective control, respectively, [d]inhibited activity

It was shown that at environmentally relevant levels (1 nM), BPA is capable of binding and activating the mutant receptor to induce endogenous expression of PSA (prostate specific antigen) (Hess-Wilson *et al.,* 2007).

BPA exerted its effects at a dose of 10 nM (0.3 μg/kg bw/day) after prenatal administration, which is 100 times lower than 50 μg/kg bw/day (Yan *et al.*, 2008).

BPA is an extremely weak estrogen requiring 2000 to 5000 higher concentrations compared to E2 to exhibit the response (Cited in Li and Li, 1998).

***Conclusion from the results of mechanistic in vitro studies***

It was shown based on existing evidence (Wetherill *et al.,* 2007) that:

- BPA can act as an estrogen; its effects are, however, cell type specific.
- Timing (developmental stage) of exposure and exposure dose/concentration are critical.
- When BPA binds to classic nuclear estrogen receptors and induces specific ERE binding, BPA is usually less potent than estradiol.
- When BPA action is mediated by estrogen receptors outside the nucleus, its potency is as high as that of estradiol, ranging within the pico- and nano-molar concentrations.
- Because of cell-type specific expression patterns and the role of varied specific co-regulatory factors, the effects of BPA might be different in individual cell types and these effects can vary depending on intrinsic and extrinsic influences.
- BPA is not simply a SERM (selective estrogen receptor modulator).
- BPA exerts pleiotropic cellular and tissue-type specific effects and non-monotonic dose–response at the cellular and intracellular levels at low physiologically relevant concentrations.

The published scientific literature on human and animal exposure to low doses of BPA in relation to *in vitro* mechanistic studies reveals that human exposure to BPA is within the range that is predicted to be biologically active in over 95% of people sampled. The wide range of adverse effects of low doses of BPA in laboratory animals exposed both during development and in adulthood is a great

cause for concern with regard to the potential for similar adverse effects in humans. Recent trends in human diseases relate to adverse effects observed in experimental animals exposed to low doses of BPA. Specific examples include the increase in prostate and breast cancer, uro-genital abnormalities in male babies, a decline in semen quality in men, early onset of puberty in girls, metabolic disorders including insulin resistant (type 2) diabetes and obesity, and neurobehavioral problems such as attention deficit hyperactivity disorder (ADHD) (vom Saal *et al.*, 2007).

## Exposure source

Human exposure to BPA occurs primarily via hydrolysis of polycarbonate plastics and epoxy resins, resulting in low concentration of free BPA in food and liquids (Crain *et al.,* 2007; Mercea 2009). This makes dietary consumption the major mode of human exposure (Crain *et al.,* 2007).

Consumer exposure to BPA may occur through oral and dermal exposure. Oral exposure occurs mainly via consumption of food and beverages (dietary exposure) (EFSA, 2006).

Concentrations of BPA in canned liquid infant formula product analysed in Canada ranged from 2.27 to 10.2 ng/g with an average of 5.12 ng/g, which is below the specific migration limit (SML) of 0.6 µg/g (Cao *et al*., 2008).

The levels of residual BPA in polycarbonate (PC) are generally below 100 mg/kg. Several studies have been published examining the potential of BPA to migrate from PC into foodstuffs or food simulating liquids. Migration levels reported in the literature are generally well below the SML of 0,6 µg/g (cited in Mercea, 2009).

The table 2 below summarizes the intake estimates for different age groups. The Scientific Committee on Food considers these to be realistic worst-case estimates. They are based on acceptable data from studies of migration into actual foods and beverages under normal conditions of processing, storage and use, apart from the estimates for wine, for which only tests with simulants were available (SCF, 2002).

Table 2: intake estimates of BPA for different age groups (SCF, 2002)

| Consumer group | Type of food | Amount consumed/day | Concentration BPA (µg/kg) | Intake estimate (µg/kg bw/day) |
|---|---|---|---|---|
| Infant 0-4 mo 4.5 kg | Formula | 0.7 litre | 10 | 1.6 |
| Infant 6-12 mo 8.8 kg | Formula | 0.7 litre | 10 | 0.8 |
| Infant 6-12 mo 8.8 kg | Canned food | 0.38 kg | c.20 | 0.85 |
| Child 4-6 years 18 kg | Canned food | 1.05 kg | c.20 | 1.2 |
| Adult 60 kg | Canned food | 1.05 kg | c.20 | 0.37 |
| Adult 60 kg | Wine | 0.75 litre | 9 | 0.11 |

## Level of exposure

Conservative dietary exposure assessments on BPA have been made by the Panel on Food Additives, Flavourings, Processing Aids and Materials in Contact with Food of EFSA for adults, infants and children. A comparison of estimates of daily BPA intake is shown in table 3. Table 4 shows a range of estimated daily intakes in people based on sources of exposure (NTP, 2008).

Using literature for contamination in the environment (water, air, soil) and food contamination (can surfaces, plastic containers), the daily human intake of BPA was estimated at less than 1 µg/kg body weight/day. Alternatively, the European Commission's Scientific Committee on Food estimated BPA exposure to be 0.48 – 1.6 µg/kg body weight/day from food sources, while Thompson *et al*. estimated that New Zealanders consume as much as 4.8 µg/day from dietary sources alone

(Vandenberg *et al.,* 2007).

The probable daily intake of BPA due to consumption of canned liquid infant formula analysed in Canada were estimated for infants from premature to 12-18 months of age. The maximum probable daily intake of BPA was 1.35 µg/kg bw for 0-1 month-old infants (Cao *et al*., 2008).

Table 3. Comparison of estimates of daily BPA intake for the US population based on NHANES urinary BPA data with recent international estimates based on external exposure assessments (lakind and Naiman, 2008).

| | 50th % | 95th % | | Reference |
|---|---|---|---|---|
| *Intake estimated from urinary BPA (ng/kg-day)* | | | | |
| All (ages 6–60+ years) | 50.5 | 274.2 | — | This study |
| Adults (20–60+ years) | 33.4–56.3 | 233.1–289.3 | — | |
| Children (6–11 years) | 67.4 | 310.5 | — | |
| Adolescents (12–19 years) | 77.3 | 347.6 | — | |
| *Intakes estimated using environmental measures (ng/kg-day)* | | | | |
| Children (1.5–5 years) | 60.8–71.4 | 328–342 | | Wilson et al. (2007) |
| Adults | 0 | 41 | Canned foods | Thomson and Grounds (2005)[a] |
| Infant — 3 months | — | 200 | Breast milk | EFSA (2007)[b] |
| Infant — 3 months | — | 2300 | Infant formula fed with glass or non-PC bottle | |
| Infant — 3 months | 4000 | 11,000 | Infant formula fed with PC bottle | |
| Infant — 6 months | 8300 | 13,000 | Infant formula fed with PC bottle and commercial foods/beverages | |
| Child — 1.5 years | — | 5,300 | 2 kg commercial foods/beverages | |
| Adult | — | 1,500 | 3 kg commercial foods/beverages | |
| Infant — 0–5 months | 28–55[a] | — | Breast milk, formula, toys, air | Miyamoto and Kotake (2006) |
| Infant — 6–11 months | 160–180 | — | Breast milk, formula, air, toys, baby food | |
| Child — 1–6 years | 1200 | — | Food, drinks, tableware, air | |
| Child – 7–14 years | 550 | — | | |
| 15–19 years | 360 | — | | |
| >19 years | 430 | — | | |
| Adult | — | 996[c] | Canned trout | Miyakawa et al. (2006) |
| Adult | 8.4[d] | — | Hospital meals | Higuchi et al. (2004) |

[a]Average values estimated for males.
[b]EFSA estimated exposures based on "typical" and "conservative" BPA migration values. For the purposes of comparisons in this table, we equate "typical" with the 50th percentile and "conservative" with the 95th percentile.
[c]Miyakawa et al. assumed a 50-kg individual consumes 200 g trout daily at a maximum BPA concentration of 249 ng/g.
[d]Higuchi et al. give an average estimate of 0.42 µg/day and a body weight for the average Japanese as 50 kg.
—, no estimate available.

Table 4. Range of estimated daily intakes in people based on sources of exposure (Source: NTP (2008) draft brief on BPA)

| **Population** | **BPA (µg/kg bw/day)** |
|---|---|
| Infant (0-6 months) formula-fed | 1-11 |
| Infant (0-6 months) Breast -fed | 0,1-1 |
| Infant (6-12 months) | 1,65-13 |
| Child (1,5 – 6 years | 0,043- 14,7 |
| Adult- general population | 0,008-1,5* |
| Adult - occupational | 0,043 -100 |

*The European Union (2003) calculated an extreme worst case scenario of ~ 9 µg/kg bw/day based on 1.4 µg/kg bw/day from food plus ~ 7 µg/kg bw/day from wine. The high estimated intake from wine (0.75 L wine/day with 650 µg bisphenol A /L = 325 µg BPA/day, or ~7 µg/kg bw/day, from wine) was based on an extraction study conducted with an epoxy resin that is sometimes used to line wine vats. A study published subsequent to the evaluation by the European Union identified a maximum concentration of 2.1 µg bisphenol A /L in wine (cited in NTP, 2008).

***Biomonitoring***

Studies have determined that BPA can be measured in humans in serum, urine, amniotic fluid, follicular fluid, placental tissue, and umbilical cord blood (Vandenberg *et al.*, 2007; Calafat *et al*., 2008). BPA crosses the maternal-fœtal placental barrier (Vandenberg *et al.,* 2007).

Because orally administered BPA is rapidly and completely excreted, urine is considered the body fluid most appropriate for assessment of BPA exposure (EFSA, 2006).

Urinary concentrations of BPA were analysed in the general adult population of the United States, using data from the national health and nutrition examination survey 2003-2004. BPA was detected in 92.6% of persons ≥ 6 years of age with total concentrations ranging from 0.4 µg/L to 149 µg/L. Children had significantly higher concentration of BPA (4.5 µg/L) than adolescents (3.0 µg/L) and adults (2.5 µg/L) (Calafat *et al*., 2008).

Levels of BPA ranging from 0.3 to 5 ng/mL (~1-20 nM) are present in adult and fœtal human plasma, urine and breast milk (Hugo *et al.*, 2008).

Dirtu *et al.* (2008) obtained a median concentrations for BPA in 21 Belgian human serum samples of 0.71 ng/mL.

Assessment of human BPA exposure by biomonitoring of urinary excretion of bisphenol A metabolites in the general population gives an estimated average daily total exposure to BPA of up to 7 µg BPA/adult/day and upper range exposures up to 10 µg BPA/adult/day (0.16 µg BPA/kg bw/day for a 60 kg person) in the USA and 0.04 to 0.08 µg/kg bw/day in Japan (95 % confidence interval). The discrepancy between the levels of exposure estimated through urinary biomarkers and the levels of exposure estimated below by combining food consumption data with BPA concentrations in the diet is likely to be due to the conservative assumptions made (EFSA, 2006).

Since there is a strong focus on polycarbonate plastic and polyester can coatings, other exposure sources might be overlooked.

**TDI**

The panel on Food Additives, Flavourings, Processing Aids and Materials in Contact with Food (AFC) of EFSA and US EPA have established a **Tolerable Daily Intake (TDI) of 50 µg/kg body weigh**t for BPA. Whereas Health Canada established the provisional tolerable daily intake (**pTDI) for BPA at 25 µg/kg body weight.**

**Maximal limit**

The specific migration limit (SML) for BPA is set to 0.6 mg/kg in food or food simulant (EC, 2004; Belgian Official Journal 29/07/2005).

**Estrogenic potency**

- Relative binding affinity

Relative binding activity of BPA is $10^3$ to $10^5$ weaker compared to E2.

- Uterotrophic activity

The **NOAEL**s for uterotrophic effects following oral administration of BPA range from **40 - 400 mg/kg bw/day**, with the exception of a single rat study reporting a low effect level (25% increase in uterine weight) of 10 mg/kg bw/day with a **NOAEL of 1 mg/kg bw/day** (SCF, 2002).
The uterine wet weights were significantly increased by BPA at 300 mg/kg /day in uterotrophic assay using Sprague-Dawley immature female rats (Kim *et al.,* 2005). In addition, the increase in uterine blotted weights also showed a similar pattern to that of uterine wet weights (Kim *et al.,* 2005).

**%TDI**

The level of exposure for adult- general population range between 0.008 – 1.5 µg/kg bw/day (NTP, 2008), daily intake for infant 6 - 12 month: 1,65 - 13 µg/kg bw/day (NTP, 2008).

%TDI range between 0.016 - 26%.

## References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