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HEALTH RISK OF EXPOSURE TO BISPHENOL A (BPA)

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ABSTRACT

Bisphenol A (BPA) belongs to chemicals that are produced in large quantities worldwide. It is commonly used as monomer in polycarbonate synthesis, plasticizer in the production of epoxy resins, as well as an additive for the elimination of surfeit of hydrochloric acid during the polyvinyl chloride (PVC) production. BPA is not only used in the production of plastics intended to a direct contact with food, including plastic packaging and kitchenware, but also in inner coatings of cans and jar caps. There are various routes of human exposure to this substance such as oral, by inhalation and transdermal. The main sources of exposure to BPA include food packaging and dust, dental materials, healthcare equipment, thermal paper, toys and articles for children and infants. BPA is metabolized in the liver to form bisphenol A glucuronide and mostly in this form is excreted with urine. Due to its phenolic structure BPA has been shown to interact with estrogen receptors and to act as agonist or antagonist *via* estrogen receptor (ER) dependent signalling pathways. Therefore, BPA has been shown to play a role in the pathogenesis of several endocrine disorders including female and male infertility, precocious puberty, hormone dependent tumours such as breast and prostate cancer and several metabolic disorders including polycystic ovary syndrome (PCOS). Because of the constant, daily exposure and its tendency to bio-accumulation, BPA seems to require special attention such as biomonitoring. This observation should include clinical tests of BPA concentration in the urine, which is not only one of the best methods of evaluation of the exposure to this compound, but also the dependence of the daily intake of BPA and the risk of some endocrine disorders.

Key words*: bisphenol A, BPA, estrogens, endocrine disrupting chemicals*

STRESZCZENIE

Bisfenol A (BPA) należy do substancji chemicznych produkowanych na świecie w znacznych ilościach. Używany jest jako plastyfikator i półprodukt w syntezie żywic epoksydowych, tworzyw sztucznych poliwęglanowych oraz jako dodatek do usuwania nadmiaru kwasu chlorowodorowego przy produkcji polichlorku winylu (PCW). BPA nie tylko jest używany do syntezy tworzyw sztucznych służących do produkcji materiałów mających bezpośredni kontakt z żywnością, włączając opakowania z tworzyw sztucznych oraz sprzęt kuchenny, ale także stanowi składnik lakierów do pokrywania wewnętrznych powierzchni puszek metalowych przeznaczonych do żywności i napojów. BPA stosowany jest w produkcji poliwęglanów (PC) i żywic epoksydowych, wykorzystywanych w produkcji wyrobów do kontaktu z żywnością. Może być także stosowany, jako przeciwutleniacz i inhibitor w procesie polimeryzacji tworzyw sztucznych, m.in. polichlorku winylu (PCW). Narażenie na BPA może zachodzić drogą pokarmową, wziewną oraz przez skórę, a głównymi źródłami ekspozycji są opakowania żywności, kurz, materiały stomatologiczne, sprzęt medyczny, papier termiczny, a także zabawki i artykuły przeznaczone dla niemowląt i dzieci. BPA jest metabolizowany w wątrobie do glukuronianu bisfenolu A i w tej postaci jest usuwany z moczem. Ze względu na swą fenolową strukturę BPA wykazuje zdolność jako agonista lub antagonista do interakcji z receptorami estrogenowymi poprzez estrogenowe szlaki sygnalizacyjne. W wyniku takiego działania BPA odgrywa rolę w patogenezie zaburzeń endokrynnych włączając zaburzenia płodności u kobiet i mężczyzn, przedwczesne dojrzewanie, nowotwory hormonozależne, jak rak piersi oraz rak prostaty oraz schorzeń metabolicznych włączając zespół wielotorbielowatych jajników (PCOS). Biorąc pod uwagę stałe, codzienne narażenie na BPA z wielu źródeł oraz tendencje do bioakumulacji uzasadniony jest monitoring biologiczny tego związku. Powinien on w szczególności uwzględniać monitoring BPA w moczu, jako skuteczną metodę szacowania narażenia na ten związek, umożliwiając jednocześnie badanie zależności pomiędzy narażeniem na BPA a ryzykiem występowania niektórych chorób wynikających z zaburzenia czynności układu endokrynologicznego.

Słowa kluczowe*: bisfenol A, BPA, estrogeny, związki endokrynnie czynne*

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INTRODUCTION

Bisphenol A (BPA) belongs to chemicals that are produced in the large quantities. It is commonly used as a plasticizer and an intermediate in the synthesis of epoxy resins, polycarbonate plastics [29] as well as an additive for the elimination of surfeit of hydrochloric acid during the polyvinyl chloride (PVC) fabrication. BPA is widely used in the production of healthcare equipment [52], dental composites [13], contact lenses, spectacle lenses, toys, storage media and window foils [2]. BPA is one of the Food Contact Materials (FCMs), which means that it is used in the preparation of plastics for the manufacture of materials that have direct contact with food [10], plastic packaging, kitchenware, jar cap coatings, and the wall of cans that isolates the food from metal, therefore preventing its corrosion [8].

It is estimated that in 2008 the total world production of BPA was approximately 5.2 million tons [2]. The world's largest producers are the United States (22.9% of global production), Taiwan and Japan (13.1% and 13%, respectively). Synthesis of BPA in Poland is about 12 000 tons per year (0.3% of the world production) [42]. The highest percentage of BPA is used as a component of the polycarbonate (74% of the total amount of produced BPA) and the epoxy resins (nearly 20%). As a result of the mass production, a large number of derivatives of BPA are released into the environment, which consequently leads to increasing pollution and contamination of the soil and groundwater [22]. It is estimated than China itself (where 3.6% of the global amount of BPA is synthesized) produces annually approximately 5 000 tons of post-production waste [57].

HUMAN EXPOSURE TO BPA IN EVERYDAY LIFE

BPA is a widely used compound in daily life. Therefore, there are various routes of human exposure to this substance such as oral, by inhalation and transdermal. The main sources of exposure to BPA include food packaging and dust, dental materials, healthcare equipment, thermal paper, toys and articles for children and infants. Food products are the major source of BPA exposure, which is an order of magnitude higher than for other routes [20]. The most important source of dietary exposure to BPA is canned foods, but it may also be present in fresh foods such as meat, milk or eggs, when animals are bred in the polluted areas or watered with the contaminated water [51]. In addition, the presence of BPA was detected in the food products stored in the cardboard boxes [41].

BPA is widely used in the manufacture of cans for food preservation and for the inside coatings of jar caps [23, 41]. It is used to prevent the direct contact of food with the metal, to ensure the thermal stability and the mechanical strength of the can [8]. Coatings that are the most commonly used for this purpose are made of epoxy resins. Approximately 9% of BPA produced annually is used for the production of the lining material in cans [23]. Heating cans during sterilization or food preparation causes the BPA to leak into the can content from the epoxy coating of the can wall and therefore, increases the potential of BPA dietary exposure [9]. The highest increase of BPA concentration was observed after heating the product at 121°C for 90 minutes. The temperature of heating food products turned out to be more relevant for the migration level of BPA than the time of the heating [30]. Sterilization of the canned food causes migration of the 80-100% of the unconjugated BPA to the content of the can and it seems to depend on the conditions of the process and the ingredients of the product [24]. The foods with lower pH and higher fat content contain higher concentrations of BPA [38]. Contamination with BPA may also be caused by the migration to food stored in polycarbonate plastics (reusable containers, polycarbonate water bottles and drink dispensers) or prepared for consumption, such as bottles for infants and children, especially during heating and microwave cooking [53].

BPA can also migrate into dust from laminate flooring, adhesives containing epoxy resins, paints and household electronic equipment [27]. This compound was detected in 95% of 56 dust samples, with the concentrations ranging between 0.8 μg to 10 μg per gram of dust [18, 36]. Higher values were detected in dust from offices and laboratories, mainly because they were equipped with a vast quantity of furniture and electronic devices. Home exposure among children and infants may be higher due to the presence of commonplace items containing BPA, which very often are being taking by children in to the mouth, as well as by the inhalation of the contaminated air [7]. The exposure through dust was estimated to be less than 5% of the total exposure to BPA [21]. Exposure resulting from polluted air is less than 0.4 ng/kg body weight per day in adults, whereas in infants is estimated to be 5.3 ng/kg of body weight per day [35].

Dental materials consist of monomers that may contain BPA, particularly in the form of bis-GMA (bisphenol A-glycidyl methacrylate). This compound is often released from the dental fillings, sealants or materials used to rebuild the crown of the tooth [13]. It has been shown that the highest concentration of BPA was in the saliva of the patient immediately after acquiring the dental fillings and decreased afterwards. However, chronic exposure to BPA released from dental materials in small doses for a long time cannot be excluded [17]. After applying the reconstruction of

a molar tooth crown, 13 μg to 30 mg BPA per day has been shown to be released [51], which may suggest that dental treatments can be a significant source of BPA exposure, especially in the case of patients who have many dental fillings [20].

Small amounts of BPA (0.3-0.35 μg) can be released from several medical devices, which contain polycarbonate or polysulfone plasticizers such as contact lenses, probes, inhalers, intravenous cannulas, catheters, neonatal incubators or haemodialysis apparatus [6, 21, 26].

BPA is also used in the production of paper for thermal printing in cash registers and payment card terminals. Exposure to BPA from thermal paper occurs through the contact of unwashed hands with food or mouth directly, as well as transdermally [21].

It has been shown that thermal paper receipts are the second, after dietary exposure, most common source of BPA exposure in people over the age of three [16]. Several studies show that the cashiers having prolonged contact with such receipts, presented higher concentration of this compound in the urine compared to the general population (2.4 μg/g and 1.2 μg/g, respectively) [5]. The overall exposure to BPA migrating from thermal paper also depends on the frequency and time of use and cleanliness of hands. It has been estimated that occupational exposure after ten hours of work as a cashier is 71 μg per day whereas in general population it ranges from 7.1 μg to 42.6 μg per day [4].

Long-term exposure to BPA may be also due to the contact with toys and products intended for infants and young children, such as baby dummies and teethers that may be put into the mouth, for several hours during the day. Saliva BPA concentration was shown to be 0.14 – 2.1 μg/l saliva for rattles and 0.11 μg to14 μg/l saliva for pacifiers, after 24h contact with such products [31]. One minute exposure of saliva with pacifiers and teethers caused the presence of BPA at the concentration of 0.3 μg/l and 5.9 μg/l, respectively [53].

METABOLISM AND TOXICOKINETICS OF BISPHENOL A

BPA is metabolized in the liver by the uridine 5'-diphospho-glucuronyl transferase (UGT), which catalyzes the glucuronidation of BPA (Figure 1) [56]. BPA can also be metabolized into other substances such as BPA-sulfate or bisphenol-3,4-quinone [55].

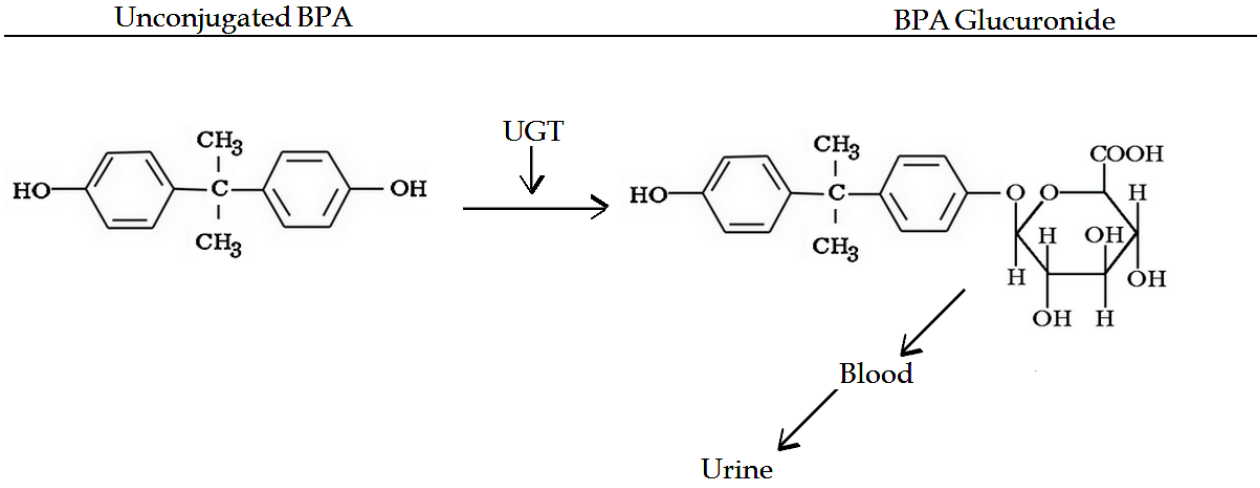

Figure 1. Glucuronidation of BPA in human

The half-life of BPA in the human body is estimated to be 5.4 hours [48].

HEALTH RISKS RELATATED TO BPA EXPOSURE

Due to its phenolic structure BPA has been shown to interact with estrogen receptors and to act as agonist or antagonist *via* endocrine receptor (ER) dependent signalling pathways (Figure 2) [36]. Therefore, BPA has been shown to play a role in the pathogenesis of several endocrine disorders including female and male infertility, precocious puberty, hormone dependent tumours such as breast and prostate cancer and several metabolic disorders including polycystic ovary syndrome (PCOS) [12].

Increased levels of urinary BPA concentration were correlated with a reduced number of sperm in the ejaculate, as well as its reduced motility and viability [33, 46]. The pathomechanism of the fertility disrupting potential of BPA in women as well as in men seems to be due to its estrogenic activity in the hypothalamus which in turn disrupts the proper function of the GnRH

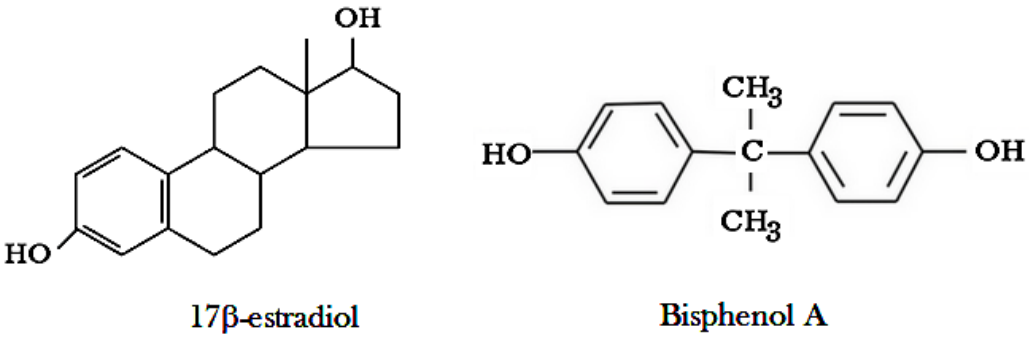

Figure 2. Structural similarity of BPA to 17β-estradiol

pulse generator thus the adequate secretion of the FSH and LH is impaired [14].

Data from animal experiments show that BPA exposure can also be the cause of precocious puberty. Prenatal rat exposure to BPA concentrations of 2 μg/kg body weight per day accelerated puberty in comparison to the control group [28]. It seems that the main mechanism of precocious puberty due to BPA exposure is due to its weak estrogenic activity, which through the positive feedback mechanism stimulate the activity of the GnRH pulse generator, therefore giving the rise in the pituitary LH and FSH secretion [43].

There are reports on a potential role of BPA in the pathogenesis of breast cancer. Studies conducted *in vitro* have shown that the exposure of the human breast cancer cell line to BPA increased its proliferation and caused increased oxidative stress [54]. Similar results were obtained for the MCF-7 estrogen receptor positive cells (ER +), where low levels of BPA significantly increased its proliferation and the expression of the progesterone receptors [32]. High serum BPA concentrations in postmenopausal women also correlated with the mammographic density of the breast tissue [47]. It is also suggested that occupational exposure to BPA increased incidence of breast cancer [11].

BPA may be one of the factors that contribute to the development of prostate cancer. Studies conducted in men with prostate cancer showed a much higher concentration of BPA in the urine of those patients in comparison with the control group [50]. *In vitro* studies have shown that BPA induces the proliferation of the androgen-sensitive human prostate cancer cells [54]. In rats treated with BPA an increase of prostate and epididymis weight was also observed [25]. Moreover, exposure to BPA *in utero* contributed to prostate enlargement in the male offspring [39].

Obesity is a metabolic disorder in which BPA has also been shown to have an impact. Animal studies have shown a correlation between prenatal exposure to endocrine disrupting chemicals, including BPA, and the prevalence of obesity, impaired glucose tolerance and lipid metabolism in mice [40]. Mice exposed to 10 mg BPA/kg body weight per day had higher concentrations of plasma triglycerides, and increased body weight in four months of age comparing to the control group. An endocrine disorder, in the pathogenesis of which BPA may also be involved, is the polycystic ovary syndrome (PCOS) which is the most common endocrinopathy among women of child-bearing age [44]. In patients with PCOS, especially obese ones, BPA serum concentrations were significantly higher compared to healthy controls [49]. The pathogenesis of PCOS is very complex. One of the proposed mechanisms by which BPA may be involved in the pathogenesis of this syndrome is through the activation of the hypothalamic GnRH pulse generator leading to a constant increase of plasma LH concentrations which in turn stimulate the ovarian androgen production and impair proper ovarian follicle development [3, 34]. In addition, BPA has been shown to directly increase ovarian androgen synthesis [58] (Figure 3).

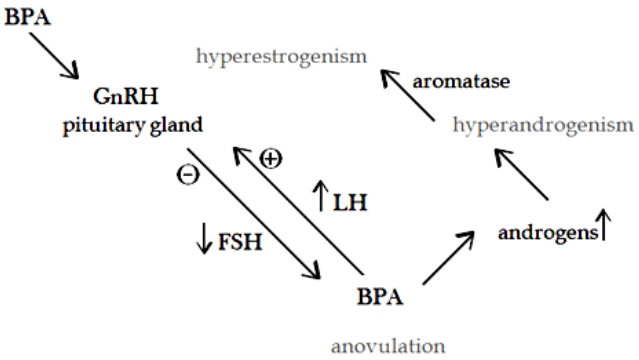

Figure 3. Proposed mechanisms of the BPA action in the pathogenesis of PCOS

BPA AS AN ENDOCRINE DISRUPTING CHEMICAL

According to the European Food Safety Authority (EFSA), an endocrine disrupting chemical is every synthetic or natural compound that meets the following criteria: presents endocrine activity, causes adverse

health effects as well as link between its endocrine activity and adverse affects is believable [15].

As aforementioned, BPA has been shown to present a weak estrogenic activity and therefore may disrupt the proper function of the endocrine system [10]. Thus many international authorities express its concern about the BPA exposure, especially among groups with higher susceptibility to EDC [45]. EFSA applied a total uncertainty factor of 150 (for inter- and intra-species differences and uncertainty in mammary gland, reproductive, neurobehavioural, immune and metabolic system effects) to decrease recommended Tolerable Daily Intake (TDI) from 50 μg/kg bw/day to 4 μg/kg bw/day as a temporary TDI (t-TDI) [16].

As BPA meets all the above criteria it is indisputable that BPA belongs to endocrine disrupting chemicals [1]. It is of human benefit to estimate the exposure to BPA throughout biological monitoring ie. measuring BPA concentration directly in human fluids like blood, urine or breast milk [11]. Thus, biomonitoring seems to be the best method of an assessment of BPA total intake from diverse sources, because of many routes of exposure to this compound.

CONCLUSIONS

Taking into account numerous sources of BPA and endocrine disrupting potential of this chemical it seems to be advisable to introduce a nation-wide biomonitoring in order to evaluate health risk for man with the special attention paid to perinatal and child exposure. Such monitoring may also provide a valuable tool for searching relations between exposure to BPA and prevalence of hormone-related disorders.

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