

Bisphenols

Subjects: [Anatomy & Morphology](#)

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Bisphenols (BPs), and especially bisphenol A (BPA), are known endocrine disruptors (EDCs), capable of interfering with estrogen and androgen activities, as well as being suspected of other health outcomes.

Bisphenol A

bisphenols

endocrine disruptors

thyroid hormones

thyroid cancer

1. Introduction

Bisphenol A (BPA) is a monomer in the manufacture of polycarbonate plastics and epoxy resins widely used in diverse consumer products such as food and liquid containers, protective coatings inside metallic food and beverage cans and medical devices, as well as in flame retardants and thermal papers^[1] [24]. It is one of the 2000 endocrine disruptors known as "highest volume" chemicals, with an annual production of at least 8 million tons throughout the world^[2].

2. Bisphenols in the Environment and Humans

BPA can be released from both effluent discharge of manufacturing plants and from transport, processing, and disposal of waste of BPA-containing products in landfills and incinerators^[3]. Less than 1% of environmental BPA has been estimated to occur in the atmosphere, where it undergoes photo-oxidation and breakdown^[4]. Nonetheless, the presence of BPA in the environment, though at low levels and despite the short half-life, is ubiquitous^[5].

Due to its lipophilicity, detectable levels of the unconjugated form of BPA were measured in adipose tissue, brain, liver, and breast milk in humans (Table 1a). Moreover, BPA can pass through the placenta and amniotic fluid thereby exposing the fetus, as well as the developing infant, to exposure and accumulation^[6] (Table 1a).

The first safety standard for humans set by the US-Environmental Protection Agency in 1988, adopted by the Food and Drug Administration as the reference dose and based on the LOAEL for BPA, was 50 micrograms per kilogram of body weight per day^[7]. In 2013, the re-evaluation of BPA exposure and toxicity led the European Food Safety Authority to considerably reduce the safe level of BPA from 50 to 4 µg/kg/day (31). Human exposure to BPA is continuous and widespread, and diet is likely the major source of exposure in all population groups because of the ability of BPA to migrate from polycarbonate containers and metallic cans to food and beverages^[8]. In 2011, the European Union banned the manufacture of baby bottles containing BPA^[9], followed in 2012 by the Food and Drug Administration^[10]. Infants and toddlers exhibit the highest estimated external average exposure because of their elevated consumption of food and beverages per kg of body weight^[8] (Table 1a). Other routes of exposure are represented by inhalation of outdoor and indoor air, ingestion of domestic dust, dermal contact with thermal paper and cosmetics, and, for children, mouthing of toys^[8]. The estimates for exposure to dietary and non-dietary sources are at least one order lower than the tolerable daily intake set by the European Food Safety Authority, except daily intake of infants fed with canned liquid formula in polycarbonate bottles (Table 1a).

BPA has a half-life in humans of about 6 h^[11]. Following the oral exposure, in humans BPA is absorbed from the gastrointestinal tract and then metabolized in the liver, where it is primarily conjugated with glucuronic acid to the non-active BPA-glucuronide, which is the main metabolite

in urine and blood^[11]. Urinary total BPA (conjugated + free), considered the most appropriate biomarker to assess human exposure^[12], was detected among the different age classes in 88% to 98% of volunteers who participated in the National Health and Nutrition Examination Survey^[12]. Significantly higher concentrations have been detected in children than in adolescents and adults whereas BPA levels measured in the blood of adults are approximately one order of magnitude lower than those found in the corresponding urine^[13] (Table 1a).

Several structural analogues were introduced in the market to replace BPA^[14]. Bisphenol F (BPF; 4,4-dihydroxydiphenylmethane), bisphenol S (BPS; 4,4-sulfonyldiphenol), and bisphenol Z (BPZ; 1,1-bis(4-hydroxyphenyl)-cyclohexane) are used in epoxy resin products^[15], in cleaning products and thermal paper^[16], and in highly heat resistant plastic materials and electrical insulation^[17], respectively. BPAF (1,1,1,3,3,3-hexafluoro-2,2-bis(4-hydroxyphenyl)propane) is a fluorinated derivative widely used in the manufacturing of polycarbonate copolymers with 10,000 to 500,000 pounds annually produced in the United States^[18]. BPA substitutes have been detected in various environmental matrices, and, with a few exceptions, their concentration values in urine are lower than those of BPA^[19] (Table 1b).

Tetrabromobisphenol A (TBBPA), a persistent compound synthesized by bromination of BPA initially replaced polybrominated diphenylthers, at present is the most widely employed brominated flame retardant, with a reported 2011 volume of 120 million pounds in the United States^[20]. In the last years, tetrabromobisphenol S (TBBPS) and tetrachlorobisphenol A (TCBPA) have been extensively used as alternatives to TBBPA^[21]. TBBPA is measured in the environment and in human body^[22], and TBBPA exposure represents a significant health risk especially for children residing in an e-waste processing region^[23] (Table 1c).

Table 1. Concentration of bisphenols in the environment and human body, and estimated exposure by age groups to bisphenol A (a), principal bisphenol A substitutes (b), and halogenated derivatives of bisphenol A (c).

(a) Bisphenol A		
Environmental Matrix	Concentration	Reference
Surface water	nd-1.95 µg/L	[24]
Sediments (industrialized areas)	nd-13,370 µg/kg dry weight	[18]
Soil	<0.01-1000 µg/kg	[6]
Indoor dust	nd-39.1 µg/g	[25]
Atmosphere	10 ⁻³ -1.74 ng/m ³	[26]
Landfill leachate (hazardous waste site)	Up to 17,200 µg/L	[27]
Human Body	Concentration	Reference
Brain	Mean: 0.91 ng/g	[28]
Liver	Mean: 1.30 ng/g	[29]
Adipose tissue	Mean: 3.78 ng/g	[28]
Breast milk	Mean: 0.61 µg/L	[29]
Blood (adults)	Mean: 0.20 µg/L	[13]
Cord blood	Mean: 0.13 µg/L	[13]

Urine (European adult population)	Geometric mean: 2.5â3.6 Âµg/L	[8]
Urine (North America children)	Geometric mean: 1.3â3.7 Âµg/L	[8]
Urine (North America adults)	Geometric mean: 1.0â2.6 Âµg/L	[8]
Age Group/Source of Exposure	Average External Exposure	Reference
Infants (0â3 month)/Formula fed from polycarbonate bottles	2.4 Âµg/kg/day	[30]
Infants (0â6 month)/Formula fed from non-polycarbonate bottles	0.03 Âµg/kg/day	[8]
Infants (6â12 month) and toddlers (12â36 month)/Diet	0.375 Âµg/kg/day	[8]
Infants (6â12 month) and toddlers (12â36 month)/Oral dust and toys	0.007â0.009 Âµg/kg/day	[8]
Infants (0â12 month) and toddlers (12â36 month)/Inhalation	0.7 Âµg/kg/day	[8]
General population (>3 years)/Diet	0.116â0.290 Âµg/kg/day	[8]
General population (>3 years)/Thermal paper	0.059â0.094 Âµg/kg/day	[8]
General population (>3 years)/Cosmetics	0.002 Âµg/kg/day	[8]
General population (>3 years)/Inhalation	0.2â0.4 Âµg/kg/day	[8]
(b) Principal Bisphenol A Substitutes		
Environmental Matrix	Concentration	Reference
Surface water (BPF)	nd-2.850 Âµg/L	[24]
Sediments in industrialized areas (BPF)	nd-9650 Âµg/kg dry weight	[18]
Indoor dust (sum of several bisphenols including BPF, BPS, BPZ)	0.00083â26.6 Âµg/g	[26]
Human Body	Concentration	Reference
Urine (BPS: general populationâUSA/Asian countries)	Geometric mean: 0.030â1.18 Âµg/L	[31]
Age Group	Estimated Exposure	Reference
Children and adolescents (<20 years)âUSA/Asian countries (BPS)	Median: 0.009 Âµg/kg/day	[31]
Adults (â¥20 years) â USA/Asian countries (BPS)	Median: 0.004 Âµg/kg/day	[31]
(c) Tetrabromobisphenol A		
Environmental Matrix	Concentration	Reference
Atmosphere (e-waste dismantling site)	66.01â95.04 ng/m ³	[32]
Indoor dust	42.21â46,191 ng/g dry weight	[23]

Sediments	Up to 518 ng/g	[33]
Soil (industrialized areas)	1.64â7758 ng/g dry weight	[34]
Surface water	0.85â4.87 Î¼g/L	[33]
Human Body	Concentration	Reference
Breast milk	4.110 ng/g lipid weight	[35]
Cord serum	Mean: 0.199 ng/g fresh weight	[35]
Age group/Source of Exposure	Average External Exposure	Reference
Infants/Breast-feeding	<0.00018â0.171 Î¼g/kg/day	[36]
Infants/Dust ingestion (e-waste recycling site)	0.00031â0.054 Î¼g/kg/day	[23]
Adults/Dust ingestion (e-waste recycling site)	0.00004â0.0075 Î¼g/kg/day	[23]
Adults/High fish consumers	0.00026 Î¼g/kg/day	[36]

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