Bisphenol A – an Environmental and Human Threat

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Summary

Bisphenol A (BPA) is a chemical substance primarily used as a plasticizer in food packaging production. Unfortunately, it has become a ubiquitous environmental pollutant. The main route for human exposure is the consumption of contaminated food and beverages. Contamination can occur during the production and transport, or due to unsuitable storage conditions; but most common, the contamination is a result of leaching from the packaging containing BPA. Excess exposure to BPA is associated with various health conditions, including cardiovascular disorders, diabetes, various types of cancer, hepatotoxicity, and metabolic and immune function. Literature indicates disrupted endocrine activity and reproductive problems as the main health concerns in humans. The aim of this paper is to review and critically discuss the literature that relates occurrence of BPA in food/beverages and adverse effects on human health, and to point out the most relevant discoveries. So far, BPA has not been found in unprocessed food, which means that it originates from food and beverage packaging, especially from plastic packaging and cans. The migration of BPA from packaging increases during exposure to sunlight and higher temperatures. In addition to food and beverages, people are exposed to BPA through equipment used in medical treatments. Therefore, there is a strong need for better and evidence-based recommendations and regulations related to BPA.

Key words

bisphenol A, environment, food, water, human health

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Received: December 8, 2020 | Accepted: February 16, 2021

Introduction

Materials made of plastics are commonly used in everyday life for various purposes: in packaging, building and construction, the automobile and electronic industry. The use of plastic materials for packaging in the food industry has been increasing substantially during the last few decades (Euronews, 2015), seeing plastic as a relatively cheap material, which helps in ensuring food safety, and reduces food waste (European Comission, 2018b). Plastic materials are used as primary packaging, which is in direct contact with food, or as secondary packaging, which is often used in food transportation.

In the bottle filling industry, bottles are made of various polymers: primary packaging is usually produced of high-density polyethylene (HDPE) and low-density polyethylene (LDPE), while polystyrene (PS) is mostly used for insulating packaging (Guart et al., 2011). According to the reports of Bolgar et al. (2008) and Piringer et al. (2008), polymers used for packaging are supplemented by various additives like agents against fogging, colors, lubricants, antioxidants, UV absorbers, etc. These additives enhance the characteristics of the packaging, but, unfortunately, they also make the safety of the packaging questionable due to the potential diffusion of additives into the packaging-contained liquids (Biscardi et al., 2003). Literature (Biles et al., 1997; Casajuana et al., 2003; Loyo-Rosales et al., 2004; Le et al., 2008; Gallart-Ayala et al., 2011) contains reports showing that bisphenol A (BPA), as one of the additives, ends up in these liquids.

BPA or 2,2-Bis (4-hydroxyphenyl) propane is an organic compound with two phenol functional groups, and the molecular formula of $(CH_3)_2C(C_6H_4OH)_2$ (Fig. 1). It is a colorless solid at room temperature; the melting point is between 153 and 156 °C while the boiling point is at 200 °C (U.S. Environmental Protection Agency, CompTox Chemicals Dashboard). BPA is combustible and may form explosive dust clouds (Cameo Chemicals, Chemical Datasheet, 4,4'-isopropylidenediphenol). It is soluble in organic solvents, but poorly soluble in water. In its free form, BPA is somewhat lipophilic, with experimentally determined log P values of 3.32 (U.S. Environmental Protection Agency, CompTox Chemicals Dashboard). BPA is used as an intermediate in the production of polycarbonate (PC) plastics and epoxy resins. PC plastics can be found in various food container productions, including baby bottles and water bottles. In order to prevent direct contact of food and metal in the production of food cans, epoxy resins are used as coating (Cao et al., 2008). BPA is a known environmental pollutant. In living organisms, BPA mimics the structure of estrogen, binds to estrogen receptors, and alters secretion of the hormones. Unfortunately, the human population is exposed to BPA on a daily basis from various sources because plastics are used as a substitute for glass packaging (Lee et al., 2016). Routes of exposure to BPA can be parenteral (dermal and inhalation) and enteral (digestion) (Kim et al., 2003; Masuda et al., 2005; Yannai, 2004). However, humans are mostly exposed through the consumption of food and beverages stored in plastic containers, bottles and cans (Srivastava et al., 2019). As reported by Lee et al. (2018), BPA was found in human urine, blood, placentas, mother's milk, and umbilical cords.

As researchers are becoming increasingly aware of the risks that arise from the presence of BPA, they have begun to find ways to eliminate it. Removal techniques include biodegradation, oxidation, and straining through various membranes (Potakis et al., 2017; Xiong et al., 2017; Zhao et al., 2018).

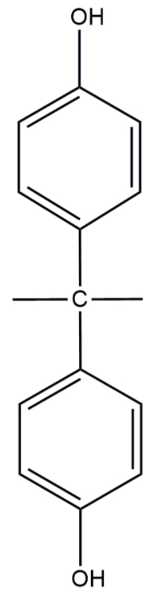

Figure 1. Molecular structure of Bisphenol A

The aim of this paper is to review the literature that focuses on linking the occurrence of BPA in food and beverage items used in households on an everyday basis, their industrial production and storage with human health. Exposure through medical equipment is also included.

BPA has been studied since 1960 (Fregert and Rorsman, 1960) and the number of papers published per year has been generally increasing. But, a significant increase in the number of papers started with the year 2014, around 1.500, to about 16.000 in period from 2014 to 2020 in Science Direct database only (www.sciencedirect.com). Therefore, the year 2014 was chosen as the cutoff point for this review. Since 2014 almost 7.000 research papers have been published using key words bisphenol A or BPA and food and environment, according to Science Direct database (www.sciencedirect.com). Fig. 2. shows ranking of journals according to number of research papers published, stating those keywords.

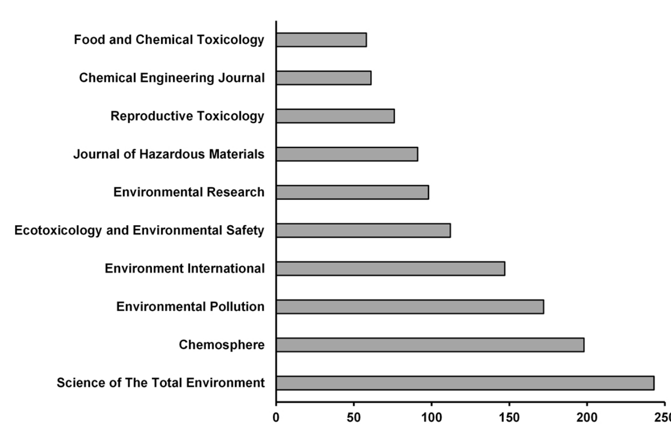

Figure 2. Rank of top 10 journals according to number of research articles containing key words BPA and food and environment published in the period from January 1st, 2014 to February 15th, 2021

We presented only a chart using keywords BPA and food and environment, although the chart using keywords bisphenol A and food and environment is very similar. In this review, we cited only articles available through our library system, as well as a great number of legal documents such as directives, laws, ordinances, etc.

The Occurrence of BPA in the Environment

BPA in Water

It was reported that the occurrence of endocrine-disrupting chemicals (EDCs) in aquatic ecosystems could affect the reproductive systems of animals (Guillette et al., 1994; Oehlmann et al., 2006; Hayes et al., 2010). These effects are manifested through infertile eggs, low testosterone levels, a reduction in penis size, a reduction in anogenital distance, and the feminization of male organisms. Therefore, the occurrence of BPA in the environment presents a severe risk not only for related flora and fauna, but for humans as well.

The European Union, as a community of highly developed countries, is not immune to BPA occurrence in water. Thus, BPA concentrations in municipal sewage sludge in Norway ranged from120 to 6500 ng g^{-1} (dry weight), while values from 14 to 800 ng L^{-1} were reported for surface waters in the Czech Republic (Šauer et al., 2021). In surface and near-bottom water of the Gulf of Gdansk, reported values of BPA were up to 277.9 ng L^{-1} (Staniszewska et al., 2015). The Vistula River, snow melting in the coastal zone, and atmospheric transportation were pointed as the major sources of BPA in the Gulf. Factors affecting BPA concentrations are tourism in the coastal region, water temperature, and dissolved oxygen concentration. Čelić et al. (2020) examined the occurrence of BPA and other EDCs in the waters of Serbia. The analysis included municipal and industrial wastewaters, surface waters impacted by municipal and industrial wastewaters, and drinking waters from urban and rural areas. BPA was detected in 20 – 47% of examined samples. The highest concentrations, with values ranging between 6.4 and 338.2 ng L^{-1}, were detected in industrial wastewaters. Therefore, it was not surprising that surface waters with industrial impact were between 1.8 and 105.7 ng L^{-1}. Municipal wastewaters had lower BPA concentrations, ranging between 0.5 and 40.9 ng L^{-1}, while concentrations of BPA in surface waters with municipal impact were between 0.6 and 31.2 ng L^{-1}. The lowest BPA concentrations were detected in drinking water: those from rural area had values between 2.6 and 6.2 ng L^{-1}, while those from urban areas had a somewhat wider range: between 2.5 and 35.6 ng L^{-1}. The generally higher BPA concentration observed in industrially impacted waters confirms that industrial discharges are important water-pollution points (Čelić et al., 2020).

BPA in Air

Many researches considering exposure to BPA are directed towards food, water and other consuming products as sources of human exposure, while dermal exposure and inhalation from atmosphere are poorly understood. Graziani et al. (2019) researched the current levels of BPA in particulate matter in urban areas of Córdoba, Argentina. They analyzed spatial-temporal trends and the influence of meteorological parameters. The results showed a decrease in BPA concentration with increased distance from emission sources; more precisely, higher BPA levels were detected in industrial areas, a little lower in the city center, while the lowest concentrations were detected at the university campus. Also, a higher prevalence was detected in colder months. The most influencing variables were wind speed, temperature, atmospheric pressure, and relative humidity. They also noted that daily values of BPA in air were unpredictable and depended mainly on the emission sources and punctual events that released BPA into the atmosphere. Xue et al. (2016) examined the occurrence of bisphenols, BPA diglycidyl ethers, and novolac glycidyl ethers in indoor air in Albany, New York. The authors estimated inhalation exposure as well. In bulk air, the geometric mean concentration of BPA was 0.43 ng m-3, with highest concentrations detected in auto repair shops and cars. The results of the estimation of inhalation exposure showed that teenagers had the highest exposures to BPA, with 5.91 ng per day, while the values of body weight (bw) normalized estimations were the highest for infants, with 0.24 ng kg^{-1} bw day^{-1} (Xue et al., 2016).

BPA in Soil

Composted municipal solid waste can affect all aspects of the environment if it is not properly disposed, seeing as leachate can contaminate the surrounding soil and waters. Since substances circulate in nature, contaminants can also reach nearby farmlands, thereby endangering crops. It was reported (Bahmani et al., 2019) that BPA, as one of these contaminants, affects the growth and the development of plants. Results showed that 10 ppm of BPA on *Arabidopsis thaliana* reduces fresh weight and inhibits primary root growth by inhibiting cell elongation and the division of the main root. Langdon et al. (2019) studied preliminary human health and assessed the ecological risk for organic contaminants in composted municipal solid waste generated in New South Wales, Australia in order to identify and prioritize contaminants. Phenols were primarily characterized as high-priority contaminants, but the authors noted that this assessment was likely to be overly-conservative because of their rapid degradation in soil. Other contaminants were found in concentrations ranked below the screening criteria and below the limit of reporting.

Exposure to BPA through Consumption Goods

BPA in Food

Exposure to BPA through food has been researched since 1982, mostly based on various plastic and metal food packaging (National Toxicology Program, 1982.). Frozen food is most often packed in plastic bags or in plasticized cardboard boxes, while fresh food is often found in plastic containers. Milk and dairy products can be packed in Tetra Pak® packaging and PET (polyethylene terephthalate) bottles. It is known that chemicals like BPA can migrate from food packaging into the food and thus cause risk to human health.

According to Gorecki et al. (2017), the main route of human exposure to BPA is food. They based their research on previous estimates in which almost 20% of dietary exposure to BPA in the French population was from food of animal origin, but they pointed out that the source of the contamination had not been precisely identified. Therefore, they decided to analyze 322 samples of non-packed meat. Their main objectives were to update the estimation of the exposure of the French population, and to identify the source of contamination of these foodstuffs. Their results showed that the contribution of meat to the total dietary BPA-exposure of pregnant women, adults, and children, was up to three times lower than the previous estimates. Conjugated forms of BPAs were not detected in the analyzed samples, which led to the conclusion that BPA content in the analyzed meat was present not due to animal metabolism, but that it arose postmortem, i.e., during food production. As in the previous researches, Gorecki et al. were unable to specifically identify the sources of contamination. Another research regarding food was published by Adeyi and Babalola (2019). The authors compared unprocessed food with canned food. In packed food, the highest concentrations were found in vegetable oils (0.41 – 28.4 ng g^{-1}), while in palm oils the concentrations of BPA ranged between 2.35 and 11.6 ng g^{-1}. In canned beef, the concentration of BPA ranged between 5.88 and 21.3 ng g^{-1}; in canned chicken, it ranged between 2.94 and 6.36 ng g^{-1}, while no BPA was detected in raw meat. These results regarding meat also show that the main source of BPA in meat is the production processes. Researchers also examined food of aquatic origin. In frozen fish, the concentrations of BPA ranged between 0.78 and 7.85 ng g^{-1}, in dried fish between 2.28 and 9.40 ng g^{-1}, in canned fish between 1.66 and 26.3 ng g^{-1}, and in crayfish between 1.20 and 13.0 ng g^{-1}. When studying dairy products, the authors examined raw cheese, wherein BPA was not detected, processed cheese, wherein the concentrations of BPA ranged between 1.45 and 3.43 ng g^{-1}, and evaporated milk or unsweetened condensed milk, with BPA concentrations ranging between 0.20 and 4.80 ng g^{-1}. In samples of aquatic food and dairy products, higher concentrations were again found in canned food, thereby confirming previous conclusions.

The potential uptake and distribution of BPA in edible crops were determined based on examining lettuce and tomato, both grown in a greenhouse (Lu et al., 2015). Simulated reclaimed water was spiked with BPA at environmentally relevant concentrations. The results showed higher concentrations in lettuce (80.6 – 128.9 μg kg^{-1} BPA) than in tomatoes (18.3 – 26.6 μg kg^{-1} BPA). The results also showed that the estimated daily intake of BPA through the consumption of vegetables ranged between 8.9 and 95.1 μg, depending on the exposure route.

By examining the occurrence of bisphenols and related compounds in honey from European and non-European countries, as well as from a food simulant, all stored in selected corresponding containers, Česen et al. (2016) noticed that honey samples contained BPA in concentrations of up to 107 ng g^{-1}, while BPA concentrations in the food stimulant were up to 42.2 ng mL^{-1}. The authors suggested that the detected BPA in honey probably derived from a source other than the final packaging.

Another way of food and beverage exposure to BPA is the usage of packaging the inner surface of which is covered by plastic film (paper boxes). In the research of Sungur et al. (2014), various foodstuffs packed in paper boxes (milk, fruit juice, cream, pudding, and tuna) were compared with foodstuffs packed in glass jars and metal cans (green peas, garniture, corn, tomato paste, pepper paste, pickles, mushrooms and beans). The lowest BPA concentrations were found in food that was packed in glass jars, ranging between "not detected" and 399.21 μg kg^{-1}, then in those from paper boxes, ranging between 36.48 and 554.69 μg kg^{-1}, and, finally, the highest concentrations were detected in canned food, ranging between 21.86 and 1858.71 μg kg^{-1}. A comparison between the results with expiration dates and the amount of sodium chloride and glucose led to the conclusion that the amount of BPA increased with an increase in the amount of glucose and NaCl, as well as by the food being closer to the expiration date.

Commercial milk-based dairy products, such as milk, milk powder, reconstituted and fermented milk, are made by different production processes during which final products can be contaminated with BPA (Cui et al., 2020).

Cheng et al. (2017) developed the UHPLC-MS/MS method for a high throughput screening of 21 bisphenols, BP diglycidyl ethers and their derivatives in dairy products. They analyzed 23 dairy products from a local market and found 12 target analytes in seven samples. BPA was detected in three samples of milk beverages in concentrations ranging between 33.8 and 127.2 μg kg^{-1}. Since all three milk beverages were packed in metal cans with metal lids, the authors assumed that BPA had probably leached from the internal protective lining of the packaging. Santonicola et al. (2019) examined concentrations of BPA in cow milk samples collected on the farm through manual or mechanical milking, and those from the cooling tank. The lowest concentrations were detected in mechanically milked samples (mean concentration of 0.580 μg L^{-1}), then in manually milked samples (mean concentration of 0.757 μg L^{-1}), while the highest ones were detected in milk from the cooling tank (mean concentration of 0.797 μg L^{-1}). Although all concentrations were below the tolerable daily intake (TDI) recommended by the European Food Safety Authority (EFSA) (4 μg kg^{-1} bw), the researchers concluded that this presented a public health concern. Šturm et al. (2020) exposed lactating dairy sheep to repeated dietary and subcutaneous administration of 100 μg kg^{-1} bw. The results implied that, most likely, only free BPA could cross the barrier between blood and the mammary gland. Less than 0.1% of the dose was found in milk samples, leading to the conclusion that the main source of BPA in milk was leaching from packaging.

The most infant formulas are based on cow's milk (American Academy of Pediatrics, 2020). According to Cirillo et al. (2015), BPA concentrations in infant formulas were between 0.003 and 0.375 μg g^{-1}. The authors did not report significant differences in BPA concentrations between liquid and powdered milk. Therefore, they concluded that contamination was more related to the production process, rather than to leaching from containers.

Several researchers examined breast milk and commercial milk based infant formulas. Their results showed higher concentrations of free BPA in commercial than in breast milk, indicating that breastfeeding should always be the first feeding option in early life (Martínez et al., 2019). Very low concentrations of BPA in breast milk were confirmed by research performed on women in France (Deceuninck et al. 2015); the concentrations were between <LOQ and 1.16 μg kg^{-1}. A similar research was conducted in Canada, where total BPA was detected in 25.9% of the examined human milk samples, in concentrations between <0.036 and 2.5 ng g^{-1}, while free BPA was detected in 16.5% of the examined samples, in concentrations ranging between <0.036 and 2.3 ng g^{-1}. Based on the low frequency of detection of free BPA in human milk samples, the researchers concluded that dietary exposure to BPA for Canadian breast-fed infants was expected to be somewhat lower compared to exposure of formula-fed infants (Cao et al., 2015).

Humans can also be exposed to BPA through food contacting papers (FCP). Accordingly, Zhou et al. (2015) analyzed FCPs on BPA and its chlorinated byproducts. They took 74 FCP samples from all around the world (mostly China, USA, Japan, and Europe). BPA was widely detected in FCP samples, but in concentrations below LOQ, which was 83 ng g^{-1}. Chlorinated byproducts were detected in less than half of the samples, and their concentrations mainly depended on the bleaching processes used in paper production. Furthermore, it was shown that BPA, and some of its chlorinated byproducts, could migrate from coffee filters into the coffee solution.

BPA exposure by diet can also affect other species. Thus, the analysis of canned dog food (Koestel et al., 2017) showed the presence of BPA which, in a two-week exposure, caused a significant increase in the concentration of circulating BPA in blood and fecal samples. Furthermore, the results suggested a positive correlation between elevated BPA concentrations and increased plasma bicarbonate concentrations, which can be associated with fecal microbiome alterations. Short-term feeding by canned food increased the circulating BPA concentrations in dogs comparable to the amounts detected in humans. Greater BPA concentrations were associated with serum chemistry and microbiome changes. Since dogs share our internal and external environments, their health should also be considered when it comes to the exposure to various chemicals, including BPA.

BPA in Drinking Water and Beverages

Drinking water and beverages can be found in various packaging as well. Drinking water from water supply systems is usually transported to the end user through plastic pipes made of polyethylene (PE) or polyvinyl chloride (PVC). Bottled drinking water and non-alcoholic beverages are often packed in glass and PET bottles, while alcoholic beverages are most often packed in glass bottles.

The evaluation of potential exposure of a significant part of the French population to alkylphenol and bisphenol contaminants due to water consumption (Colin et al., 2014) showed that concentrations of target compounds were lower in treated water than in the raw one, which implied a relative effectiveness of certain water treatments for the elimination of these compounds. The analysis of tap water (Cheng et al., 2016) supplied through PVC pipes, stainless steel and galvanized pipes showed higher concentrations of BPA in PVC pipes than in stainless steel and galvanized ones. This suggests that PVC pipes are a potential source of human exposure to BPA. In addition, Rajasärkkä et al. (2016) found that leaching of BPA from different age epoxy lining in drinking water pipes was increasing with older technology and warmer water. Preliminary research of drinking water in Pretoria and Cape Town, using yeast estrogen screen, showed estrogenic activity; therefore, Van Zijl et al. (2017) examined samples of drinking water taken from various distribution points. The samples were collected seasonally over four sampling periods. The analysis revealed occurrence of BPA (0.01 to 28.83 ng L^{-1}), but the levels were comparable with data obtained from other countries and were considered acceptable. Nevertheless, an acceptable health risk associated with the consumption of drinking water from water supply system remains. The determination of leaching potential and leaching kinetics of BPA from various plastic containers exposed to UV light (Rowell et al., 2016) showed that BPA was leaching from containers made from PC plastics only, and that the health risks from the consumption of bottled water increased after UV exposure. Chevolleau et al. (2016) used bioluminescent assays for the detection of hormone-like activities in natural mineral water bottled in glass and PET packaging; the packaging was exposed to various storing conditions, and the results were negative. However, they found estrogenic activity in filtered tap water, indicating that the filters themselves might be a source of BPA. Fan et al. (2014) investigated the effects of storage temperature and contact time on the leaching of BPA from PET bottles into the water they contained. They analyzed water after one week of storage at three temperatures: 4, 25 and 70 °C, and found that the BPA concentration increased more at higher temperatures. The monitoring of leaching over a longer contact period indicated that BPA concentration in water was continuously increasing until the fourth week of contact, but decreased after that point, implying that PET bottles may become stable after a certain contact period.

Other Ways of Exposure to BPA

One of the ways to be exposed to BPA is through medical treatments. Therefore, Gatimel et al. (2015) examined plastic consumables used for assisted reproductive technology (ART). BPA was not detected in the culture or the ART medium, syringes, tubes, plastic dishes, syringe stoppers, or pipette tips. It occurred in catheters for embryo transfer, and one type of syringe for embryo transfer in concentrations ranging between <LOQ (0.5 ng mL^{-1}) and 0.6 ng mL^{-1}. In three types of strippers for oocyte denudation, concentrations of BPA ranged between 0.30 and 0.61 ng mL^{-1}. Even though the research indicated leaching of BPA, the concentrations were relatively low. However, to be sure, Gatimel et al. recommended the usage of borosilicate glass strippers instead of PC made ones. Newborns in neonatal intensive care units (NICUs) are also in contact with various medical products. Those products were examined by Iribarne-Durán et al. (2019), who found BPA in three-fifths of the tested NICU items. The highest mean concentrations of BPA were detected in the three-way stopcock (>7.000 ng g^{-1}), then in patterned transparent film dressing (688 ng g^{-1}), gastro-duodenal feeding tubes (301.1 ng g^{-1}), sterile gloves (140.5 ng g^{-1}), single-lumen umbilical catheters (130.4 ng g^{-1}), and in extension sets for intravenous infusion (112.7 ng g^{-1}). The detected levels of BPA call for further research which would reveal the possible consequences for newborns and would help assess the exposure risk. Gaynor et al. (2019) examined concentrations of BPA in urine of neonates undergoing a cardiac operation, as well as their mothers. The concentrations of BPA in mother's urine ranged between 0.8 and 1.9 μg L^{-1}, while, in infant's urine, they were between 7.3 and 13.3 μg L^{-1} for preoperative samples, and between 10.8 and 18.0 mg L^{-1} for postoperative samples. Obviously, the infants were exposed to BPA through medical equipment used in cardiac operations. According to Maserejian et al. (2016), the increase in BPA concentrations in urine samples can also occur after the placing of bis-GMA-based restorations in children and adolescents. Overall, mean change in urinary BPA concentrations between pretreatment and the first day after the treatment was 1.71 ng mL^{-1}; the change between pretreatment and the third visit was 1.97 ng mL^{-1}, and between pretreatment and the final visit (approximately after six months) it was 0.29 ng mL^{-1}. It seems that the placement of a higher number of composites in children and adolescents was associated with a greater increase in urinary BPA concentrations recorded the first day after the treatment, but no significant increase was detected 14 days or six months after the treatment. Other analyses showed a decrease in BPA concentrations in urine compared to those in pretreatment.

Bacle et al. (2016) investigated the potential overall exposure to BPA during hemodialysis treatment in patients suffering from end-stage renal disease. Their results showed a corroboration of the hypothesis stating that a significant amount of BPA may migrate from dialyzers. Furthermore, the results indicated that BPA came from the water used in dialysate production (8.0 ± 5.2 ng L^{-1} on average), as well as through the dialysis machine and dialysate cartridges, which leads to a dialysate contamination of 22.7 ± 15.6 ng L^{-1} on average. The authors considered all sources of BPA contamination during a hemodialysis session and calculated that the highest daily exposure of hemodialyzed patients could reach up to 140 ng kg^{-1} bw.

The Effects of BPA on the Human Health

There are four paths by which a substance can enter the body: inhalation, skin (or eye) absorption, ingestion, and injection. Once the substance is absorbed into the body, it is commonly metabolized; nevertheless, it can be stored in the body or excreted from the body as well. Hazardous substances are not always harmful only in their original form; very often metabolism byproducts of these substances are also harmful, sometimes even more harmful than the original substance. For example, chlorine is used for water disinfection, and, in proposed concentration, does not present a risk for human health; yet, some disinfection byproducts are carcinogenic (University Nebraska, 2012).

Performing test on animals is a common approach in studying the adverse effects of potentially hazardous substances. Consequently, the research of Kim et al. (2004), performed on rats, showed that the blood-brain barrier is ineffective in preventing BPA transfer from plasma to brain, and that the liver has a higher tissue load than the kidney. In another research (Srivastava et al., 2019), female Wistar rats were exposed orally to 5, 50, 300, 600 and 800 mg of BPA kg^{-1} bw week-1 that was mixed in olive oil and administered every 168 h for 3 months, continuing through the mating, gestation, and lactation processes. The results showed that rats exposed to BPA exhibited a decrease in the fertility rate and the weight of reproductive organs (ovary and uterus), accompanied by significantly decreased levels of hormones in the non-pregnancy phase.

Another way of exposure that should be considered is prenatal exposure. Lee et al. (2019) investigated the effect that prenatal exposure to multiple environmental pollutants (including bisphenols) had on birth weight. The results indicated that exposure had a negative effect (decreasing of birth weight), even in cases where pollutants were in levels below the concentration assumed as required for direct effect. Prenatal exposure to EDCs, including BPA, is associated with various health problems, such as obesity and diabetes diseases in childhood, as well as with reproductive, behavioral and neurodevelopment problems. The estimation of prenatal exposure to BPA through food consumption of pregnant women living in Tarragona County (Spain) showed that canned fruits and vegetables, followed by canned meat and meat products, were the major contributors to the total dietary intake of BPA (Martínez et al., 2017). Despite dietary variations among the participants, the intake of the chemical was considerably lower than the respective TDI value established by the EFSA. Internal dosimetry showed that BPA might have a greater effect on developing organs in young or unborn children than in fetuses (Martínez et al., 2017).

Early-life chronic exposure to various environmental contaminants, including BPA, may affect central tissues and cause inflammation and apoptosis with severe implications for metabolism. The Developmental Origins of Health and Disease (DOHaD) concept articulates events in the developmental phases of life, such as intrauterine, lactation, and adolescence, to later-life metabolism and health. During these developmental phases, humans are more susceptible to environmental changes, which may cause various health problems later in life (Almeida et al., 2019). Some of the problems are obesity, metabolic syndrome, etc.

The accumulation of BPA in a human body can cause many health problems: from easy-to-repair single-strand DNA breaks (SSBs) to error-prone double-strand DNA breaks (DSBs). Jalal et al. (2018) found that the human liver could efficiently metabolize BPA via glucuronidation and sulfation pathways, but the by-product of metabolism, bisphenol-o-quinone could act as a DNA adduct. In addition, they analyzed how BPA could interact with several signaling pathways that might eventually lead to disease morphology, and even tumorigenesis. Even though they found no clear link between BPA and carcinogenicity, Jalal et al. suggested conducting further research. Various studies (Bodin et al., 2014, Ahn et al., 2018; Howard, 2019) were conducted on the connection between BPA exposure and the development of type 1 diabetes mellitus (T1DM). The studies included prenatal exposures, exposures during childhood, and exposures in adults over 21. The results implied that BPA might increase the risk of T1DM, but further research is necessary. Radwan et al. (2018) examined the correlations between BPA concentrations in urine and semen quality. The median concentration of BPA in urine was 1.87 μg L^{-1}, quantified in more than 98% of the analyzed samples. The results showed an increase in total sperm sex chromosome disomy and in the percentage of immature sperm, while motility was decreased. Despite the fact that the authors concluded that BPA exposure was associated with poorer semen quality, they suggested future studies to confirm their statement. BPA also decreases anogenital distance after prenatal exposure as described by Mammadov et al. (2018). In their research, the authors measured the anogenital distance in newborns, and BPA levels in the cord blood. The mean anopenile distance was 45.2±6 mm, and anoscrotal distance was 21.9±5.4 mm in boys; the mean anoclitoral distance was 33.8±6.6 mm, and the mean anofourchette distance was 12.2±4.9 mm in girls. The mean cord blood BPA level was 4.75±2.18 ng mL^{-1}. The results showed a statistically significant correlation between the anoscrotal distance and high cord blood BPA levels above the 90th percentile in boys, while changes in anogenital distance in girls were not statistically significant.

Detecting BPA

BPA concentrations have been detected in various matrices, from environmental ones, like air, soil, and water, to food and biological matrices, such as urine, blood, breast milk, umbilical cord, placenta, etc. Therefore, the main concern in BPA analysis is sample preparation, while detection itself is usually based on gas chromatography (GC) or liquid (LC) chromatography coupled with mass spectrometry (MS) detection. In method development, it is desirable to have LOD and LOQ as low as possible, especially for trace materials.

Cao et al. (2018) tested solid phase extraction (SPE) as a sample preparation method for GC-MS analysis, and got acceptable values of recovery for various matrices, including water and some beverages. They successfully determined BPA concentrations ranging between 0.022 and 0.030 ng g^{-1} for products packed in PET bottles, and between 0.085 and 0.320 ng g^{-1} for canned products. In order to improve the LC-MS method, Pernica et al. (2015) applied pre-column derivatization by dansyl chloride, which significantly increased method sensitivity (up to 1000 times). The optimal conditions, in terms of achieving high sensitivity, included acetonitrile as the solvent, a reaction performed during 60 min at 60 °C, a pH value set to 10.5, and a concentration of dansyl chloride of 0.5 mg mL^{-1}. Linear calibration was performed in a concentration range of 1-1000 ng mL^{-1}, with LOD and LOQ values ranging between 0.02 and 0.25 pg per injection, and between 0.08 and 0.83 pg per injection, respectively. The median BPA concentration obtained for bottled waters was 4.7 ng L^{-1}.

One of the modern approaches in analytical chemistry is the application of biosensors, which generally provides rapid determination with high sensitivity and specificity; the low-cost of this approach is its additional great feature. Mirzajani et al. (2017) developed a biosensor for the determination of BPA. It allowed single step detection of BPA within 20 seconds in a range between 0.001 and 10 pM, with a LOD value of 152.93 aM. Successful testing of the developed BPA biosensor (performed on canned foods) confirmed the high potential of this approach and its application in on-site food monitoring.

Legislation Regarding BPA

BPA has become one of major concerns of regulatory agencies all around the world. According to the U.S. Environmental Protection Agency (U. S. Environmental Protection Agency, 2010), the intake limit for BPA is 0.05 mg kg^{-1}bw day^{-1}, while the EFSA and the European Commission (EC) have significantly lower TDI values to 0.004 mg kg^{-1} bw day^{-1}. The EC has also set a specific migration limit for BPA in food of 0.5 mg kg^{-1} (European Food Safety Authority, 2015; European Comission, 2018a; U.S. Environmental Protection Agency. 2010).

BPA is still permitted for use in food contact materials and medical equipment in the European Union. Nevertheless, stricter measures regarding BPA are being gradually introduced. Thus, BPA has been prohibited in manufacturing PC infant feeding bottles since 2011, and some countries, like France, have already forbidden the production of food containers containing BPA (The European Food Information Council, 2014). A similar situation is noted in other developed world countries. In the United States, 13 states banned BPA from various products, mostly those made for children. For example, in 2011, California prohibited the manufacture, sale and distribution of bottles or cups which contain BPA at a detectable level above 0.1 parts per billion, if the containers were designed for children three years of age or younger; Delaware prohibited the sale of bottles or cups containing BPA if those containers were designed for children under four years of age (National Conference of State Legislatures, 2015). Some authors point out that, unfortunately, there are practically no BPA restrictions in developing countries across Africa, South-East Asia, and South and Central America (Baluka et al., 2016). On the other hand, in Singapore, baby bottles and cups are no longer made from PC plastics but from polyether sulfone (PES) plastic, which does not contain BPA (Singapore Food Agency, 2017).

Conclusion

Recent literature provides increasing evidence showing that environmental BPA can be adverse for human health, particularly in everyday consumer behavior, due to the biologically relevant BPA levels that can be found in food containers and beverage bottles. The endocrine disrupting potential is the most researched, but BPA has been related to reproductive and developmental effects, metabolic diseases, neurological and behavioral diseases as well. Therefore, understanding both the source and the extent of exposure, is critical for translating scientific findings into public health intervention and monitoring strategies in order to promote policy changes.

Acknowledgements

The authors would like to acknowledge the financial support of the Croatian Science Foundation through project entitled *Advanced Water Treatment Technologies for Microplastics Removal* (AdWaTMiR, IP-2019-04-9661) and of the Operational Program for Competitiveness and Cohesion 2014 – 2020 through the project entitled *The Potential of Microencapsulation in Cheese Production* (KK.01.1.1.04.0058).

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