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Food safety and public health: the paradox of bisphenol A

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ABSTRACT

The overwhelming burden that bisphenol A (BPA) has caused humanity demands clarity as the global society agitates for a safer food packaging component. BPA is a structural component used in hardening of plastics and lining of various food and beverage containers to protect food from contamination and extend shelf life. The study review several literatures on BPA exposures, BPA toxicokinetics, BPA pharmacokinetics, epidemiology and ecological impacts of BPA. Our findings posits that even though BPA does not have a long span *per se*, its influence and accumulation in human body has a negative long term effect which could lead to several dangerous health implications such as cancer, obesity and fertility problems. These findings challenge the long-standing scientific and legal presumption of BPA's safety and recommends possible safety measures that can be taken in order to reduce exposure to BPA and few of such actions includes; public awareness about BPA and its presence in our daily consumption, negative effects of BPA to the environment and to the human body and finally, thorough investigation of the presence and threshold limit of BPA in plastics and canned foods.

Keywords: BPA, food safety, human health, ecology

1. INTRODUCTION

Food quality control is a global concern in that food safety is pivotal for the survival of all living organisms involved in the ecological food chain. There is no gain saying that the global society in the last 8 decades has achieved significant strides in her quest for rapid economic growth through industrialization. However, myriads of industrial products have presented threats that may now be considered deleterious to our survival and development. Examples of these products include pesticides, heavy metals, polycyclic aromatic hydrocarbons (PAH), polychlorinated biphenyls (PCBs), electromagnetic radiations and more interestingly are the bisphenol A products.

Bisphenol A (mostly abbreviated as BPA) is essentially an organosynthetic compound used as a structural component in the production of polycarbonate plastics, epoxy resins and other food storage containers. It was first discovered in 1891 by Russian chemist Aleksandr Dianin [1]. Indeed, It is a high production volume chemical common to the packaging and container (P&C) industry owing to its economical value and ubiquitous nature. It is present in the lining of canned foods and drinks, medical devices, compact discs, dental sealants, toys, water bottles, sport equipments, thermal papers used in sales receipts and many other modern products that human uses on a daily basis.

BPA has long been regarded as a valuable chemical since its use cut across various sectors of the global economy such as food-and-beverage, household products, metal industry, building and construction industry and pharmaceutical sectors etc. Advances in food processing and food packaging have unarguably contributed positively towards sustaining global food security. For instance, food packaging can retard product deterioration, retain the beneficial effects of processing, extend shelf-life, and maintain the quality and safety of food and also provide consumers with ingredient and nutritional information [2]. Also, these advances have gradually made it possible to replace some crude packaging materials such as earthenware, calabash, wooden materials, leaves, stalk, fibre, ropes etc. which may be liable to damage or contamination by micro-organisms, air, moisture and toxins.

Following the widespread usage of BPA for over 50 years [3], a plethora of studies have reported its occurrence in ecosphere such as air [4], water [3,5], soil [6], sediment[7], indoor dust[8], and human tissues [9,10].

Concerns regarding the safety and side effects of BPA began to emerge in the late 1990s when BPA was found to leach out of plastics into experimental animal subjects resulting in prevalence of chromosomal anomalies in offspring [11]. In 2005 the European Union banned the manufacture of bisphenol F diglycidyl ether as a food packaging material [12].

It is estimated that 93 % of the world's population has traces of BPAs in their bodies [13]. It can be found in almost every part of the human body, even in the breast milk. Daily dietary intakes, based on concentrations measured in food, vary widely, but have been estimated in Europe to be about 0.2 μg/kg body weight in breast-fed babies, 2.3 μg/kg body weight in formula-fed babies using non- polycarbonate plastic (PC) bottles, 11 μg/kg body weight in formula-fed babies using PC bottles, and 1.5 μg/kg body weight in adults [14].

Assessment of daily human exposure to BPA in the general population by biomonitoring of urinary excretion of BPA metabolites also varies widely, but has been estimated to be up to 0.16 μg/kg body weight in the USA, and 0.04-0.08 μg/kg body weight in Japan [14]. The main mechanism by which most people are exposed to BPA is through leaching from plastic-food products (i.e. through diet) while air, dust, and water are other

possible sources of exposure. BPA in food and beverages accounts for the majority of daily human exposure. The degree to which BPA leaches from polycarbonate bottles into liquid may depend on the temperature of the liquid or bottle, the age of the container, pH of the food or fluid content.

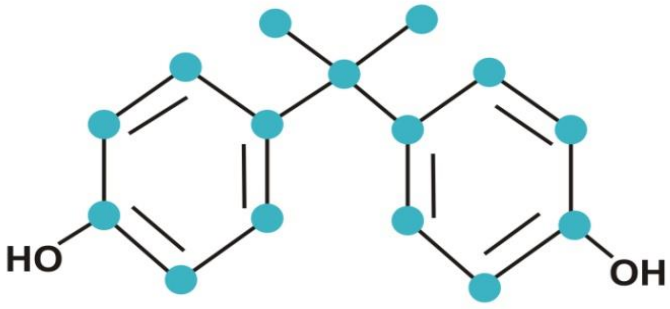

Figure 1. Chemical Structure of Bisphenol A (IUPAC Name: 2, 2-bis-(4-hydroxyphenyl) propane; 4, 4′-Isopropylidenediphenol; CAS no. 80-05-7).

Various studies have linked BPA exposure to severe health implications such as diabetes, liver enzyme abnormalities, cardiovascular disease [15], recurrent miscarriage [16] and nervous system disorders [17,18].

In this study, an overview of the literature regarding physiochemical characteristics of BPA is provided, followed by industrial production and emission of BPA, the effects of BPA on human health, the fate of BPA in ecosystem, metabolism of BPA the ecological impacts of BPA and possible measures to mitigate human exposure to BPA.

Physicochemical characteristics of Bisphenol A

BPA is an organic compound with two phenol functional groups. Hence, it is a white flake [19] with molecular mass of 228.291 g/mol. It has a very weak solubility in water (0.03 g/100 ml) though soluble in acetic acid [20] and in aqueous alkaline solution, alcohol, and acetone; slightly soluble in carbon tetrachloride [21]. It exerts hormone like properties at high dosages. It has a boiling point of 360.5 °C at 760 mm Hg [22], melting point of 153 °C [23] and vapour pressure of 4.0×10^{-8} mm Hg at 25 °C a negligible [22], density of 1.195 at 25 °C /25 °C [19]. When heated to decomposition it emits acrid and irritating fumes [24].

Bisphenol A Production and its Emission

BPA, a key intermediate in the phenol value chain is produced by the hydrochloric acid-catalyzed condensation reaction of two molecules phenol with one molecule of acetone while bubbling hydrogen chloride through the mixture [25]. In the production process phenol and acetone are injected into a reactor filled with a cation- exchanger. Conversion to bisphenol A occurs at about 75 °C. The mixture passes into a concentrator where it is freed of water and acetone under reduced pressure.

Bisphenol A crystallises out when cooled and is then washed with phenol and distilled out under reduced pressure [26]. Impurities are tri- or mono- hydroxyl by-products, which can be removed by distillation and extractive crystallization under pressure [27]. Two grades of

bisphenol A are produced. The more expensive (in terms of production cost) polycarbonate grade contains a maximum of 0.2% 2,4-isopropylidenediphenol to ensure superior optical and toughness properties. The epoxy grade may contain up to 5-7% 2,4- isomer, but in commercial practice generally contains less and may be essentially the same purity as polycarbonate grade.

BPA may be released into the environment through its use and handling, and permitted discharges [25]. The leaches of BPA from baby bottles, cans and flasks to food are part of the most common emission of BPA. Two possible mechanisms for the release of BPA are: i) the release of BPA from polycarbonate or epoxy resin particles caused by diffusion. Hence, the release of BPA from polycarbonate containers into food depends on the contact time, temperature, and type of food; ii) the formation of BPA from polycarbonate or epoxy resin particles caused by chemical disintegration (i.e. by hydrolysis).

After the manufacturing process of polycarbonate, the residual BPA present in it get hydrolysed (i.e. catalyzed by hydroxide (–OH) in contact with aqueous food and stimulants) [28]. It has also been shown that BPA can be emitted to the skin from certain types of thermal printing paper, such as some types of cashier's receipts, insignificant amounts [29]. Likewise, there is no doubt that polycarbonate and epoxy resin particles are emitted to municipal wastewater. For instance, PC are processed to any kind of casings of electrical and electronic appliances for in and outdoor use, and to several vehicle components as panes, bumpers, covers and body work parts [30].

A study to quantify the leaching of bisphenol A into water, using various samples of plastic waste cut into small pieces, soaked in water for two weeks at room temperature in the dark, and the concentration of bisphenol A in the water determined by gas chromatography /mass spectrometry (GC/MS) showed that the amount of bisphenol A leached from the plastic wastes varied from undetectable to 139 μg/g [31]. The detection limit was 2 ng/g when 100 g of plastic waste was used. A sample of synthetic leather, presumed to consist of PVC yielded the highest concentrations. Around 11% of the amount of BPA in this material leached to water in two weeks.

This section describes what happens to BPA when it enters the natural environments and the impact of BPA on the environment. The fate of bisphenol compounds in the aquatic environment is of great concern in terms of both human health and environmental risks. To some extent, most forms of packaging pose environmental hazards. For instance, plastic bags can clog drains, become entangled with aquatic organisms or disrupt the digestive tracts of birds and other animals. Likewise, polystyrene that is often used for take-out food and beverage containers can similarly pose physical hazards for marine and aquatic life if it ends up in rivers or ocean environments. Such materials are slow to degrade and so can persist in the environment, including in landfills.

Meanwhile, polyvinyl chloride (PVC) plastics can release some other contaminants such as dioxins and furans — both persistent carcinogens — if subjected to incomplete combustion as can happen in environmentally substandard landfills, particularly in places where garbage dumps are routinely burned to reduce volume as they often are in cities in Africa and other part of the world. The report of earlier study on air sampling at a plastics processing firm indicated a BPA concentration of 0.208 μg/m^3, providing evidence for dermal and inhalation BPA exposure to plastics industry workers [32].

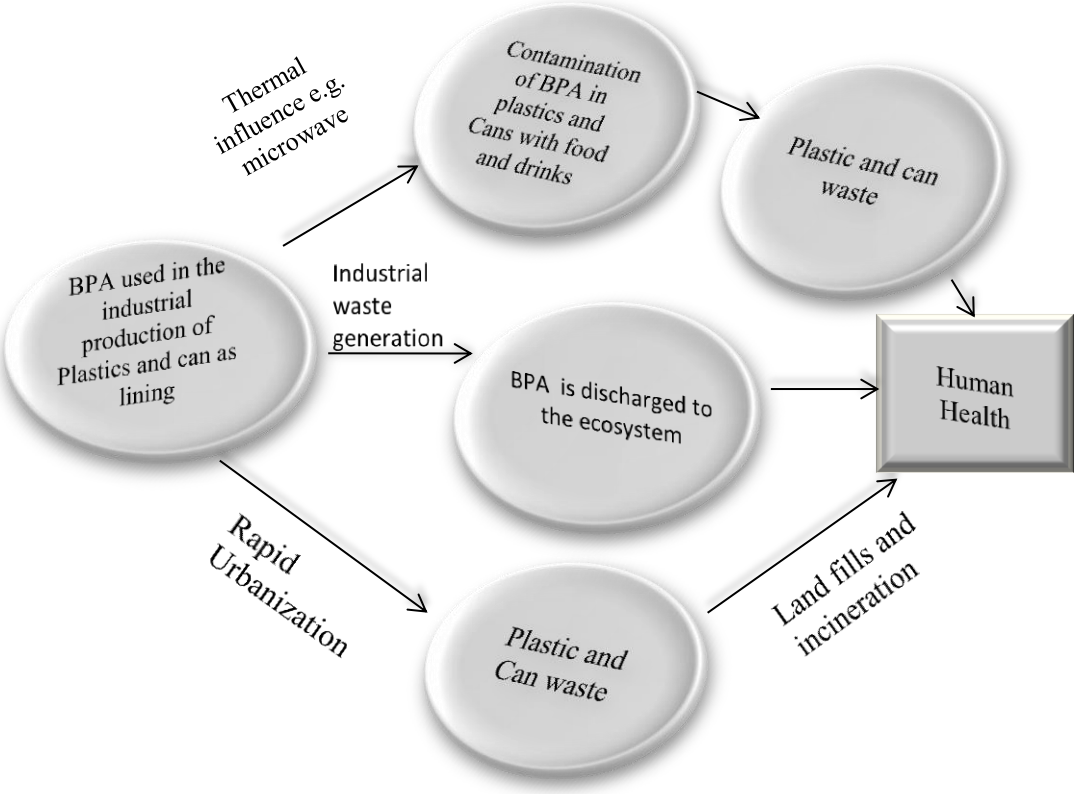

Fig. 2 Ecological impact of BPA and the fate of BPA in ecosystem

BPA has been found in lakes, rivers, and the ocean as well as in sediments and soils. Aquatic wildlife could be endangered by contaminated waste water discharges [33]. While most reported levels of BPA in fresh water are low (i.e. <1 μg/L), some of the higher levels reported in the environment have caused adverse effects in laboratory experiments [34]. The crux of our discussion here is that BPA can leach from BPA-based products into the aquatic environment; bioaccumulate and might be persistent and become an ecological burden through spreading of its metabolites to the ecosystem. But plants can rapidly absorb BPA through their roots from water and metabolize it to several glycosidic compounds. Glycosylation, the main route of BPA metabolism in plants, leads to loss of estrogenicity of the parent compound [34]. Two oxidative enzymes, peroxidase and polyphenol oxidase, are associated with BPA metabolism [35,36].

Photolysis and photo-oxidation are the main non-biological pathways of BPA breakdown in the aquatic environment. Though photodegradation of BPA is reported to be slow in pure water [34], it can still be accelerated by: a) dissolved organic matter, including humic and fulvic acid [37-39]; b) reactive oxygen species, such as hydroxyl radicals, peroxyl radicals and singlet oxygen [39-41]; and/or c) ions, like ferric and nitrate ions [38,39,42].

In a study on leaching and absorption of BPA after application of dental sealants to adult participants, 5.8-105 ppb (ng/mL) BPA was detected in saliva, but no BPA was detected in serum samples (5 ng/mL limit of detection [LOD]) collected 1 hour to 5 days post administration [43]. Studies generally suggest that BPA-degrading bacteria exist throughout

aquatic environments but that they cannot completely degrade BPA leading to the accumulation of some recalcitrant metabolites, such as BPA-glucuronides. When examining microbial interactions with BPA, both the ability of these organisms to biotransform BPA (i.e. reduces impacts on other biota) and the potential for BPA to impair the ecological functioning of these same microorganisms are important considerations.

2. METABOLISM OF BISPHENOL A

In mammals (e.g. rats), bisphenol A metabolism occurs through a partial conversion into phenols increasing their urinary content in a free and bound form. Bisphenol A is passed unaltered and in the form of glucuronides from the body through urine and feaces [44]. When administered as a single dose by gavages to male CFE rats, 28% of the 14C labeled bisphenol A was excreted in the urine (primarily as the glucosamide) and 56% in the feaces (20% as free bisphenol A, 20% as a hydroxylated bisphenol A, and the rest as an unidentified conjugate). No carbon-labeled residues were detected in animals killed after 8 days [45]. Earlier report on BPA toxicokinetics observed in common frog (*Rana temporaria*) at two experimental temperatures (7 and 19 °C) shows that BPA exposure at different concentrations does not have any constant effect on bioconcentration factors (BCFs) at the different temperatures [46]. Another toxicokinetic study of bisphenol A (BPA) in F344 rats, cynomolgus monkeys and chimpanzees shows that the systemic clearance of BPA in primates is considered to be close to that in humans due to the similarity of the hepatic blood flow-rate. The major elimination route of BPA metabolites in primates is assumed to be renal excretion, as in humans, because the enterohepatic circulation that was observed in rats was not observed [47]

Toxicity Mechanism of Bisphenol A

BPA has a short half-life in the body and is thus considered a relatively less cumulative chemical [48] and most of the dose absorbed as BPA is glucuronidated in rat liver and intestine following oral exposure [49]. Due to the short half-life of BPA, this chemical is excreted rapidly from the body by forming BPA glucuronidates or BPA sulfates during the metabolic process [50].

The mechanism of BPA (as endocrine disruptor) on human health may act in at least 3 different ways viz:

1. They may act directly as ligand for steroid hormone nuclear receptors (e.g. oestrogen, androgen, thyroid hormone receptors etc.). For instance, BPA may bind with oestrogen receptor (17ß-oestradiol) in order to induce a cellular response.
2. The second mechanism is based on stimulation of the endogenous production of 17ß-oestradiol. The aromatase (CYP19) enzyme is a key player in steroid synthesis as it catalyzes the irreversible conversion of androgens into estrogens [28].
3. Third mechanism could be the diminishing of 17ß-oestradiol degradation or BPA acting as an androgen receptor antagonist. The excretion of 17ß-oestradiol is typical indirect hormone regulation [51]. BPA is anti-estrogenic through the inhibition of 17ß-oestradiol induced transcription (62, 54 mg/kg bw) and oestrogenic through prolactine production (67,4-45 μg/dag) and *in vitro* Yeast ER assay (75, 5000-15000 less potent than E2) [52].

Bisphenol A and Gene Expression

Bisphenol A has a short half-life and effect of its exposure on human genome takes a long period of time to manifest. This poses difficulty in defining the fundamental association between BPA and its effect. This could be due to ubiquitous nature of BPA [53]. Understanding the molecular mechanisms by which environmentally relevant doses of BPA interfere with the human system function offers important basis of deregulated metabolic processes. Deregulated genes could be involved in such metabolic disorders through the possible impairment of respective system functions.

Various molecular studies have demonstrated that a large number of genes that are modulated by BPA induce negative health effects [54]. Gene such as *PPAR*, *C/EBP*, *LPL*, *GLUT 4*, *CYP19*, *GPAT* and *DGAT*, and Leptin (*OB*) are modulated by BPA exposure during adipocyte differentiation and it affects expression and subsequently modulates adipose tissue functions. [55-58] tested whether there could be any physiological and/or functional significance effect in gene expressed by adipocytes due to changes caused by BPA. Three pro-inflammatory genes *CCL20*, *IL18*, and *IL1B* were expressed as revealed by qRT-PCRs. These experiments confirmed that BPA promotes inflammation in mature adipocytes after showing that secretion of deregulated cytokines IL1B, IL18, and CCL20was about three times, two times and six times higher than it was in control cells with values of 14.4 pg/10^6 cells vs. 4.17 pg/10^6 cells, 20.16 pg/10^6 cells vs. 10.98 pg/10^6 cells and 18.74 pg/10^6 cells vs. 3.25 pg/10^6 cells respectively [58]. CCL20 functions in immunoregulatory and inflammatory processes as well in metabolism. Also, there is distinct correlation between *CCL20* BMI [59].*IL18* and *IL1B* are important regulators of inflammatory responses. Their expression and secretion in adipose tissue increase in metabolic disorders [60,61].

It is revealed that bisphenol A exposure alters developmental gene expression in the foetal rhesus macaque uterus [62]. They found out that uteri exposed to BPA had significant differences in gene expression compared to controls. The genes found include *HOXA13*, *WNT4*, and *WNT5A*, and their alterations are critical in modulating reproductive organ development and/or adult function. In SKBR3 breast cancer cells and CAFs lacking estrogen receptor (ERs), studies showed that BPA induces the expression of the GPER target genes c-*FOS*, *EGR-1*, and *CTGF* through the G protein-coupled receptor GPER/EGFR/ERK transduction pathway using specific pharmacological inhibitors and gene-silencing procedures [63].

3. HEALTH EFFECTS OF BISPHENOL A

Bisphenol A is an endocrine disruptor, which can mimic the body's own hormones such as estrogen and may lead to negative health effects. Endocrine disruptors cause adverse health effects in humans and wildlife subsequent to changes in endocrine function. Most human exposures to BPA result from its use in food and beverage containers. BPA can leach into food from containers lined with epoxy resin coatings, and from polycarbonate plastic products. BPA exposure from eating canned food or drinking canned soda is often higher than exposure from drinking out of a polycarbonate beverage container. Warming the plastic, such as in a microwave, increases the leaching of BPA into liquids; temperature appears to be a more important factor in leaching than the age of the container. BPA leaches out of the can

liner into the food or drink, especially when the food is acidic such as tomato-based products or sodas. These are some of the areas of concern on human health:

Hormonal effect

Scientist has reached a common understanding that numerous environmental chemicals including BPA can interfere with complex endocrine signaling pathways. BPA is an endocrine disruptor that can affect health at very low doses particularly when exposures occur during gestation or in early life thus disrupting normal hormonal signaling and response. It has been associated with reproductive abnormalities such as lower sperm counts, hormonal changes, enlarged prostate glands, abnormalities in the number of chromosomes in eggs, and pre-cancerous changes in the breast and prostate. Low doses in parts per billion and even parts per trillion have been shown to have effects on laboratory animals and human breast cells [64]. According to the U.S. Centers for Disease Control and Prevention, 93 percent of Americans have detectable levels of BPA in their bodies [65].

Reproductive and developmental effect

Endocrine disruptors cause adverse health effects in humans and wildlife subsequent to changes in endocrine function. BPA is among the chemicals identified as a potential endocrine disruptor based on its estrogenic properties. Studies in laboratory animals have focused on understanding the consequences of BPA for estrogenic activity taking into account the variety of estrogen receptors (ER) and estrogen binding molecules as well as their functions in different reproductive processes and different stages of the life cycle. Estrogen has a pervasive effect on body function in both males and females through a variety of mechanisms. The action of BPA at ER*ƒ*i, ERs, estrogen related receptor (ERR), and the estrogen membrane receptor (mER) has been documented [66]. Epigenetic effects of BPA have also been demonstrated [67;68]. Furthermore, the estrogen receptor belongs to a large family of gene products (i.e. the nuclear steroid hormone receptor super-family), which have some ligand cross reactivity.

This family of nuclear receptors is present in all known vertebrates [69]. For example, both estrogen and BPA bind to the thyroid receptor and antagonize the androgen receptor [66]. Some consideration should be given to the relevance of the findings in laboratory animals (mostly mice and rats) to marine life. As an estrogenic agent, BPA is thought to act through the oestrogen receptor (ER). However, invertebrates have a variant ER (based on DNA sequencing) which does not bind oestrogen. Simpler animals, including the metazoan trichoplax have DNA protein similar to ER, termed the oestrogen related receptor (ERR), which also does not bind oestrogen [70]. BPA binding to the invertebrate ER and the ERR has not been determined. In a study of 77 women, higher serum BPA was found in women with a history of recurrent miscarriage than in controls [16].

In another study [71], 19 women with polycystic ovary syndrome and 7 obese women were found to have higher serum BPA than the 19 women used as control in the experiment. Additionally, significant correlations were found between serum androgen measures and serum BPA. Another outcome from a similar experiment found higher serum BPA in males than in either normal women or women with polycystic ovary syndrome and confirmed the correlation with testosterone across groups [72]. A third study found lower concentrations of serum BPA in women with complex endometrial hyperplasia with malignant potential as

compared to controls with normal endometrium or with simple endometrial hyperplasia of a benign nature [73].

Obesity effect

The rate of obesity has been observed to have greatly increased over the past 20 years [74]. An estimated one-third of U.S. adults are overweight. More than one-third of U.S. children are overweight or at risk for being overweight. There is a strong association between obesity and a number of health issues such as diabetes, coronary heart disease, hypertension, and gall bladder disease. In the past, obesity has been viewed as a result of reduced physical activities and increased caloric intake. Data from recent studies, however, suggest that exposure to chemicals that perturb the critical pathways of adipogenesis, lipid metabolism or energy balance could also initiate or exacerbate obesity.

BPA is one of the chemicals that are now considered a candidate under the environmental obesogen hypothesis [75,76].The study of environmental obesogen is an outgrowth of endocrine disruptor research. Hormones are key players in the development and maintenance of adipose tissues. In adults, sex steroids together with growth hormone have fat mobilizing properties (i.e. anti-adipogenic). Whereas, cortisol and insulin have lipogenic effects [75]. Major targets for oestrogen action in adipocytes include the reduction in lipogenesis via direct inhibition of adipocyte lipoprotein lipase expression [77]. However, BPA is an example of a compound with ER agonist activity that behaves as an obesogen under specific conditions or when exposure occurs during sensitive developmental windows. Obesity can be defined by a body-mass-index (BMI) equal to or greater than 25 kg/m^2; a value derived from the mass (weight) and height of an individual.

Human data on the relationship between BPA exposure and obesity are sparse. Non-occupational exposure to BPA in 20 women was investigated in Southeast Spain [78]. Their BMI data were consistent with the finding by the European Protective Investigation into Cancer and Nutrition in 2002 that suggested these women were overweight and BPA was detected in 55 percent of the adipose tissue samples. In a Japanese study, the investigators compared the serum levels of BPA between non-obese and obese women [71]. The non-obese group consisted of 19 women, with a mean age of 27.5 and BMI of 19.7. Whereas, the obese group consisted of seven women with a mean age of 28.8 and BMI of 28.5. Takeuchi et al. [71] found that BPA serum levels were significantly higher in the obese group ($P<0.05$), demonstrating a positive association between BPA and obesity in this study.

Thyroid effect

Thyroid hormones (THs), thyroxine (T4) and triiodothyronine (T3) all have diverse functions. They are essential to brain development, influence growth via stimulation of growth hormone, and regulate basal metabolic rates, as well as lipid and carbohydrate metabolism [79]. Environmental chemicals can disrupt THs function by preventing their biosynthesis via the inhibition of iodide uptake or thyroid peroxidase activity or interfering with the activity of transthyretin that transports THs to target tissues. They can also increase the metabolism of THs via deiodinases and uridine diphosphate glucuronyl transferase or perturbing their binding to thyroid hormone receptors (TRs) [80]. The resulting hypothyroidism or thyroid hormone dysregulations in adults may lead to fatigue, weight gain, weak pulse, cold intolerance, mental sluggishness, and depression. Such dysregulation during

the perinatal period, on the other hand, could cause cretinism in the affected person. Cretinism is characterized by having a short stature, poor motor skills, moderate to severe mental retardation. BPA has been found in serum of pregnant women, in amniotic fluid and in cord blood and placenta [81,82]. Exposure to BPA in uteri could affect TR and result in mental retardation and dwarfism similar to those caused by hypothyroidism during critical windows of development.

Immune system effect

The immune system is our main defense mechanism against invading microorganisms or tumor growth. Suppressing the immune system may weaken our defense capabilities. Overstimulation of the immune system during an infection, however, can cause extensive collateral damages, spill-over destruction of surrounding but otherwise healthy tissues that may prove fatal in some instances. Dysregulation of the immune system in other situations may lead to autoimmunity attacking one's own tissues without cause or provocation. The immune system is under tight, complex regulation to ensure that it continues to function at the optimal range. Existing data suggest that BPA could perturb this regulatory apparatus, leading to weakened defense capabilities or detrimental overstimulation of immune functions as an end result. It appears that BPA can either act directly or indirectly via the neuroendocrine system to affect the immune system.

It has been known that both the thyroid and sex hormone neuroendocrine systems are immunoregulators [83] and it should not come as a surprise that BPA, which is known to disrupt thyroid and oestrogen functions, can potentially impact the immune system. Against the above background, it should be intuitive that BPA, which is known to disrupt thyroid and oestrogen functions, can potentially impact the immune system. No literature was found on BPA's effects on the human immune system. Data from literature, however, indicate that current research focuses on the oestrogenic effect of BPA on immune functions. In an *in vitro* system, [84] using immune cells from BALB/c mice demonstrated that BPA enhanced innate immune response by increasing cytokine production including tumor necrosis factor (TNF) and IL-1 in macrophages, and stimulated both T and B cells in adaptive responses. IL-2 and IFN-γ was used as markers for Th1 response and IL-4 for Th2 response, and found that BPA stimulated Th1 cells to produce IFN-γ and Th2 cells to express IL-4. The study concluded that BPA does not preferentially activate the Th1 or Th2 path. *In vivo*, BPA also enhanced Th1 or Th2 response, depending on the doses administered [85-87]. In addition, prenatal exposure to BPA was shown to augment both Th1 and Th2 responses in adulthood [88]. BPA appears to possess complex immuno-modulating effects. It may stimulate or suppress the immune system. It may also alter immune response pathways. BPA's immunosuppressive effects can potentially compromise our abilities to flight infections. It is more difficult to interpret BPA's immune-stimulative effects. Existing data do not provide conclusive evidence that such stimulatory effects can predispose the affected individuals to autoimmunity or allergy

Nervous system effect

BPA has both indirect and direct effects on the nervous system. Since gonadal hormones in conjunction with other neurotrophins regulate cell death, neuronal migration neurogenesis, and neurotransmitter plasticity, BPA, in disrupting sex hormone functions, can affect brain development [89]. A dose-dependent (0-100 μmol/l) inhibitory effect of BPA on

neural stem cell migration and proliferation has been found [90]. In disrupting thyroid functions, BPA can also affect the development of the nervous system because thyroid hormones play an important role in prenatal and neonatal development of the brain [17]. Early hypothyroidism, for example, caused stunted dentritic growth in hippocampal CA3 neurons, resulting in cognitive effects including impaired memory, spatial perception, and attention problems [18]. In addition, BPA may directly cause neurodegeneration. BPA was shown to produce oxidative stress and induce apoptosis in neuronal cells [91] Experimental data from literature indicate that BPA has a significant impact on the dopaminergic system and hippocampal associated cognitive functions, as well as having a neurodegenerative effect. The implication of BPA's apoptotic property is that exposure to BPA may cause premature neuronal cell death. In that vein, BPA may be a risk factor for a wide range of neurodegenerative diseases.

BPA and Carcinogenesis

BPA exposure can trigger carcinogenesis [92]. Notably, perinatal BPA exposure has recently been found to act as a carcinogen in the liver, increasing the incidence of hepatic tumors in 10 month old mice [93]. It appears that BPA can affect lysophosphatidic acid receptors important in key cellular functions and in turn may be one of the underlying mechanisms in BPA-induced tumorigenesis [94].

The carcinogenic effects of BPA have been studied most often with respect to reproductive organs such as the mammary glands, ovaries and testes. Perinatal exposure to BPA at environmentally relevant levels in rats has been linked to mammary carcinogenesis in the rat dam [95] and mammary gland adenocarcinoma in the female offspring as early as post natal day 90 [96]. Moreover, BPA exposure has also been linked to the development of prostate carcinogenesis in both rats [97] and human prostate epithelium [98].

4. PREVENTIVE MEASURES TO AVERT BPA EXPOSURE

i. **Use BPA-free products:** Because of consumer concerns, some countries and some states in the US have taken action on BPA. Canada, the European Union, and selected US States/Counties have phased-out the use of BPA in some products. Manufacturers are creating more and more BPA-free products. Endeavour to look for products labelled as BPA-free. There is a tendency that any canned food or plastic product that is not labelled BPA-free or marked with recycle codes 3 or 7 may contain BPA. Use baby bottle that are BPA free. Before getting dental sealants, an individual should check with the dentist about the ingredients in the products they use, as some formulations may leach bisphenol-A

ii. **Reducing consumption of canned foods:** Efforts towards reducing the use of canned foods is simply an effort towards achieving a BPA free environment, since most cans are lined with BPA-containing resin. People can reduce their exposure to BPA by choosing fresh, unpackaged foods whenever possible.

iii. **Avoid heat.** Regulatory agencies on food and drug safety such as the National Institute of Environmental Health Sciences advises that public should avoid microwaving polycarbonate plastics or putting them in the dishwasher because small amounts of BPA may leach into foods or beverages stored in polycarbonate containers during heating.

Although polycarbonate is strong and durable, but over time it may break down from overuse at high temperatures. Avoid heating plastics even the so called "microwave-safe" plastic can leach chemicals into food when heated.

iv. **Use alternatives.** Use glass, porcelain or stainless steel containers for hot foods and liquids instead of plastic containers. Glass jars are easy to clean and can be reused for serving, drinking, storing, freezing and heating foods.

v. **Public Awareness:** Non-profit campaigns and health-advocacy groups have devoted years to alerting the public about how the chemical Bisphenol A, known as BPA, may cause hormone disruption—which is of particular concern for young children and pregnant women.

5. BPA TREATMENT

The ingestion of probiotics may be a possible treatment for BPA-orally exposed individuals since probiotics can reduce intestinal absorption by boosting BPA excretion and this will definitely go a long way in suppressing BPA's adverse effects on human health. Probiotic supplements as it is widely available in the pharmaceuticals will help to infuse or deliver several millions of 'good' bacteria (microflora) to our digestive tract. Recent studies suggest that certain strains (*i.e., Bacillus*) are able to effectively biodegrade BPA at high rates (10 mg/dm^3) under anaerobic conditions [99].

6. CONCLUSION AND RECOMMENDATIONS

In this article the adverse effects of BPA are highlighted with a special focus on reproduction, behaviour, and carcinogenesis and the potential epigenetic mechanisms by which BPA acts. There is strong evidence that the oestrogenic and anti-androgenic effects of BPA can negatively impact brain and reproductive organ development by binding to multiple receptor targets both in and out of the nucleus. More research is needed to articulate if the mechanisms by which BPA induces changes in non-human animals can be extrapolated to humans. Regular and thorough testing for BPAs in food and drinks is pivotal to avoiding its possible health effects on consumers.

Based on our findings, the following recommendations should be taken are:

i. There is the need to take appropriate and pragmatic steps in ensuring food safety and quality for domestic consumption and export. Regulatory agencies should strengthen bio-monitoring programs of deleterious chemicals such as BPAs in order to eliminate risk.

ii. Packaging technology should balance food protection with other issues, including energy and material costs, heightened social and environmental consciousness, and strict regulations on chemical pollutants and disposal of municipal solid waste.

iii. To manage possible risks arising from BPA emissions, the major sources of contamination need to be investigated while BPA contamination from municipal treatment plants need to be determined.

iv. In order to reduce ecological burden through BPA leaching, household products (e.g. plastic bags and polystyrene) should be recycled or reuse and thus, a new recycling paradigm (convenient and ecofriendly recycling options) should be considered.

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