REVIEW PAPER

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BISPHENOL A – APPLICATION, SOURCES OF EXPOSURE AND POTENTIAL RISKS IN INFANTS, CHILDREN AND PREGNANT WOMEN

KAROLINA MIKOŁAJEWSKA[1], JOANNA STRAGIEROWICZ[2], and JOLANTA GROMADZIŃSKA[1]

[1] Nofer Institute of Occupational Medicine, Łódź, Poland
Department of Toxicology and Carcinogenesis, Laboratory of Environmental Biochemistry
[2] Medical University, Łódź, Poland
Department of Toxicology, Faculty of Pharmacy

Abstract
Bisphenol A (BPA) is used in the chemical industry as a monomer in the production of plastics. It belongs to a group of compounds that disturb some of the functions of human body, the endocrine system in particular. Extensive use of BPA in manufacturing products that come in contact with food increases the risk of exposure to this compound, mainly through the digestive tract. Literature data indicate that exposure to bisphenol A even at low doses may result in adverse health effects. The greatest exposure to BPA is estimated among infants, children and pregnant women. The aim of this review is to show potential sources of exposure to bisphenol A and the adverse health effects caused by exposure to this compound in the group of particular risk.

Key words:
Bisphenol A, Exposure, Children, Pregnant women, Dietary exposure, Neurodevelopment

INTRODUCTION

Applications of bisphenol A

Bisphenol A (BPA) is an organic compound classified to the group of phenols. Its name according to the International Union of Pure and Applied Chemistry (IUPAC) is 4,4'-dihydroxy-2,2-diphenylpropane, CAS no. 80-05-7 [1]. It is produced synthetically by the reaction of phenol with acetone in the presence of a strongly acidic ion exchange resin as a catalyst. Bisphenol A is highly soluble in ethanol, acetic acid and diethyl ether, and less soluble in water [2].

Bisphenol A is an important ingredient in the production of polycarbonates, epoxy resins and polyester resins [3] as well as in the production of thermal printer paper [4]. Due to the high strength over a wide range of temperatures (–40–145°C) and hardness, resistance to acids, and transparency polycarbonates are extensively used in industry [5]. They are used, *inter alia*, in manufacturing products that come in contact with food (reusable bottles, including baby bottles, containers for beverages and foods) and toys for babies and children, as well as in the production of medical equipment, lenses for spectacles, packaging media, compact discs and window panels [3,6–8]. Epoxy resins are also used as coating for water pipes in houses and in the production of paints covering internal surfaces

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Corresponding author: K. Mikołajewska, Nofer Institute of Occupational Medicine, Department of Toxicology and Carcinogenesis, Laboratory of Environmental Biochemistry, św. Teresy 8, 91-348 Łódź, Poland (e-mail: kmikolaj@imp.lodz.pl).

of metal cans for food storage [3,9]. Bisphenol A derivatives are also components of dental sealants and composite resins that are increasingly being used in dentistry [10]. Widespread application of bisphenol A in plastic industry causes an increased demand for this chemical substance and, in consequence, may pose a risk to human health.

ROUTES OF EXPOSURE TO BPA

An increased exposure to BPA may be caused *inter alia* by environmental pollution (dust, air, drinking water, surface water, wastewater, leachate from landfills) [3,11–17]. Bisphenol A may enter the human body by ingestion, inhalation or dermal contact. However, it is believed that the main exposure of humans to BPA occurs by ingesting foods and drinks contaminated with bisphenol A from polycarbonate bottles and cans coated with epoxy resins [18–21]. Despite that, other sources of exposure to this compound may be equally important even from the standpoint of, for example, biological monitoring. Research on the routes of exposure to that compound has continued for many years now. However, opinions about the risks resulting from exposure to BPA are still being disputed and all sources of exposure to BPA have not been identified yet [21].

Dietary exposure

Bisphenol A is well absorbed by the oral route. Due to its properties, bisphenol A can be easily released from the polymer product, in which it is present, and migrate into the environment. The ester bond connecting the BPA molecules in polycarbonates or epoxy resins is hydrolyzed during heating or in acidic or alkaline medium [1]. As a result, free BPA is released and it migrates into the food, beverages and into the environment. In addition, migration is enhanced by repeated washing with detergents, rubbing and sterilization [22].

Nevertheless, no reports on exceeding the limit of migration (ML) or tolerable daily dietary intake (TDI) for this compound, also under extreme use conditions, are accessible in the literature [19,20,23–26].

Based on the studies conducted at multiple research centers worldwide, the tolerable daily intake *per os* of this compound has been set at 0.05 mg/kg body weight/day as a safe dose for humans [22,27].

In a study on food stored in cans coated with epoxy resin under conditions corresponding to the sterilization process (canning), significant amounts of BPA, 70–90 μg BPA per 1 kg of the medium were detected in the preserved foods or model (food-simulating) liquids [22].

Goodson et al. (2002) found that the average content of BPA in meat products was 110 μg BPA/kg of meat (17–380 μg/kg) [18]. Assuming that the average portion of meat per standard meal is about 170 g, the possible intake of BPA may be as high as 18.7 μg per meal. As to the currently tolerable daily intake of an average adult weighing 75 kg, BPA intake would be equal to 0.25 μg BPA/kg b.w./day, which is over 200 times less than the acceptable value. Thomson and Grounds (2005) [19], who studied foods marketed in New Zealand, found that concentrations of bisphenol A in fish ranged from < 20–109 μg/kg. In individual samples, bisphenol A concentrations reached 109 μg BPA/kg of tuna fish, while for beef meat the corresponding value was 98 μg BPA/kg of canned beef. In the drinks, BPA concentration was below 10 μg BPA/kg. The values obtained by those authors were below the limit of migration of BPA into food, determined for the European Union (EU) countries Specific Migration Limit (SML) = 3000 μg BPA/kg of food or model (food-simulating) liquid [22]. Based on the data from over 4300 adults in New Zealand, it has been estimated that, assuming the average body weight of ca. 75 kg, the average dietary exposure to BPA would be 0.008 μg BPA/kg b.w./day. The most severe exposure determined in the study was 0.29 μg/kg b.w./day [19], which was well below the TDI for BPA.

Brede et al. (2003) [20] evaluated BPA migration into model (food-simulant) liquids from the bottles intended

for infant feeding. The authors subjected the bottles to a variety of procedures, including: multiple washing, cooking and brush abrasion. After the bottles had been filled with water (100°C) and stored for 1 h, mean BPA concentration determined in the new bottles was 0.23 μg BPA/l of the liquid (range: 0.11–0.43–μg/l), while for the bottles subjected to 51 washing cycles in the dishwasher, the average concentration was 8.4 μg BPA/l (range: 3.7–17 μg BPA/l), while after 169 washing cycles the corresponding value was 6.7 μg BPA/l (range: 2.5–15 μg BPA/l).

The conditions under which the measurements had been taken were far from the true conditions [21], as baby foods should be prepared in water at a much lower temperature, so the estimated value of the BPA migration might be overrated.

Ehlert et al. (2008) [23] also did not show any significant migration of BPA to the water from feeding bottles in the triple cycle of microwave heating. The reported concentrations ranged from below 0.1 to 0.7 μg/l. Maragou et al. [24] after 12 bottle sterilization cycles noted decreased BPA migration to water (2.4–14.3 mg/kg). Exposure of infants to BPA that migrated from feeding bottles into the water or milk ranged from 0.2–2.2 mg/kg b.w./day.

Bisphenol A concentrations in soft drinks and foods stored in cans with epoxy coating also have been analyzed. The determined BPA concentrations did not exceed 7 μg BPA/l of liquid. However, the average concentration of BPA in canned foods was 40 μg BPA/kg. Based on that data, value of the migration level of BPA was estimated to be 10 μg/l and the upper level was estimated at 50 μg BPA/l, thus enabling assessment of the likely exposure to BPA depending on food intake. Significantly higher BPA levels, 100 μg/l, were determined for infants 0–6 months of age due to predominance of the liquid dairy products fed from plastic bottles capable of releasing significant amounts of bisphenol A [22].

There has been much research done on dietary exposure to BPA, depending on the age and the source of food intake [22]. According to data reported by EFSA [22], breast milk fed infants are at the lowest risk of the dietary exposure: 0.2 μg/kg b.w./day. In the 3-month-old infants fed milk from bottles made of polycarbonate plastic, the exposure is 4 μg/kg b.w./day for normal levels of migration, or 11 μg/kg b.w./day for the high levels of migration. Although these values are significantly lower than the currently valid safe dose, research on the safety of exposure to low doses of BPA in children continues. Bisphenol A exposure of 6–12-month-old infants varies depending on the type of food intake, particularly of milk and other beverages, including water, fruit juice and other foods stored in plastic containers, with the possible risk of exposure to 8.3 or 13 μg BPA/kg b.w./day, depending on the scenario of migration [22].

In addition, taking into account the highest level of BPA in model (food-simulating) liquids (5 μg BPA/kg), exposure from this particular source is low, ca. 0.3 μg of BPA/kg b.w./day [28].

The highest values of exposure to BPA have been determined among infants and young children due to their frequent contact with feeding bottles, toys and other items containing BPA. Under normal conditions, migration of bisphenol A from plastic bottles into the water or milk for infants is estimated to range from below 10 to 20 μg BPA/l of liquid [29].

As can be seen from the above data, exposure to this compound through a diet gradually declines with age, and in children aged 1.5 years it is 5.3 μg BPA/kg b.w./day [22,30], while in adults it is 1.45 μg BPA/kg b.w./day, after taking into account all the factors that may affect these values (such as body weight, the amount of food eaten and beverages drunk and the levels of BPA due to migration of this compound to beverages and foods) [22].

Exposure to BPA at all ages, both in children and adults, is well below the value of the maximum safe dose, so basically the intake of BPA from food in such small quantities is not likely to pose a risk to human health. However,

risk assessment should also take into account other routes of exposure. Data on the toxicological reference values and dietary exposure to BPA are summarized in Tables 1–4.

Environmental exposure

Dust and air

Bisphenol A may be present in the dust [3]. It is believed that dust may be important in the case of exposure of children, who are playing on the floor and frequently happen to put their hands into their mouth [31]. However, because of the low vapor pressure of bisphenol A (5.3×10^{-9} kPa at 25°C), inhalation exposure to this compound is likely to be a small part of the overall exposure to BPA [32].

Current tolerable values for daily soil/dust ingestion for children differ, depending on age. Table 5 shows the central tendency and the high end recommendations for tolerable daily ingestion (in mg/day) of soil, dust or soil + dust for children, and also for adults [33,34].

Assuming complete BPA absorption by the lungs, the estimated daily exposure to BPA is 0.008–0.014 μg/person/day, while the daily exposure to BPA by eating foods contaminated with BPA is 1.7–2.7 μg/person/day [7], so the inhalation exposure is about 200 times lower than the dietary BPA intake with food.

According to Geens et al. (2009) [12], the average intake of BPA by an adult human is 0.4 ng BPA/kg b.w./day.

Table 1. Reference values of bisphenol A (BPA) determined from research results

Parameter	Tolerable value of BPA	Reference
Tolerable Daily Intake (safe dose for humans)	0.05 mg/kg b.w./day (50 μg/kg b.w./day)	27
Specific Migration Limit for European Union	3 000 μg/kg food	22
Concentrations of BPA migration to foods and beverages	10 μg/l	22
	50 μg/l (high concentration)	22
Concentrations of BPA migration for 6-month infants	100 μg/l	22

Table 2. Concentrations of bisphenol A (BPA) determined in different matrices

Matrice	Concentration of BPA	Reference
Canned foods	40 μg/kg (70–90 μg/kg food or simulants)	22
Canned beverages	< 7 μg/l simulants	22
Meat products	110 μg/kg meat (17–380 μg/kg meat)	18
Beef	98 μg/kg	19
Fish	< 20–109 μg/kg	19
Beverages	< 10 μg/kg	19
Migration to water from plastic bottles for infants	< 10–20 μg/l	28
Migration to water from plastic bottles for infants (water 100°C)	0.23 μg/l (0.11–0.43 μg/l)	20
Migration to water from plastic bottles for infants after multiple washing in the dishwasher	2.5–17 μg/l	20
Migration to water from plastic bottles for infants after heating in microwave oven	< 0.1–0.7 μg/l	23
Migration to water from plastic bottles for infants after sterilization	2 400–14 300 μg/kg	24

Table 2. Concentrations of bisphenol A (BPA) determined in different matrices – cont.

Matrice	Concentration of BPA	Reference
Dust	< 0.5–10 200 μg/kg	36
	553 μg/kg dust (117–1 486 μg/kg dust)	11
	1 460 μg/kg dust (535–9 730 μg/kg dust)	12
	820 μg/kg dust	37
	6 530 ng/g (4 865–8 380 μg/kg) in offices	12
Air	0.734 ng/m^3 (0.1–1.8 ng/m^3) (inside)	13
	< 0.1–2.5 ng/m^3 (outside)	13
	0.004–17.4 ng/m^3	15
	4.55 ng/m^3 (0.2–17.4 ng/m^3)	15
	1.04–4.51 ng/m^3	13
Drinking water	0.0011 μg/l (0.0005–0.002 μg/l)	16
River water	0.0047 μg/l (0.0005–0.014 μg/l)	16
Industrial and municipal wastewater, leachate from landfill	0.016 μg/l	16
	41 μg/l (28–72 μg/l)	17
	18 μg/l (2.5–50 μg/l)	17
	21 μg/l (10–37 μg/l)	17
	n.d.–5.8 μg/l	
	< LOD–2.5 μg/l	17
Paper	40 μg/kg paper	51
	550–24 100 μg/kg	51
	190–26 000 μg/kg	49
	0.05–1 810 μg/kg	50

n.d. – non–detectable; LOD – limit of detection.

Table 3. Bisphenol A (BPA) intake by adults from different sources

Source of intake	Daily intake of BPA for adults	Reference
General intake	0.0004 μg/kg b.w./day	12
General exposure to BPA from different sources	0.008–1.5 μg/kg b.w./day	12, 35
Dietary exposure (Canned food and beverages)	0.008 μg/b.w./day	19
	max 0.29 μg/kg/day	19
	0.57–6.9 μg/day	19
	1.7–2.7 μg/person/day	7
	1.45 μg/kg b.w./day	22
	1.56–10.453 μg/day	40
Daily exposure to BPA through inhalation	0.008–0.014 μg/person/day	7

Table 3. Bisphenol A (BPA) intake by adults from different sources – cont.

Source of intake	Daily intake of BPA for adults	Reference
Dust	0.029–0.244 μg/day	12
	0.0084–0.109 μg/day	36
Dental	0.215 μg/day	40
Exposure to BPA from thermal paper / other than thermal paper	71 μg/day (exposure by 10 h/day)	4
	0.017–0.541 μg/day (general population)	53
	1.303–40.59 μg/day (occupationally exposed)	53
	0.0001 μg/day (other paper)	53
	0.0001–1.41 ng/day (paper currencies)	54
	0.0007–14.1 ng/day (paper currencies – occupational)	54

Table 4. Bisphenol A (BPA) consumption by children from different sources

Source	Daily intake of BPA for children	Reference
Dietary exposure	1.088–4.992 μg/day	40
	1.7–2.7 μg/day	14
General exposure to BPA of infants fed from plastic bottles	0.2–2.2 μg/kg b.w./day	24
Exposure to BPA of infants fed breast milk	0.2 μg/kg b.w./day	22
Exposure to BPA of 3-month infants fed from polycarbonate bottles	4 μg/kg b.w./day (according to its normal concentration of migration)	22
	11 μg/kg b.w./day (according to high concentration of migration)	22
Exposure of 6–12-month infants to BPA, depending on food intake	8.3 μg/kg b.w./day (according to its normal concentration of migration)	22
	13 μg/kg b.w./day (according to high concentration of migration)	22
Exposure of 1.5 year old children to BPA, depending on intake of commercially available foods and beverages	5.3 μg/kg b.w./day	30
Exposure to BPA from different sources	0.043–14.7 μg/kg b.w./day	12, 35
Dental materials	0.215 μg/day	40
Inhalation of airborne dust	0.0078–0.014 μg/day	14
Dust	0.042–0.435 μg/day	36
	0.073–0.975 μg/day	12

Exposure to BPA from other sources is 0.008–1.5 μg/kg b.w./day for adult person and 0.043–14.7 μg/kg b.w./day for 1.5–6-year-old children, in whom the value of exposure to dust is negligibly low (Table 3,4) [12,35].

Widespread use of BPA in household products (carpeted floor, boards, adhesives, paints, electric devices, etc.) [36], has increased the interest in the dust as a matrix to study BPA content.

Table 5. Values of admissible daily intake of bisphenol A (BPA) with soil, dust, and soil+dust [33,34]

Exposure factor	BPA intake (mg/day)				
	children/teenagers				adults[a]
	6 weeks < 1 year[a]	1 < 6 year[a]	3 < 6 year[b]	6 < 21 year[a]	
Soil	30	50	200	50	20
Dust	30	60	100	60	30
Soil+dust	60	100	200	100	50

General population: [a] central tendency; [b] upper percentile.

Völkel et al. (2008) [11] detected BPA in dust house samples (N = 474) at concentrations from 117 to 1486 μg/kg dust (median (Me): 553 μg/kg dust; mean (M): 661 μg/kg dust).

Similar concentrations of BPA in house dust samples (USA, Massachusetts) were recorded by Rudel et al. (2003) [37]. The average concentration was 820 μg/kg dust, but the analysis was carried out in 118 samples.

In turn, higher concentrations of bisphenol A in dust collected from 18 houses and 2 offices in Belgium were reported by Geens et al. (2009) [12]. BPA determined in house dust samples was at higher concentrations than the concentrations observed by Völkel et al. [11] in 2008 and Rudel et al. [37] in 2003. Bisphenol A concentrations ranged from 535 to 9730 ng/g (Me: 1460 ng/g dust), whereas in the 2 samples of office dust they were 4.5 times higher – 6530 ng/g dust (4865–8380 ng/g) [12].

In 56 dust samples, Loganathan and Kannan (2011) [36] detected BPA at concentrations from < 0.5 to 10 200 ng/g (Me: 843 ng/g; M: 422 ng/g). In 44 samples of dust collected in houses from 2 other localizations in 2006 and 2010, the concentrations ranged < 0.5–2320 ng/g.

Wilson et al. (2001) [13] studied the content of BPA in the indoor air of the daily care facilities in North Carolina, USA. The concentrations determined there were from < 0.1 to 1.8 ng/m^3 (0.734 ng/m^3) in the air inside the premises and comparable concentrations of BPA, < 0.1–2.5 ng/m^3, were assayed in the air outside the facilities. Simultaneously, concentrations in floor dust samples were a bit higher (1.04–4.51 ng/m^3), however, the differences in concentrations were not significant, probably due to a small number of the study samples.

In urban areas of India, Japan, China and New Zealand, Fu and Kawamura (2010) [15] detected much higher concentrations of BPA in the air, from 0.004 to 17.4 ng/m^3, i.e., much higher than those reported by Wilson et al. (2001) [13]. BPA concentrations in rural areas of China were 0.030–0.240 ng/m^3 (N = 5). The highest level of average BPA concentration in the air – 4.550 ng/m^3 (0.2–17.4 ng/m^3; N = 49) – was reported in India (Cennai, India, 2007) [15].

Wilson et al. (2007) [14] examined environment of 257 children at the age of 1.5–5 years, in randomly selected households and care facilities in North Carolina and Ohio, USA. They studied BPA concentrations in environmental samples (soil, indoor and outdoor air, house dust) and personal samples, inter alia hand wipes. Wilson et al., also analyzed solid and liquid foods, and drinking water. Moreover, BPA was detected in children's liquid and solid food samples, in below 70% and over 80% of the samples, respectively. In addition, BPA was detected in over 50% of the samples of food preparation surface wipes, hard floor surface wipes, indoor air and transferable residue samples. They found BPA almost in all the samples from hand wipes of children [14].

Despite low volatility of BPA, BPA may be released into the atmosphere from industrial sources [6] or by uncontrolled

burning of household waste, plastics or electronic products [15,38,39]. Those sources do not seem to be of any significant consequence to the environmental exposure of the population [40]. Inhalation of BPA may be significant only in the case of occupational exposure, but the influence of the dietary intake of BPA with dust has not been completely explained yet [12].

Conclusions from these studies suggest that the dust and air dust are not the main sources of exposure to BPA, despite the fact, that the release of BPA from these sources is quite high. However, these values are not greater than the estimated ones, both for children and adults.

Water

Bisphenol A is often found in water at concentrations of the order of a few ppm (1 ppm corresponds to 998.859 μg/l). Analytical procedures for the determination of BPA in water are rather difficult, therefore, in order to assess the risk of human exposure to BPA from this particular source, the method of determination of BPA in water must be accurate and sensitive [41]. Literature data point to high occurrence of this compound in water and its release to the environment [42]. It is important to know how much BPA is present in the environment in order to be able to assess the risk from it as the endocrine disruptor [43].

Bisphenol A is one of the most frequently detected endocrine disruptors in the environment [44]. Bisphenol A, and also other endocrine disruptors, are not completely eliminated from the effluents during their processing in the wastewater treatment plants. Moreover, bisphenol A may be released to the environment from BPA-contaminated waste buried in soil. Bisphenol A may be also released from the soil and contaminate ground water [16].

Kuch and Ballschmiter (2001) [16] tested samples collected from wastewater treatment plant, surface waters (river, lake) and drinking water in South Germany. Bisphenol A was detected in all the tested samples of drinking water, with the mean value of 1.1 ng/l (range: 0.5–2 ng/l). In the river water the concentration of BPA was 4.7 ng/l (range: 0.5–14 ng/l), whereas the waste water contained 16 ng/l (4.8–47 ng/l) of BPA.

The highest concentration of BPA, 28–72 μg/l (M: 41 μg/l, N = 4), was observed by Fürhaker et al. (2000) [17] in the samples of waste collected from a paper manufacturing plant. Samples of waste from chemical industry contained 18 μg/l (range: 2.5–50 μg/l, N = 4); BPA content of household and municipal influent was 21 μg/l (range: 10–37 μg/l, N = 7). Bisphenol A concentrations in the wastewater treatment plant effluent ranged from non-detectable (n.d.) to 2.5 μg/l (household, food industry, hospital, washing and cleaning up company).

Daily intake of bisphenol A with drinking water may be negligibly low compared to the consumption with beverages and food products in contact with BPA-containing wrappings [16]. However, a reliable assessment of exposure to BPA should also take into account sources other than the dietary intake.

Other sources of exposure

Dental materials

Other source of BPA, which may influence the risk of exposure includes dental materials. It is likely that bisphenol A, as a pollutant formed during the synthesis of dental fillings, can be released to the human saliva through enzymatic hydrolysis by esterases found in saliva [10,45,46].

Fung et al. (2000) [45] observed that BPA is detected in saliva 1 h after filling the defect, and becomes non-detectable after 3 h, whereas in serum it is not detectable after 24 h. In saliva, the concentration of BPA ranged from 5.8 to 105.6 ppb. This is 250 times lower than in the studies carried out by Olea et al. (1996) [43], where the concentrations in saliva ranged from 3.3 to 30.0 ppm [43,45]. These differences could be due to different quantities of dental sealant used to fill the defect (50 mg – Olea et al., and 8 or 32 mg – Fung et al.). Fung et al. [45] showed that max 8 mg sealant can be placed on the occlusal surface

of a molar tooth without significantly affecting the occlusion. Those authors report that BPA may be absorbed orally, but blood BPA levels are below the detection limit. What is more, they did not observe adverse health effects. This data show that BPA is not absorbed chronically into the system, and systemic BPA accumulation is not likely. Still, BPA intake from a dental sealant is much lower than the dose of BPA from the dietary intake.

Arenholt-Bindslev et al. (1999) [47] analyzed saliva collected at 3 stages: immediately after filling, 1 h and 24 h after placement of a dental sealant. Average fill weight was 38±3 mg. Bisphenol A concentration determined in the test samples immediately after placement of the sealant was 1.43 ppm (0.3–2.8 ppm), whereas after 1 h and after 24 h the concentrations of BPA in saliva were ≤ 0.1 ppm (below the limit of detection). An estrogenic activity was observed in saliva samples only immediately after placement of the dental sealant, and it was significantly different ($p < 0.05$) from the concentration in saliva control samples (morning saliva on fasting).

Olea-Serrano et al. (1999) [48] observed slightly higher amounts of BPA (90–865 μg) in saliva collected after 1 h from applying the sealant (50 mg). Samples containing the highest amounts of BPA showed estrogenic activity in the proliferation assay.

These values provide useful data for the assessment of risk to people, even if there were no adverse health effects resulting from exposure to BPA from this source.

Paper

Although not much has been reported about dermal exposure to BPA, the exposure does occur, especially through dermal contact with products containing BPA (e.g., thermal printer paper) [4]. However, dermal exposure is considered to be negligible, since the skin penetration of BPA is below 10% [32]. It is relevant only in the context of occupational exposure, e.g., during production, treatment and processing of BPA, and also direct dermal contact with BPA found on the surface of thermal paper. Receipts, faxes, prints from cash machines are printed this way.

People who are particularly exposed include those who have frequent contact with thermal paper, for at least 10 h daily. In such instances, the possible exposure to BPA in cash register attendants may reach the value of 71 μg/day (which is 42 times less than the current tolerable daily intake (TDI), assuming that body weight is 60 kg). Research has shown that exposure to BPA through contact of the thermal paper with dry skin is about 10 times lower than in the case of wet or greasy hands. That is when the greatest quantity of BPA adheres to the surface of the skin. However, about 90% of BPA can be removed from the skin by washing with water. After 2 h following the transfer of BPA to the skin of the fingers, as much as 73% of the compound can be removed from the surface of the skin. This means that a portion of BPA can penetrate into the deeper layers of the skin, and that portion is difficult to wash off with water [4]. The above data show that pregnant women working with cash registers may be at risk of exposure to BPA.

Ozaki et al. (2004) [49] observed higher concentrations of BPA in the recycled paper (0.034–0.36 mg/kg) than in the virgin materials (0.19–26 mg/kg).

Lopez-Espinosa et al. (2007) [50] analyzed paper containers for storing take away foods in terms of content of hormonally active chemicals, e.g., BPA. In the food packaging materials they determined concentrations of BPA from 0.00005 to 1.81 mg/kg paper. Whereas Vinggaard et al. (2000) [51] determined higher concentrations of BPA than Lopez-Espinosa et al. (2007) [50] in extracts of virgin paper ranging 0.03–0.1 mg/kg and 0.6–24.1 mg/kg in recycled paper (kitchen rolls) [50,51].

Some cigarette filters may contain up to 25% of BPA, and may be an important source of exposure to this compound, especially in pregnant female smokers [52].

Exposure to BPA from other sources is significantly lower than its dietary intake, and does not exceed the safe limits.

Total exposure to BPA may be the sum of exposure from all the sources, and may depend on age, gender as well as other factors. Health effects of the exposure have not been completely explained, therefore, exposure to BPA from the known sources should be limited, especially in infants, children and pregnant women. Determination of exposure from all the sources may be essential, if only to exclude contaminants and facilitate reliable assessment of dietary exposure.

ABSORPTION AND DISTRIBUTION

Research published in 2002 shows that when bisphenol A enters the body *per os*, it is rapidly absorbed in the gastrointestinal tract and is metabolized in the liver and the intestine [55,56].

Most of the ingested BPA is excreted with the urine in a form of inactive metabolites of BPA (bisphenol A glucuronide [7] and bisphenol A sulfate [22,56]) within about 6 h ($t_{1/2}$ = 5.4 h), and BPA is almost completely eliminated within 24 h [7,22,55,56]. Total (free plus conjugated) BPA concentration is often used to assess exposure level to all the sources of BPA [57].

Because BPA is quickly excreted from the body, concentrations detected in human urine and blood may indicate a greater intake of this compound with drinks and food than it is presumed [58].

In adults, based on the study, the estimated daily removal of bisphenol A with urine was 1.2 μg/day (0.21–14 μg/day). This corresponds to 0.02 μg BPA/kg/day (< 0.003–0.23 μg BPA/kg/day). Urinary BPA excretion in healthy adults between consecutive days (N = 5) varied from < 0.58 to 13 μg/day (M = 1.3 μg/day) [59].

Because BPA is well absorbed into the body by ingestion, pregnant women, infants and young children are particularly vulnerable to BPA. The risk of adverse health effects in children may be due to the increased absorption or decreased excretion of BPA from the body [60], and also due to several factors, such as e.g., body weight, metabolic rate, but also a diet appropriate to the age (eating foods contaminated with BPA), or contact with BPA from dust by playing on the floor. Furthermore, children often take different objects into their mouth. The most vulnerable group appears to be the population of neonates and infants up to 6 months of age [60], because neonates and infants up to 6 months are characterized by a reduced glucuronidation activity, whereas older children have a mechanism similar to adults [61–63].

Pregnant women are not directly at risk of adverse BPA activity, because their metabolic ability is not impaired [60]. Whereas, it is believed that the fetus is at a real risk of exposure [60,64].

Despite this, it is believed that exposure of the fetus depends on the concentration of BPA in the blood of the mother, because the human placenta does not metabolize BPA and consequently fetal should be protected from adverse effect of BPA by maternal metabolism [60]. Nevertheless, there are reports in which children of the mothers exposed to BPA had significantly higher levels of BPA than the children of mothers who were not exposed, indicating that pregnant women should avoid exposure to this compound. Balakrishnan et al. (2010) [64] observed, that insignificant amount of BPA can cross the placenta even in low concentrations, especially at a constant exposure to BPA. They also showed, that there is a real risk in the case of free BPA.

BIOMONITORING

The aim of biomonitoring is to provide reliable results of determinations of exposure to BPA from various sources [65]. To assess the daily dose using the results of monitoring, it is essential to have suitable knowledge about the sources of pollution, possible routes of exposure, as well as knowledge of the toxicokinetics [7,66]. Urine or blood are typically used to assess exposure to BPA [9,67]. However, urine is predominantly used for the analysis of BPA, because urine sampling is non-invasive and sample volumes are often large [57].

Concentrations of BPA in blood are lower than in urine. Additionally, concentrations of BPA in blood rapidly decrease after exposure, hence, urine is a better matrix for this purpose [68]. Blood samples are useful for studies of stable compounds but are also important in the analysis of metabolism and elimination of the compounds that are not stable. In turn, for practical reasons, urine samples are collected once a day, and because half-life of BPA is short, the concentrations contained in the urine reflect only the exposure which occurred shortly before urine collection [67].

Many potential problems associated with the analysis of BPA in biological samples have been identified. Due to the ubiquity of BPA in the environment, the main difficulty is posed by the complexity of the analytical matrix, which can cause interference with the signal of the analyte, low concentrations of analytes, complicated sample preparation procedures, low stability of the analytes and sample contamination.

Biological samples should be frozen as quickly as possible because BPA metabolites in the urine samples at room temperature are spontaneously hydrolyzed to the parent BPA, even when the storage or processing time is relatively short [69,70]. Moreover, contamination of samples by the bisphenol A from the environment can cause false positive results, especially at low concentrations. Such interferences are a problem in interpreting the results of BPA concentrations in biological matrices.

When evaluating results of the monitoring, it is important to exclude contamination from the materials used for collection, storage of the samples, as well as from solvents, reagents, and materials used for the preparation and analysis of the samples [11,16,56,71,72]. A number of different BPA determination methods that prevent contamination of a sample have been developed [73]. Also, specific solvent purification procedures were used and plastic laboratory dishes, pipettes, syringes were replaced by those made of glass in most of sample processing steps [71].

Many scientists worldwide continue research on human exposure to BPA [3,11,57,74–76].

Data from the accessible literature show that current levels of urinary and plasma BPA concentrations are often close to the limit of quantification (LOQ). Most of the analyzed samples contained total BPA at levels of < 10 ng/ml [74,75,77]. In maternal blood, concentrations of free BPA were up to 22.3 ng/ml (range: 0.5–22.3 ng/ml) [78] and 0.3–18.9 ng/ml in maternal plasma, and 0.2–9.2 ng/ml in fetal plasma [73], whereas high concentrations of BPA were observed in neonates (geometric mean: 30.3 ng/ml; range 1.6 – 946 ng/ml) [79].

Until 2008, BPA in urine was determined in a small number of samples. Concentrations of BPA determined in 11 urine samples by Tsukioka et al. (2004) [81] ranged from 0.01 to 0.27 μg/l. However, Fukata et al. (2006) [80] who analyzed 52 urine samples, detected free BPA at 0.24 μg/l and 0.35 μg/l only in 2 of the samples [80,81].

In Europe, Völkel et al. (2008) [11] conducted an analysis of 474 urine samples that were collected in 2005–2008. Those included 315 archival samples and a total of 159 samples collected from children aged 5–6 years and 18 samples from 52-year-old co-workers of the authors. Of the 315 archival samples, free BPA was detected only in 22 samples at concentrations below 2.5 μg/l (which is about 800 times less than the TDI). Most of the samples did not contain detectable concentrations of free BPA. Thus, it is reasonable to assume that BPA exposure is not likely to be a potential risk for adults.

Similarly, there were no children who exceeded the TDI, even in the worst case scenarios [11]. The study involved 474 participants. Free BPA was detected in 287 of those participants at concentrations ranging from below the detection limit (LOD) of 0.3 ng/ml to 2.5 ng/ml. In order to check potential sources of contamination of the samples, household dust was collected from the people who did not provide their urine samples, and the determined average concentration of BPA was 553 μg/kg dust (117–1486 μg/kg dust) [11].

In Germany, Völkel et al. (2011) [82] analyzed urine samples collected from 47 infants aged 1–5 months. The infants were hospitalized because of low birth weight. Total BPA was determined in 38 samples of urine at concentrations ranging from below the limit of detection (LOD) to 17.85 ng/ml. The mean determined concentration was below the limit of quantification (LOQ) of 0.45 ng/ml. Concentration of BPA 17.85 ng/ml was determined only in 1 urine sample collected from a 4-month-old infant. Free BPA concentrations above the LOQ were determined only in 3 urine samples. Given the tolerable daily intake (TDI) dose of 50 μg/kg, the highest determined concentration was well below the TDI.

Babies at an early age are able to convert BPA to the corresponding metabolites [82,83]. Völkel et al. (2011) [82] reported that the conversion to BPA biologically inert metabolites (glucuronide or sulphate) takes place both in adults and infants, because a higher level of total BPA is observed relative to the free BPA. Data show that higher concentrations of total BPA could be caused by exposure to medical materials, since they were not tested for their BPA content [79].

By contrast, it was found that the median urinary concentrations of BPA among the infants (28.6 μg/l) were about one order of magnitude higher than the median concentration (3.7 μg/l) and almost twice the 95th percentile concentration (16 μg/l) among 6–11-year-old children who were examined as part of the NHANES 2003–2004 study [75,79]. These data suggest that exposure to BPA among the infants in this study was much higher than in general population and that > 90% of the BPA excreted with the urine was in its conjugated (e.g., glucuronide, sulfate) form [79].

In turn, Casas et al. (2013) [84] analyzed a cohort of pregnant women (N = 479, samples were collected in the 1st and the 3rd trimesters of pregnancy) and their children (N = 130) from birth to 4 years of age. Bisphenol A was detected in almost all the samples of urine of pregnant women and children, except for 3 samples collected in the 3rd trimester of pregnancy, in which the BPA concentration was below the LOD. It has been shown that the creatinine-adjusted concentration of BPA was greater in the first than in the 3rd trimester ($p = 0.02$), and that the highest mean concentration of BPA was recorded in children. In women, the maximum concentration was 122.8 μg/g creatinine, i.e., over 3.5 times higher, compared to the highest concentration indicated in children, which was 33.3 μg/g creatinine.

Among children and adolescents aged 6–21, Frederiksen et al. (2013) [85] examined 129 participants of the "Copenhagen puberty study from 2006 to 2008." The average concentration of BPA determined in the urine was 1.37 ng/ml. Children aged 6–10 had significantly higher concentrations of BPA in the urine (< 3 ng/ml) ($p < 0.001$). Similarly, among younger children, relatively higher daily rates of excretion of BPA (< 70 ng/kg b.w./24 h) were observed than in older children and 17–21-year-old adolescents, < 1 ng/ml and < 30 ng/kg b.w./24 h, respectively.

Zhang et al. (2013) [86] studied children (1–5-years-old: N = 10) and women (pregnant: N = 30, and non-pregnant: N = 10), and fetuses (N = 30) from whom blood samples were collected. The highest concentration of BPA in blood was determined in children (2.60 ng/ml, M ± standard deviation (SD) = 3.18±1.16 ng/ml, range: 1.20–8.76 ng/ml). Slightly lower concentration was observed in pregnant women (0.60 ng/ml, M±SD = 3.58±4.25 ng/ml, range: < 0.10–29.0 ng/ml), adults (0.11 ng/ml, M±SD = 0.20±0.18 ng/ml, range: < 0.10–2.27 ng/ml), fetal cord blood (0.08 ng/ml, M±SD = 0.13±0.12 ng/ml, range: < 0.10–0.79 ng/ml). The lowest concentration of BPA was observed in fetuses [86].

Probably fluids given by a drip may also provide BPA to the blood of pregnant women. It is a matter of concern that the concentrations of BPA in the blood of children were significantly higher than in the adult women. The study includes too few samples, so it can be considered rather as a pilot study in systemic exposure to BPA in children

and pregnant women [86]. Furthermore, concentrations in the blood can vary over time, so it can be unreliable [87].

TOXIC EFFECTS OF BPA IN HUMANS

Health effects in pregnant women

Miscarriages

Little it is known about the effects of high exposure to BPA on recurrent miscarriage and immunoendocrinological disorders. Authors of the Nagoya City 2001–2002 study investigated women (N = 45) with a history of miscarriages from 3 to 11, in the 1st trimester of pregnancy. Serum bisphenol A levels were analyzed, and additional tests were performed, *inter alia*, tests for hyperprolactinemia, hypothyroidism, diabetes, hysterosalpingography, immunoassays (antinuclear antibodies (ANA), natural killer (NK) cell activity, antiphospholipid antibodies (APL), and chromosome analysis for both partners. The mean concentrations of BPA in the blood of the patients were 2.59±5.23 ng/ml, while in the women from the control group (N = 32) the mean concentration of BPA was 0.77±0.38 ng/ml.

The ANA-positive patients had significantly higher concentrations of bisphenol A than the ANA-negative patients (p = 0.025). During the study, in 17 patients who miscarried for the 2nd time, BPA concentrations were 4.39±8.08 ng/ml (M±SD; median (Me): 0.71 ng/ml (range: 0.28–29.43 ng/ml). The trend was higher, but not significant compared to the patients whose pregnancy was successful (M±SD = 1.22±1.07 ng/ml, Me = 0.91 ng/ml, range: 0.22–3.85 ng/ml). High exposure may be associated with recurrent pregnancy loss, particularly in the ANA-positive patients [88]. However, this is the only study that focused on the effect of BPA on human miscarriages. Besides, the number of subjects was small.

Premature deliveries

Similarly, there are very limited data on the relationship between BPA exposure and premature births. There is one report of a possible impact of BPA. For this purpose, Padmanabhan et al. (2008) [78] measured the BPA concentrations in 40 pregnant women. However, no differences were found in the duration of pregnancy and birth weight of children compared to BPA concentration in the mothers.

Cantonwine et al. (2010) [89] measured concentrations of BPA in the urine samples collected in the last trimester of pregnancy from a small group of Mexican women. Bisphenol A was detected in 80% of the women at concentrations from below 0.4 ng/ml to 6.7 ng/ml (geometric mean (GM): 1.52 ng/ml, N = 48). This study showed initially that the women who delivered before the 37th week of gestation had a higher concentration of BPA in the urine (GM: 1.84±1.86 μg/l) than the women who delivered after the 37th week of pregnancy (GM: 0.97±0.92 μg/l) (p = 0.01) [89]. Exposure of pregnant women to BPA can affect the frequency of premature deliveries, but the number of relevant reports is too small to unequivocally validate this relationship.

Calafat et al. (2009) [79] studied 42 infants from the Neonatal Intensive Care Units (NICU) of 2 hospitals (institutions A and B) in Boston (Massachusetts). The subjects of this study were low-birth weight infants having corrected gestational age (< 44 weeks – gestational age at birth plus age after birth), staying 3 consecutive days under neonatal intensive care unit (NICU) care (indwelling catheterization, enteral feedings, parenteral nutrition, ventilation) and diagnosed with developmental and metabolic abnormalities and congenital anomalies. Infants with impaired "hepatic enzyme function or structural integrity (e.g., biliary atresia)" were excluded from the study. The BPA urine concentration was determined in all the samples collected from the infants. The average concentration was 30.3 μg/l (range: 1.6–946 μg/l).

Baby care products containing di(2-ethylhexyl) phthalate (DEHP), could cause increase in the concentration of total BPA. Di(2-ethylhexyl) phthalate is also added

to poly(vinyl chloride) (PVC) as a plasticizer, for example to medical materials. The infants briefly exposed to this products had concentration of BPA over 8.5 times lower than the infants who were exposed with high intensity to the products containing DEHP (95% CI: 3.36–22.8, $p < 0.0001$). However, exposure of infants to BPA through baby care products has not been confirmed [79].

Moreover, in assessing the adverse effects of BPA on gestation length, also other factors that may affect premature delivery should be taken into account.

Children's development

Birth weight

Exposure of pregnant women may affect fetal development. As reported by Miao et al. (2011) [90] birth weight was significantly lower in the children of mothers exposed to BPA than those of the not exposed mothers. The same is true for the children whose fathers were exposed, compared to the children of not exposed fathers. However, the difference was not significant. The authors conducted a study on the impact of BPA on the birth weight of children whose parents, during pregnancy, were exposed to BPA in the workplace. It was observed that exposure to BPA in the workplace was associated with a decreased birth weight of neonates. The progeny of fathers exposed to BPA had birth weight which was by 90.75 g lower than the average weight – 3308.60±539.91 g ($p = 0.10$), and the progeny of mothers exposed during pregnancy had birth weight lower by 168.40 g (M±SD: 3299.40±428 g) ($p = 0.02$), compared to the not exposed group, in which the average birth weight of the newborns was 3398.74±523.61 g [90].

Chou et al. (2011) [91], observed a similar relationship. They examined blood samples from mothers and umbilical cord blood. Bisphenol A concentrations determined in the blood of pregnant women were 0.3–29.4 ng/ml (N = 97, M: 5.4±6.3 ng/ml) and in the cord blood the concentrations were < 1 ng/ml (for N = 97 mean value was (M±SD) 1.1±2.20 ng/ml). It was observed that the infants (N = 62/97) born in the group of mothers with high concentrations of BPA (BPA level: 11.7±6.4 ng/ml) had lower birth weight (3067.9±356.4 g) ($p = 0.13$) and lower BPA level (0.5±0.6 ng/ml), than the infants (N = 35/97) from the group of mothers with lower levels of BPA (BPA low level: 2.1±1.6 ng/ml) whose children had 1.4±2.9 ng BPA/ml and birth weight – 3212.9±241.2 g ($p = 0.13$) [91].

In turn, Phillippat et al. (2012) [92] observed a rather opposite effect, i.e. an increase in the birth weight. In the second BPA concentration tertile (2.2–4.7 μg/l) they observed that the birth weight was increased by 169 g (95% CI: 14–324), whereas in the 3rd tertile (≥ 4.7 μg/l BPA concentration tertile) the increase in the birth weight was 85 g (95% CI: –62–233). A similar relationship was observed in measurements of head circumference.

Lee et al. (2013) [93] also showed effect of BPA exposure on fetal development. The authors studied the effects of prenatal exposure to BPA on birth weight, birth length vs. gender and the length of pregnancy, and observed a statistically significant relationship. Bisphenol A was detected in pregnant women's urine with GM concentration equal to 1.29 μg/l (1.87 μg/g creatinine). At the same time, average birth weight was 3287 g. A positive association was found to occur between the urinary maternal BPA levels and birth weight. Compared to the 1st tertile ($p = 0.04$), in the 2nd tertile of maternal bisphenol A level, the birth weight was significantly increased (after taking account of pre-pregnancy body mass index, maternal age, gestational age, infant gender). A significant relationship between the birth body length and BPA level was found only in male neonates ($p = 0.01$). However, Padmanabhan et al. (2008) [78] observed no statistically significant correlation between the concentration of BPA in the blood (5.9±0.94, range: 0.5–22.3 ng/ml) of mothers (N = 40, Michigan, USA) and birth weight in children (3.3±0.1 kg, range: 1.3–4.2 kg) or gestational length (38.6±0.3, range: 31.0–42.1 weeks).

Since findings from these studies suggest different data, exposure of pregnant women to BPA, especially in the workplace, should be limited.

Obesity

Cardiovascular disease in adulthood may be caused by obesity in childhood. There are reports in the literature about the problem of obesity in conjunction with BPA exposure in adults, but only few studies are accessible on BPA-related obesity in children [94].

Exposure to BPA during pregnancy can have an impact on obesity and the rapid body mass increase in children in the first 6 months of life. This relationship was examined by Valvi et al. (2013) [95]. Samples of urine were collected from pregnant women in the 1st and the 3rd trimesters of pregnancy (N = 402). In children, a sharp increase was observed within 6 months. Overweight was observed in 25% of the children aged 14 months and 21% of the children aged 4 years. The geometric mean concentration of bisphenol A was 2.6 μg/g creatinine in the 1st trimester. Similarly, in the 3rd trimester of pregnancy, BPA concentration (GM) was 2 μg/g creatinine (0.2–102.6 μg/g creatinine). Bisphenol A concentrations without creatinine correction were at similar levels, 2.1 mg/l (0.1–122.8 mg/l) and 1.8 mg/l (< LOD–103.7 mg/l; LOD = 0.1 mg/l) during the 1st and the 3rd trimesters of pregnancy, respectively [96].

However, prenatal exposure was weakly associated with an increase in waist circumference and body mass index (BMI) in children aged 4 years, compared to the rapid weight gain and growth in the 1st 6 months of life or waist circumference, or an increase in BMI at the age of 14 months. This dependence was higher among women who smoked cigarettes during pregnancy [95].

Maserejian et al. (2012) [96], after 5-year follow-up of children aged 6–10 (NECAT) who were exposed to BPA released from dental fillings, also reported no BPA concentration-related change of BMI in children with composite fillings relative to children with amalgam fillings. Changes in body fat percentage or rate of growth in the children were not observed.

In 2013, Eng et al. (2013) [97] published a cross-sectional study on the effects of urinary BPA levels in relation to obesity in children (6–18 years). They measured biochemical parameters like insulin, level of glucose, cholesterol. In that study, the authors showed an increase in the odds of obesity (BMI > 95%) with increasing quartiles of BPA (quartiles 2 vs. 1 (odds ratio (OR) = 1.74, 95% CI: 1.17–2.60, p = 0.008), 3 vs. 1 (OR = 1.64, 95% CI: 1.09–2.47, p = 0.02), and 4 vs. 1 (OR = 2.01, 95% CI: 1.36–2.98, p = 0.001) [97].

In another report, Harley et al. (2013) [98] investigated whether concentration of BPA in urine had an impact on prenatal and postnatal waist circumference, percent body fat and obesity in children at the age of 9 years. Higher BPA concentrations determined in mothers during pregnancy were correlated with a decrease in BMI, body fat, overweight/obesity among daughters aged 9 years. In addition, the results of the study did not show a significant correlation between the concentration of BPA in samples from pregnant women, compared to any measure of the size of the body of 9-year-old boys and girls [98].

In the same project (CHAMACOS), Volberg et al. (2013) [99] analyzed whether prenatal or concurrent concentrations of BPA in urine were associated with key metabolism-related hormones, adiponectin and leptin (adipokines) in 9-year-old children. It was observed that the concentration of BPA in the urine samples, in late pregnancy (26.3±2.5 gestation week) was correlated with an increased leptin in plasma in boys (β = 0.06, p = 0.01). Furthermore, it was observed that the concentrations of BPA during early pregnancy (12.6±3.9 gestation week) were mainly correlated with plasma adiponectin levels in girls (β = 3.71, p = 0.03). In 9-year-old children, statistically significant correlations between concentrations of BPA and leptin or adiponectin were not observed.

The data, however, suggest that prenatal concentration of bisphenol A has small influence on adipokine levels in 9 year olds [99].

A statistically significant correlation between concentration of BPA in urine with obesity among children and adolescents was also noted by Trasande et al. (2012) [100]. Among the 2838 participants of the National Health and Nutrition Examination Survey (NHANES), 2003–2008, at the age of 6–19 years, the median concentration of BPA was 2.8 ng/ml (range: 1.5–5.6 ng/ml). When log-transformed BPA concentrations are compared with BMI scores and obesity, the differences are statistically significant [100].

Wolff et al. (2007) [101] found in their study that girls aged 6–8 years with a BMI ≥ 85 percentile had significantly lower concentrations of BPA in the urine (2.2 mg/g creatinine). In turn, in 2008, Wolff et al. [102] reported a positive association between BPA concentrations and BMI in pregnant women, but expressed in terms of mg/l. However, no such correlation was observed when urinary concentration was specified in terms of mg BPA/g creatinine.

Khalil et al. (2014) [103] found that higher concentrations of BPA in the urine collected from 39 obese and overweight children (3–8 years, Children's Medical Center of Dayton, Ohio) were associated with adverse metabolic effects, and also with elevated diastolic blood pressure levels.

Male genital abnormalities

Exposure to BPA during pregnancy has also an impact on male genital development. Miao et al. 2011b showed that exposure during pregnancy results in a shorter AGD in male offspring. This correlation was higher in pregnant mothers exposed to BPA ($p < 0.01$) [104].

Wheeze and asthma

Spanier et al. (2012) [105] evaluated the effects of prenatal exposure to BPA in children. Bisphenol A has been detected in the urine of almost all pregnant women (N = 398) of the cohort (99%). The study suggests a link between the average exposure of mothers to BPA during pregnancy (at 16 weeks) and the increase in respiratory disorders (wheeze) in the progeny at the age of 6 months. The test in the respiratory tract of children was repeated every 6 months for a period of 3 years. The results indicate that this correlation decreases along with the age of the child.

Donohue et al. (2013) [106] conducted a study on 568 pregnant women and children 3, 5 and 7 years old. They collected urine samples from women during pregnancy and from children, and additionally, a questionnaire survey on the prevalence of wheeze according to age was performed. The research shows that prenatal BPA concentration in urine is associated inversely with wheeze in 5-year-old children ($p = 0.02$). Concentrations of BPA in the urine of 3-year-old children are positively associated with wheeze at the age of 5 ($p = 0.02$) and 6 years ($p = 0.03$). Urinary BPA at the age of 7 years correlates with wheeze at the age of 7 years ($p = 0.04$).

Concentration of BPA in urine is also positively associated with asthma at the age of 3, 5 and 7 years ($p = 0.005$, $p = 0.03$, $p = 0.04$), respectively. The average concentration of BPA in the prenatal maternal urine was 1.8 ng/ml, in 3-year-old children it was 3.8 ng/ml, in 5 year olds it was equal to 3.1 ng/ml, and 2.7 ng/ml in 7-year-old children. Concentrations of BPA in the urine of pregnant mothers were not correlated with the concentrations of BPA in the urine of children after birth. In contrast, BPA in the urine of children aged 3 years was poorly correlated with the concentrations of BPA in 7 year olds. The concentrations of BPA in the urine at the age of 3, 5 and 7 years were associated with asthma in children aged 5–12 years. This suggests that environmental exposure to BPA may lead to respiratory complications [106]. These experiments indicate that there is a link between prenatal exposure to BPA and an increase in respiratory disorders in the offspring.

However, there is a need for further additional tests to confirm these relationships.

Immune function

Clayton et al. (2011) [107], using NHANES data collected from 2003 to 2006, assessed the impact of BPA on immune disorders in children over 6 years old and adults. In children, the relationship was observed between concentration of BPA and high titer of CMV (cytomegalovirus) ($p < 0.05$), but there was no relationship between the concentration of BPA and allergy in children.

Thyroid function

Due to its endocrine disruptor characteristics, BPA may impair brain development in both humans and experimental animals, because it can bind to the thyroid hormone receptor (TR), and thereby, inhibit TR ability to regulate gene expression [108–110].

Exposure to BPA *in utero* may adversely affect thyroid function, especially in infants and youths. Proper functioning of thyroid hormones during this period (*in utero* and in early childhood) is essential for normal neurological development, hence the group at the highest risk are pregnant women and infants [111,112].

Despite this, no research is accessible that could confirm this relationship [112]. Chevrier et al. (2013) conducted a study on 476 women participating in the CHAMACOS project to see whether exposure to BPA during pregnancy and after birth has an impact on the functioning of the thyroid gland [112]. Concentrations of TSH (thyroid-stimulating hormone) in newborns and TSH, free thyroxine (T4) and total T4 levels in pregnant women were determined. There was no statistically significant association between the mean values of the concentrations of BPA and thyroid hormone concentrations in mothers. However, exposure to BPA in women during pregnancy is associated with reduction of TSH in infant boys, and decreased T4 in women during pregnancy [112].

Wang et al. (2013) [113] analyzed concentrations of BPA in the urine of an adult Chinese population (N = 3394 adults). The median concentration of BPA in the urine was equal to 0.81 ng/ml (interquartile range (IQR) = 0.47–1.43 ng/ml). Bisphenol A in the urine of the adult men and women was noted to be inversely associated with the occurrence of TSH in serum, and directly associated with free triiodothyronine in serum.

A recent study by Gentilcore et al. (2013) [114] shows that BPA, even at low doses, can cause thyroid function abnormalities. The studies *in vitro* on thyroid specificity of target line FRTL-5 showed that FRTL-5 cells were sensitive to low concentrations of BPA. Bisphenol A induces expression of genes related to the synthesis of thyroid hormone (natrium iodide symporter (Nis), Thyroglobulin (Tg), Thyroid peroxidase (TPO) in FRTL-5 cells. The mechanism of action of BPA in the cells responsible for the synthesis of thyroid hormones, however, has not been completely explained yet [114].

Neurodevelopment

Women's exposure to BPA during pregnancy can cause behavioral disorders in the progeny. To verify that hypothesis, a study on the effects of prenatal exposure to BPA on children's behavior was undertaken. Children's behavior was assessed by the Behavior Assessment System for Children 2 (BASC-2) and the Behavior Rating Inventory of Executive Function – Preschool (BRIEF-P). The average concentration of BPA detected in pregnant women was 2 μg/l, while in children it was 4.1 μg/l. The urine samples collected from the women were analyzed twice during pregnancy and after childbirth. It has been shown that an increase of the concentration of BPA in the urine of mothers has a link with the increased anxiety and depression, and poorer emotional control in their 3-year-old children [115].

A similar relationship was detected by Perera et al. (2012) [116]. Exposure to BPA during the prenatal period

may affect the behavior of children aged 3–5 years. Children's behavior was assessed using the Child Behavior Checklist (CBCL), taking into account confounding factors. Much higher concentrations of BPA were found in the urine of mothers during pregnancy (range: 0.42–73.50 μg/l) than of the children aged 3 years (range: 0.24–38.53 μg/l). There were no significant differences in the concentrations of BPA between girls and boys. However, among girls the effects of exposure to BPA on Internalizing Problems ($p < 0.1$) and Anxious/Depressed and Aggressive Behavior ($p < 0.05$) were less evident than in boys.

There was a significant correlation ($p < 0.05$) between the concentrations of BPA in the prenatal period and sex on the Emotionally Reactive, Internalizing Problems and Aggressive Behavior. In boys, an association was noted between maternal exposure to BPA in the 34th week of pregnancy and their aggressive behavior, internalizing problems, withdrawn, emotionally reactive and problems with sleep and externalizing problems. These symptoms were more common in boys who had been exposed to higher levels of BPA in the prenatal period. Among girls at low risk, problems in those areas were observed more frequently than in the girls exposed to high doses of BPA in the prenatal period. Research is continued to assess the exposure in children at older age [116].

In 2013, Callan et al. [117] published a study conducted with the participation of pregnant women exposed to BPA as a substitute for the exposure of newborns. Bisphenol A was detected in 85% of the urine samples collected from the women in the 38th week of pregnancy. Because the concentration of BPA in pregnancy is variable [53], it is not possible to conclude about the impact of exposure on effects in children. However, the study showed that pregnant women in Western Australia were exposed to BPA at concentrations that may increase the risk of behavioral and emotional effects in their descendants [117].

Braun et al. (2009) [118] observed an association between urinary concentration of BPA in the samples collected from pregnant women (mean urinary concentration of BPA = 1.8 ng/ml) with externalizing scores in 2-year-old girls. Pregnant women whose BPA concentrations had been determined involving early pregnancy (16th week of gestation) were in the phase of fetal neural development. This indicates that externalizing behaviors may be associated with prenatal BPA exposure.

Similarly, Miodovnik et al. (2011) [119] analyzing prenatal exposure to BPA and social behavior in a sample of adolescent inner-city children (Mount Sinai Children's Environmental Health Study from 1998 to 2002, 404 pairs of mother (3 trimesters of pregnancy) and 7–9-year children), suggests that environmental exposure to BPA (median concentration of BPA in urine 1.2 μg/l) of mothers during pregnancy may cause neurobehavioral effects in children.

Hong et al. (2013) [120] examined the relationship between environmental exposure to BPA and the neurobehavioral development in children 8–11 years of age (N = 1089). Determined concentrations of BPA in the urine "were positively correlated with the CBCL total problems score and negatively correlated with the learning quotient from the Learning Disability Evaluation Scale (LDES)."

In turn, during 5 years of follow-up, Maserejian et al. (2012) did not observe statistically significant relationship between BPA released from dental fillings and neurobehavioral effects in children or their physical development [96,121].

Similarly, Yolton et al. (2009) showed no association between prenatal exposure to BPA and naurobehavior during early infancy [122].

These data indicate that exposure of pregnant women to BPA may either affect the behavior of children, or may be irrelevant. In general, however, the studies clearly suggest, that there is a relationship between the level of BPA and neurobehavioral problems in children. The data about toxicological effects of BPA in children and pregnant women have been collected in Table 6.

Table 6. Effects of BPA in pregnant women and children

Type of effect and study population	Specimen analyzed	Concentration of BPA	Concentration range	Research project	Findings	Reference
Miscarriage						
77 patients aged 31.6±4.4 years with earlier miscarriage, the same patients after re-miscarriage	serum	control group (N = 32): M±SD = 0.77±0.38 ng/ml cases (N = 45): M±SD = 2.59±5.23 ng/ml	0.20–1.58 ng/ml 0.22–29.43 ng/ml	Nagoya City 2001–2002	in the women with recurrent miscarriages concentration of BPA in serum was higher than in the women whose pregnancy was succesful	88
Premature delivery						
40 pregnant women	serum		0.5–22.3 ng/ml	Michigan, 2006	there was no significant correlation between duration of pregnancy and the level of serum BPA at birth	78
60 pregnant women – birth cohort (37–38 week of gestation) – 3rd trimester of pregnancy	urine	GM = 1.52 ng/ml (N = 48)	< 0.4–6.7 ng/ml	ELEMENT, Mexico City, Mexico 2001 and 2003	association between elevated level of BPA in the urine and premature delivery was significant between the women who delivered before the 37th week of gestation and the women who delivered after the 37th week of pregnancy	89
Birth weight						
404 pregnant women – 3rd trimester	urine		0.36 (LOD) – 35.2 ng/ml	Environmental Health Study, New York City, USA, 1998–2002	relationship between birth weight and concentration of BPA in maternal urine was not significant	102
40 pregnant mothers	serum		0.5–22.3 ng/ml	Michigan, USA	there was no significant correlation between the birth weight and the level of serum BPA at birth	78
587 children (444 children of not exposed parents, 93 children of exposed fathers, 50 children of exposed pregnant mothers)				China, 2003–2008	parental exposure in the workplace correlated with a decrease in the birth weight compared to the unexposed families	90

Table 6. Effects of BPA in pregnant women and children – cont.

Type of effect and study population	Specimen analyzed	Concentration of BPA	Concentration range	Research project	Findings	Reference
pregnant women and fetal	maternal blood umbilical cord blood	mother (N = 97): GM = 2.5 ng/ml fetal (N = 97): GM = 0.5 ng/ml		Taiwan, 2006–2007	children of the mothers whose concentrations of BPA in serum were higher, had lower birth weight, male infants had smaller size for gestational age	91
191 pregnant women 24–30 gestation weeks (143 controls, 48 cases)	urine		0.4–10.1 ng/ml	EDEN cohort 2002–2006	increase in the birth weight and head circumference was associated with higher concentration of urinary BPA	92
757 pregnant women up to gestation week 20	urine	GM = 1.29 ng/ml (1.87 µg/g creatinine)		MOCEH, Korea, 2006,	there was significant relationship between prenatal exposure to BPA and birth weight, birth length, different vs. gender and duration of pregnancy	93
Child obesity						
90 girls aged 6–8 years	urine	Me = 1.8 ng/ml GM = 2.0 (3.2) ng/ml	0.36–54.3 ng/ml	USA, 2004–2005	there were significantly lower concentrations of BPA in the urine among girls in the ≥ 85th percentile for BMI	101
2 838 children and adolescents aged 6–19 years	urine	Me = 2.8 ng/ml	1.5–5.6 ng/ml	NHANES 2003–2008	obesity among children and adolescents was significant associated with higher concentration of BPA in the urine	100
498 pregnant women and 402 children aged 5 and 9 years	urine	pregnant women: Me = 1.1 ng/ml children aged 5 years: Me = 2.3 ng/ml children aged 9 years: Me = 1.6 ng/ml		CHAMACOS, UC Berkeley, 1999-2000	lower BMI, body fat and overweight/ obesity among daughters aged 9 years were correlated with higher concentration of maternal BPA in the urine	98
3 370 children aged 6–18 years	urine			NHANES, 2003–2010	higher concentrations of BPA in the urine were associated with abdominal obesity, insulin resistance and increased BMI	97

402 pregnant women (1st and 3rd trimester)	urine	1st trimester: GM = 2.6 μg/g (2.1 ng/ml) 3rd trimester: GM = 2.0 μg/g (1.8 ng/ml)	1st trimester: 0.2–138.0 μg/g (0.1–122.8 ng/ml) 3rd trimester: 0.2–102.6 μg/g (< 0.1–103.7 ng/ml)	INMA, Spain, 2004–2006	higher urinary of BPA was associated with sharp increase in the children within 6 months; prenatal exposure was weakly associated with an increase in waist circumference and BMI in the children aged 4 years, compared to the rapid weight gain and growth in the first 6 months of life or waist circumference, or an increase in BMI at the age of 14 months	95
pregnant women and children (9 years)	urine	early pregnancy (N = 131): GM = 0.9 ng/ml late pregnancy (N = 179): GM = 1.1 ng/ml 9 year children (N = 172): GM = 1.6 ng/ml		CHAMACOS	concentrations of BPA in the urine samples, in late pregnancy were correlated with increased leptin in plasma in boys and during early pregnancy the concentrations were correlated with plasma adiponectin levels in girls	99
2 200 children aged 6–18 years	urine		(< 1.5 ng/ml, 1.5–2.7 ng/ml, 2.8–5.4 ng/ml, > 5.4 ng/ml (categorized into the quartile)	NHANES, 2003–2010	higher urinary BPA was correlated with obesity, independently of age, sex, ethnicity and also serum cotinine, and urinary creatinine	94
39 children aged 3–8 years with obesity	urine	M±SD = 1.37±2.2 ng/ml (1.82±2.6 ng/g creatinine)		CMC, Ohio, USA	higher concentrations of BPA in the urine were associated with adverse metabolic effects, and also with elevated diastolic blood pressure levels	103
Male genital abnormalities						
153 sons, including 56 sons of parents occupationally exposed to BPA during pregnancy and 97 non-exposed parents		exposed mothers (N = 18): GM = 16.0 μg/g wife of exposed fathers (N = 38): GM = 2.2 μg/g unexposed mothers (N = 93): GM = 0.6 μg/g	9.1–28.0 μg/g 1.5–3.3 μg/g 0.7–0.9 μg/g	China, 2004–2008	exposure during pregnancy resulted in a shorter AGD in male offspring	104

Table 6. Effects of BPA in pregnant women and children – cont.

Type of effect and study population	Specimen analyzed	Concentration of BPA	Concentration range	Research project	Findings	Reference
Child wheeze						
365 women at 16 weeks of gestation and children to 3 years old, examined every 6 months	urine	GM = 2.4 μg/g		HOME, USA, 2003–2006	an increase in respiratory disorders (wheeze) in the children at the age of 6 months was associated with higher level of BPA in the maternal urine, and this correlation decreases with the age of the child	105
Child asthma						
women in 3rd trimester and children aged 3, 5 and 7 years	urine	mothers (N = 375): Me = 1.8 ng/ml children aged 3 years (N = 408): Me = 3.8 ng/ml children aged 5 years (N = 401): Me = 3.1 ng/ml children aged 7 years (N = 318): Me = 2.7 ng/ml	1.0–3.5 ng/ml 1.8–7.4 ng/ml 1.7–6.4 ng/ml 1.4–6.0 ng/ml	CCCEH, New York, 1998–2006	concentrations of BPA in the urine of the 3 year-old children were positively associated with wheeze at the age of 5 and 6 years; urinary BPA at the age of 7 years correlates with wheeze at the age 7 years; the concentrations of BPA in the urine at the age of 3, 5 and 7 years were associated with asthma in the children aged 5 to 12 years; concentrations of BPA in the urine of pregnant mothers were not correlated with the concentrations of BPA in the urine of children after birth	106
Immune function						
2 920 children	urine	M = 4.4 ng/ml	4.07–4.82 ng/ml	U.S. NHANES, 2003–2006	higher urinary BPA was associated with high titer of CMV, but there was no relationship between the concentration of BPA and allergy in the children	107

Thyroid function						
476 pregnant women at 12.4±3.8 and 26.2±2.2 week of gestation, and newborns	urine			CHAMACOS, USA, 1999–2000	there was no significant association between the level of maternal urinary BPA and thyroid hormone concentrations in mothers (T4); exposure to BPA in the women during pregnancy is associated with reduction of TSH in infant boys, and decreased T4 in the women during pregnancy	112
Neurobehavioral development						
350 M/C women at 16 and 26 gestational weeks, and neonates in 5 weeks	urine	GM = 1.8 ng/ml (g.w. 16) GM = 1.7 ng/ml (g.w. 26)	1.6–2.0 ng/ml 1.5–2.0 ng/ml	HOME, USA, 2003–2006	there was no association between neurobehavior during early infancy	122
a cohort of 249 M/C pregnant women; children	urine	Me = 1.3 ng/ml (birth) Me = 1.7 ng/ml (g.w. 16) Me = 1.8 ng/ml (g.w. 26)		HOME, Cincinnati, Ohio (USA)	higher urinary concentration of BPA in the pregnant women was associated with externalizing scores in 2-year-old girls	118
404 M/C women in 3rd trimester and 137 children aged 7–9 years	urine	Me = 1.2 ng/ml		MSCEHS; SRS, New York, 1998–2002	higher level of urinary BPA of the mothers during pregnancy was associated with neurobehavioral effects (autistic behavior) in their children	119
2 473 M/C women at 16 and 26 weeks of gestation, 24 h after birth, children aged 1–3 years	urine	mothers (N = 244): Me = 2.0 ng/ml children (N = 229): Me = 4.1 ng/ml		HOME, Ohio, 2003–2006	increase of the concentration of BPA in the urine of mothers has a link with increased anxiety and depression, and poorer emotional control in their 3-year-old children	115

Table 6. Effects of BPA in pregnant women and children – cont.

Type of effect and study population	Specimen analyzed	Concentration of BPA	Concentration range	Research project	Findings	Reference
198 M/C women between 24–40 weeks of gestation, 111 girls and 98 boys aged 33–47 months	urine	mothers: GM = 1.96 ng/ml children 3-year-old: GM = 3.94 ng/ml	0.24–38.53 ng/ml 0.42–73.50 ng/ml	CCCEH, New York City, 1998–2003	higher concentrations of BPA in the urine of mothers during pregnancy was correlated with aggressive behavior, internalizing problems, withdrawn, emotionally reactive and problems with sleep and externalizing problems in boys; maternal BPA was associated with Anxious/Depressed and Aggressive Behavior in girls; there were no significant differences in the concentrations of BPA between girls and boys	116
26 women in 38 weeks of gestation	urine	Me = 2.41 ng/ml	< LOD–5.66 ng/ml	AMETS, Australia, 2008–2011,	higher level of urinary BPA in the pregnant women was correlated with an increase in the risk of behavioral and emotional effects in their children	117
1 089 children aged 8–11 years	urine	Me = 1.23 ng/ml		Korea	higher concentration of BPA in the urine was correlated with the increased externalizing behaviors in girls.	120
474 children (218 boys, 256 girls) aged 6–10 years	urine			NECAT, United Kingdom, 1997–2006	there was no statistically significant relationship between BPA released from dental fillings and neurobehavioral effects in the children, or their physical development	121

M – mean; Me – median; GM – geometric mean.
CMV – cytomegalovirus; g.w. – gestational weeks; LOD – limit of detection; M/C – mother/child pairs; TSH – thyroid-stimulating hormone; T4 – free thyroxine.
ELEMENT – Early Life Exposure in Mexico to Environmental Toxicants; CMC – Children's Medical Center; NHANES – National Health and Nutrition Examination Survey (NHANES); CHAMACOS – Center for the Health Assessment of Mothers and Children of Salinas; INMA – Infancia y Medio Ambiente; HOME – Health Outcomes and Measures of the Environment; MSCEHS – Mount Sinai Children's Environmental Health Study; SRS – Social Responsiveness Scale; CCCEH – Columbia Center for Children's Environmental Health; NECAT – New England Children's Amalgam Trial; MOCEH – The Mothers and Children's Environmental Health; AMETS – Australian Maternal Exposure to Toxic Substances.

CONCLUSIONS

Due to the high volume of production, wide range of applications of BPA in products of everyday use and, consequently, potential adverse health effects, BPA toxicity is a subject of ongoing research. In addition, bisphenol A is included in the group of compounds that can cause endocrine disruption (ED) in the body [123]. The research has focused on exposure of infants and young children who have the most frequent contact with products containing BPA, but also a reduced ability to metabolize and excrete xenobiotics from the body. The mechanism of action of BPA in the body and its effect on human health are not fully understood, and give rise to many speculations. Despite this, numerous reports indicate that chronic exposure to BPA, even at low doses, can lead to many adverse health effects, such as e.g., ischemic heart disease, diabetes, obesity, but also reductions in body and organ weight, as well as other disorders and behavioral abnormalities in children.

In recent years, actions have been launched to reduce human exposure to bisphenol A. Canada has been the 1st country to include BPA in the list of toxic substances and has developed plans to reduce BPA exposure through intake. Since 2008, the Canadian Ministry of Health has banned the import and marketing of infant feeding bottles made of polycarbonate. In the European Union, since 2010, Denmark and France have banned the sale of bisphenol A-containing products that come in contact with food for children aged 0–3 [124].

In 2012, an action plan was developed for assessing the risks of dietary exposure to BPA, which was intended to evaluate the extent of absorption of BPA in the human body and its toxicity. In 2013, EFSA has issued an opinion on BPA, which recommends to assess the risk of exposure to this compound during pregnancy, mainly because of the risk to the fetus, as well as effects of the exposure during the postnatal and early childhood periods of life [125].

In 2013, EFSA in its Draft Scientific Opinion has released data on the estimated exposure to BPA. Based on the new data in children above 6 months of age (1.5 years), the highest estimated average exposure to BPA is 375 ng/kg b.w./day, and the maximum exposure to BPA is 857 ng/kg b.w./day, compared with the data that EFSA reported in 2006, where the estimated exposure based on the established conservative scenario was 5300 ng/kg b.w./day. Similarly, among children up to 6 months, the estimated exposure was much higher, up to 11 000 ng/kg b.w./day, and according to the latest assessment of exposure, it is 225 ng/kg b.w./day, which is about 50 times less than the value assumed for 2006.

Currently, human exposure to BPA is well below TDI, in spite of that, BPA toxicity is still a matter of concern. Often, studies include too few samples and/or unrealistic research conditions. Besides, the results fail to take into account exposures to BPA from other sources. In addition, external factors relating to the preparation and analysis of samples may exert a significant impact on the results due to the ubiquity of BPA in the environment. Considering that studies on the effects of human exposure to BPA at low concentrations still continue, contact of humans, and younger consumers in particular, with BPA-containing products should be limited.

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