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Toxicity of Bisphenol-A: Effects on Health and Regulations

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***Abstract*—**Bisphenol-A (BPA) is one of the highest volume chemicals produced worldwide in the plastic industry. This compound is mostly used in producing polycarbonate plastics that are often used for food and beverage storage, and BPA is also a component of epoxy resins that are used to line food and beverage containers. Studies performed in this area indicated that BPA could be extracted from such products while they are in contact with food. Therefore, BPA exposure is presumed. In this paper, the chemical structure of BPA, factors affecting BPA migration to food and beverages, effects on health, and recent regulations will be reviewed.

***Keywords*—**BPA, health, regulations, toxicity.

I. Introduction

CHEMICALLY known as 2,2- bi(4-hydroxyphenil) propan, bisphenol-A (BPA) is one of the chemicals that has widest production area in the world. As a colorless solid chemical BPA is soluble in the organic solvents but its solubility in water is very low. BPA is widely considered as the main ingredient in fastening, plasticizing, hardening of plastics, lacquering and filling materials [1].

BPA is the raw material of 71% of polycarbonate based resins and 27% of epoxy based resins which are used for coating metal based food and beverage cans [1]. Polycarbonate materials are generally noticeable in the food contact materials. These can be listed as baby bottles; food cooking/service equipments; storage containers; milk, water and other beverages' bottles/carboys; reusable beverage bottles; inner coating of cans including epoxy based resins, etc. [2]. Besides, they can be used in order to gain strength to toys, water pipes and medical tubing [3].

II. Chemical Properties

Bisphenol-A (BPA) or 4,4'-dihydroxy-2,2-diphenylpropane is an organic compound containing two phenol functional groups. It is classified as a suspicious endocrine system disrupting material [4], [5]. Fig. 1 represents the chemical structure of BPA and Table I represents the chemical properties of BPA [6], [7].

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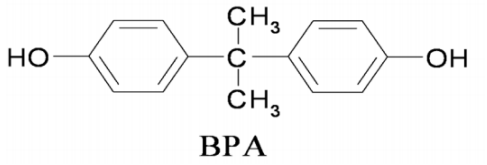

Fig. 1 Chemical structure of BPA

TABLE I
Chemical Properties of BPA

Chemical Properties	Value
CAS number	80-05-7
Molecular formula	$C_{15}H_{16}O_2$
Molecular weight	228.29
Melting point	158-159 °C
Solubility (at 20-25°C)	1000 mg/L
Vapor pressure (at 20-25°C)	7.25e-7 mmHg
Diffusion coefficient in air	0.05 cm^2/s
Diffusion coefficient in water	5.89 cm^2/s
Oral reference dose	0.05 mg/kg/day
Inhalation reference concentration	0.08 mg/m^3
Dermal absorption fraction	0.1
Gastrointestinal absorption fraction	0.5

III. Factors Affecting BPA Migration to Food

BPA migration from polycarbonates to liquids is resulted by hydrolysis diffusion catalyzed by hydroxides [8]. According to recent studies, in polycarbonate based materials; temperature, heat treatment time, destruction, water hardness and pH effect migration. In epoxy based resins; lacquering type, amount of lac used, process parameters (temperature and time), contents of the contact food material (amount of salt and oil) factors effect migration [8]-[14]. Considering the food groups, it is observed that BPA migration occurs in canned meat/fishery products and instant soups, especially when their salt and oil content is high [15], [16].

In polycarbonate bottles, pH is increased while water is boiling according to increased solubility of lime and these results in increased BPA migration. However, brushing of bottle doesn't increase BPA migration. It is difficult to determine the effect of aging. Besides, alkaline detergent residues after washing in the dishwasher also increase BPA migration. Similarly, food preparation methods that cause increase in pH also gives same effect. Food mineral composition effects are still unclear [8].

It was observed in the studies examining the migration from cans that temperature is more effective than heating time. At the same time, BPA migration in canned foods is directly affected by storage time and it was observed that BPA firstly

migrates to liquid in can and later to solid food materials. Migration occurs during the storage time even if heat treatment is finished [17]. It is important to control heat treatment temperature and time in order to decrease BPA migration from coating surface of cans.

It was also observed that in plastic containers especially in polycarbonate baby bottles according to excessive usage and scratches and also effect of sterilization resulted in high levels of BPA migration. It was observed that new polycarbonate baby bottles contain below 1.0-3.5 ppb BPA content, whereas it was measured 10-28 ppb levels in used and scratched baby bottles [17]. Erdem & Acar (2012) observed that water carboys stored at 4, 25 and 35°C for 60 days in Turkey don't contain BPA levels threatening human health. BPA levels were measured as below 450 times under the specific migration limits [18]. Table II represents several studies about BPA migration from various packaging materials at different conditions.

TABLE II
BPA MIGRATION OF SEVERAL PACKAGING MATERIALS AT DIFFERENT CONDITIONS [9], [11], [17], [19]

Packaging Material	Food or Liquid that simulates food	Test conditions	BPA levels (ppb)
Cans	Water	120°C / 90 min	82
		100°C / 9 min	2
		60°C and 90°C / 9 min	-
	Ethanol (20%)	60°C / 30 min	-
	Salt (1-10%)	121°C / 30 min	7 - 13
	Glucose (5-20%)	121°C / 30 min	16 - 18
	Oils	121°C / 30 min	7 - 8
	Sunflower oil	121°C / 90 min	403 – 646
		111°C / 135 min	11 - 73
		100°C / 9 min	< 5 - 18
	Coffee	121°C / 30 min	33 - 134
	Caffeine solvent	121°C / 30 min	9 - 124
Plastics	Water	95°C / 30 min	0.5 - 26
		100°C / 6 hours	-
		49°C / 10 days	-
PVC stretch film	Water	40°C / 10 days	-
	Olive oil	40°C / 10 days	-

IV. EFFECTS OF BPA ON HEALTH

Once in the body, ingested BPA is mainly conjugated with glucuronic acid, which is eliminated in the urine. A fraction of the absorbed BPA may also be distributed to body storage site(s) such as adipose tissue, followed by a slow, low-level release of BPA into the bloodstream [1]. BPA gives harm to endocrine system in human body and it has estrogen-like activity [20]-[25].

A. Effects on Endocrine and Reproductive System and Thyroid Hormone

Endocrine disruptors have become an important public health issue, recently [26]. Endocrine disrupting chemicals have the ability of imitate, block or interact with hormones in human body and therefore they can affect growth and reproduction [27], [28]. BPA is considered as one of these endocrine disruptors. Endocrine disruptors may cause breast cancer, irregular menstruation, endometriosis, spontaneous abortion in women, and cancer (testis, prostate), reduction of sperm count and quality in men [28]-[33]. Following perinatal exposure of rats to BPA by gavage (1.2 or 2.4 µg/kg bw/day) Salian et al. [34] noticed changes in the expression of steroid receptor coregulators in the testis. According to this study, they have observed that BPA causes reduction in sperm count and motility in male mice [34].

In mice from dams subcutaneously treated (gestational days 9–16) to 0.1–1000 µg BPA/kg bw/day. Newbold et al. [35] observed an increase in ovarian cysts, in progressive proliferative lesions of the oviduct and in tumor incidence of reproductive tissues.

BPA was initially considered to be a weak environmental estrogen based on the relative binding affinity of BPA for the classical nuclear receptors ER alpha and ER beta which were estimated to be over 1000–10,000 fold lower than that of estradiol [2]. Besides, another in vivo study on mice illustrated that below 50 mg/kg dose of BPA increase uterus weight and therefore demonstrated to induce estrogenic activity [36].

According to recent studies, it was proved that BPA inhibit the thyroid hormone levels and also testosterone synthesis is blocked by its dose per trillion [2].

B. Effects on Immune System

It is well established that estrogens play a role in the immune system and recent research shows that BPA is capable of influencing the immune system functions. According to a study on mice, it was observed that mice exposed to BPA before giving birth had increased amount of lymphocytes according to Listeria infection. Besides, cytokine production was increased and the number of regulatory T cells was decreased [37]. Exposure to BPA in growth period causes decrease in tolerance of ovalbumin antigen and increase in asthma phenotype [38], [39]. Moreover, there are evidences that exposure to BPA causes decrease in cytokine and antibody levels and therefore increase the production of antibodies [40].

C. Effects on Behavioral Disorders

Most of the studies about effect of BPA on behavioral disorders focused on effects of long time exposure to BPA. According to these studies, it was indicated that BPA causes learning and memory impairments associated with dopamine [41]. There are also studies indicating that exposure to BPA increases hyperactivity and anxiety levels [42].

D. Carcinogenic Effects

Several studies indicated that BPA exposure increases the risk for cancer [43], [44]. There are studies in the literature about BPA cause cancer types of testis, prostate, uterus, ovary cancers [2], [45]. Besides, as BPA has estrogenic characteristics it was indicated that BPA may cause breast cancer [46]. Cancer types such as breast, uterus, testis and prostate increase in all over the world was correlated with endocrine disruptors [29], [33], [44], [47].

E. Effects on Obesity

Although the effect of BPA on fat tissues is known, findings have not yet qualified on this subject. High dose exposure of laboratory animals resulted in decrease in body mass index and lack of nutrition, however in another study there was no statistical difference in body mass index, fat stores and triglyceride levels of laboratory animals exposed to BPA for 3 months [48]. Moreover, it was reported in several studies that BPA affects glucose intolerance and insulin sensitivity [49].

V. Regulations

Argument exists regarding what concentrations of BPA are dangerous to humans or wildlife, but it is clear that BPA causes potential risks and several countries have regulations about this subject. Most proposed regulation addresses human exposure through food contact materials and packaging, but several nations have assessed environmental exposure risks to BPA. Although nearly one-third and one-quarter of global BPA production occurs in the US and the European Union, respectively, BPA released into the environment is not strongly regulated in either location [50], [51]. Canada is currently the only country regulating environmental fates of BPA.

A. Regulations in USA and Canada

Although FDA stated at the past that BPA is safe for even the pregnant women and children, The National Toxicology Program Center for the Evaluation of Risks to Human Reproduction, part of the National Institutes of Health, completed a review of BPA in September 2008 and expressed "some concern" for effects on the brain, behavior, and prostate gland in fetuses, infants, and children at current human exposures to BPA. In the update of the draft assessment "BPA for Use in Food Contact Applications" in January 2010, the FDA shares at this interim stage the perspective of the National Toxicology Program that recent studies provide reason for some concern. Regarding interim public health recommendations, the FDA supports reasonable steps to reduce exposure of infants to BPA in the food supply. In addition, the FDA will work with industry to support and evaluate manufacturing practices and alternative substances that could reduce exposure of the population and is supporting the industry's actions to stop producing BPA-containing bottles and infant feeding cups for the US market. The FDA is facilitating the development of alternatives to BPA for the linings of infant formula cans [52].

Canada is the only country in the world stated the toxicity of BPA and Government of Canada banned the usage of BPA in baby bottles.

B. Regulations in EU and Turkey

The European Union (EU) has a fundamentally different philosophy on chemical regulation based on the REACH (Registration, Evaluation, Authorization and Restriction of Chemicals) policies of 2007. REACH is often considered to be the EU equivalent to TSCA and is intended to manage chemicals of concern to human and environmental health that are manufactured in or imported into the EU [53].

The European Commission conducted a thorough risk assessment of BPA in 2003, and an updated assessment in 2008. Both assessments concluded that at current levels of exposure, BPA is safe for humans and the environment [54]. However, the 2008 risk assessment called for further research on aquatic species [55].

The European Food Safety Authority also conducted extensive risk assessments on the use of BPA as a food contact material. Reports issued in 2007, 2008, and 2010 all concluded that current uses of BPA in food packaging do not pose any substantial risk to humans [56]. Dissatisfied with the lack of oversight by REACH and EFSA, several European countries proposed bans on BPA in some products intended for use by infants. France suspended sales of baby bottles containing BPA in 2010 [57]. Later that year, the EU banned BPA in baby bottles according to the findings of the EFSA risk assessments [58]. EFSA determined the daily exposure limit to BPA as 0.05 mg/kg body weight and limited specific migration level as 0.6 ppm. In Turkey, BPA usage is banned in the production of polycarbonate materials like baby bottles within the framework of compliance with EU regulations [59].

VI. Conclusion

BPA has the risk to migrate into foods and beverages as it is widely used in the world in the packaging of food and drink products. It was stated in several studies in the literature that BPA is a chemical that gives damage to endocrine system. Besides, xenoestrogens like BPA possess cancers in reproductive system (testis, ovary, breast, uterus, prostate), fertility problems (decrease sperm count and quality) correlated with endocrine system problems. Moreover, some studies reported effects on obesity and behavioral disorders. Nowadays, potential health risks of BPA have been studied more intensively.

The amount of BPA migration to food and beverages are studied according to variety of factors including temperature, time, food contents, and packaging materials. BPA usage is banned for the production of baby bottles in EU and Turkey. In Turkey, studies on BPA migration levels into water from carboys reported that BPA migration levels were not as high as it threatens human health [60]. However, more studies should be done to measure the levels of BPA migration into other foods and beverages from other storage, packaging and service equipment.

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