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The Toxic Effects BPA on Fetuses, Infants, and Children

Mujtaba Ellahi and Mamoon ur Rashid

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Abstract

Bisphenol A (BPA) is an organic synthetic compound with the chemical formula $(CH_3)_2C(C_6H_4OH)_2$ belonging to the group of diphenylmethane derivatives and bisphenols, with two hydroxyphenyl groups. BPA is the common name for 2,2-(4,4′-dihydroxydiphenyl) propane, IUPAC name 4,4′-(propane-2,2-diyl) diphenol, alternative name *p,p′*-isopropylidenebisphenol, with two phenol moieties. Its important properties include low vapor pressure, moderate water solubility, and low volatility. It is a colorless solid that is soluble in organic solvents, but poorly soluble in water. BPA is a plastic component produced in large quantities for use chiefly in the production of polycarbonate plastics and epoxy resins. BPA epoxy has a good, broad range of chemical resistance, good physical properties, and is cured using a wide variety of curing agents at ambient temperatures. The present chapter focuses on different toxic effects and the influence of BPA on different stages of human life in fetuses, infants, and children. The chapter also concentrates on how to handle BPA, its treatment, and preventive measures against BPA exposure.

Keywords: toxic effects, fetuses, infants, children

1. Introduction

Bisphenol A (BPA) is a monomer used in polymer plastic material and is used comprehensively in the manufacture of polycarbonate plastics and epoxy resins. More specifically, food packaging bottles are mostly made of polycarbonate plastics, though the resins are usually used for polishing and coating of metal products including food cans, bottle tops, and water supply pipes. BPA is also used in the manufacture of polyacrylate resins, polysulfone resins, polyester resins, flame retardants, and in the recycling of thermal paper. Dental sealants and

polymeric tooth coatings also contain BPA [1]. We are exposed BPA toxicity directly through its products or indirectly throughout contaminated surroundings. Diet (food and beverages) is the chief source of human exposure to BPA, though air, dust, and water (including skin contact during bathing and swimming) are other possible sources of exposure. It was also noted that thermal printing paper (cashier's receipts) causes contamination of human skin with BPA. However, individuals employed in the BPA industry can be exposed directly to BPA at the workplace [2]. Leaching of BPA from polycarbonate products depends on the contact time, temperature, and type of food. It takes place either through the hydrolysis (breaking H^+ and OH^- ions) of residual BPA in polycarbonate products after they are developed or through diffusion in the case of dry food products. The presence of food simulators as 50% ethanol (C_2H_5OH) or 3% acetic acid (CH_3COOH) also causes enhanced leaching of BPA in food [3]. BPA may be the bona fide endocrine disruptor that unfavorably affects metabolic homeostasis. Endocrine disrupting chemicals (EDCs) have the capability of hindering normal endocrine systems. The two EDCs, BPA and triclosan (TCS), are mass produced and widespread.

2. Discussion

2.1. Scientific concerns over BPA

There are numerous scientific concerns regarding BPA toxicity in humans, particularly in fetuses, infants, and children. The data regarding BPA distribution in the environment and potential for human exposure raise public awareness and concern about BPA. The production capacity and solid waste management of BPA products and extent of the database on biochemical properties of BPA in fetuses, infants, and children are yet to be compiled from various other databases and literature sources. The detailed mechanism of BPA enzymatic, androgenic, and neurological alterations, hematological effects and histological toxicity in fetuses, infants, and children is not convincing because of inadequate studies or traditional strategies carried out on individuals exposed to BPA [4]. It is very important to plan how to handle, dispose of, and implement protective measures against BPA exposure. There is restrained doubt regarding BPA toxicity because industries are trying their best to defend and demonstrate that BPA is not that dangerous, and some researchers have proved that BPA is less toxic than was originally thought. However, it will take a long time to fully ban BPA production and usage or introduce an alternative to the plastics industries. Because of diverse opinion, some standard procedures will have to be established for the safe removal of BPA from the environment rather than imposing a complete ban [5]. In developed countries, BPA is ever present and has been detected in nearly all human serum samples [6]. In different parts of the world, BPA has been detected in human saliva, serum, urine, amniotic fluid, umbilical cord blood, and placental tissues. BPA has also been detected in human nails, hair, the dermis, breast, and in subcutaneous and visceral adipose tissue. Most of the scientific studies (over 130) have reported seven harmful effects of BPA, including breast cancer, early puberty, heart diseases, infertility in males and females, as a catalyst for multiple negative brain variations, and obesity [7].

2.2. BPA toxicity mechanism

There are several mechanisms by which BPA affects human health. In receptor-mediated mechanisms, endocrine disturbance takes place by BPA capability to act directly as ligands (agonist) for steroid hormone nuclear receptors (NRs), in particular estrogen, androgen, and thyroid hormone receptors. In nonreceptor-mediated mechanisms, the cytochrome P450 enzymes responsible for the highly specific reactions in the steroid biosynthesis pathway are some of the molecular targets of interest, given their vital role in the formation of different highly effective endogenous steroid hormones. BPA interferes with steroidogenic enzymes and hormone transport in the form of BPA as both an androgen receptor antagonist and polychlorinated biphenyls (PCBs). BPA has been listed among the EDCs and is known for its metabolic homeostasis disturbance to block endogenous hormonal activity. Endocrine disturbance is connected with the risk of developmental problems, cancer, diabetes, obesity, and the metabolic syndrome. Also endocrine disruptors can lead to sexual sterility and interfere with fertility. BPA also causes both disruption in the function and structure of the brain and irregularities in the flow of hormones from the brain, which controls and regulates life processes. However, the probable developmental or reproductive hazard is not convincing because of incomplete data [8, 9]. Nonetheless, BPA exerts unexpected exposure outcome relationships, because low doses frequently exert stronger toxicity than higher doses because of its estrogenic and other biotic features [10]; BPA ≤5 mg/kg body weight/day during the critical phases of growth might affect healthiness later in life [11]. From a toxic dynamics point of view, it was investigated that BPA half-life was relatively short and thus it was suggested to be a fairly less cumulative chemical. Following oral exposure, most of the BPA dose absorbed was glucuronidated in rat liver and intestines, and because of the short half-life of BPA, this biochemical was excreted quickly from the body by making BPA sulfates $(SO_4)^{-2}$ or BPA glucuronidates during the metabolic progression [6, 12].

2.3. BPA toxicity and different human life stages

Numerous effects of BPA, both in humans and in animals, have been extensively studied and the target anatomy (organs) has been identified in repeat-dose bodily screening of liver, intestines, and kidneys. The effect of BPA in producing hormonal disturbance and potential associated problems of neurological, epidemiological, physical, and behavioral development were analyzed in fetuses, infants, and children [13]. A number of properties of BPA in animals have been widely examined, and objective structures recognized in repeat-dose animal studies contain intestines, liver, and kidneys. Conversely, the main concern has been those effects related to the hormonal movement of BPA and possibly the connected effects on physical, neurological, and developmental growth.

The discussion regarding the human health effects of BPA contact is restricted by a deficiency of epidemiological statistics. At present, there is not enough arithmetical influence to calculate dose effects or decide all the health penalties of exposure to BPA in humans [13]. Frequently, exposure is measured as being steady over time, with the total dose predictable by increasing exposure; it is computed as the product of attentiveness. Nevertheless, if contact is not steady over time, the similar total increasing contact delivered in various forms may create several organic effects.

2.4. BPA toxicity in the fetal stage

In the fetal stage of the human lifecycle, there is serious concern that BPA may enter the human placenta, exposing the fetus, and the consequences of BPA toxicity of "estrogenic chemicals" is more severe in the developing fetus as compared to the adult organism.

Estrogenic chemicals have the potential to restrict the steroid-dependent body of the neuro-endocrine and neurochemical systems. It is in the evolving brain that variations in the estro-genic environment affect several features of cellular reproduction, together with neuritis flexibility and branching, synaptic development, expression of neurotransmitters, cell survival, and death. Most of the human data, even though inconsistent, show that prenatal BPA exposure could seriously affect child sex-dependent behaviors [14, 15]. Many studies have recommended that BPA exposure is connected with female infertility. However, the relationship between TCS exposure and female infertility remains unidentified. Mice have been used as an animal model to study the relationship between exposure to these two chemicals and infertility [16, 17]. Slight changes in estrogen levels can lead to implantation collapse in humans and mice [17–19]. BPA and TCS have estrogenic movement in vitro and in vivo [20, 21]. BPA binds to both Estrogen receptor (ER) [Estrogen receptors (ERs) are a group of proteins found inside and on cells. They are receptors that are activated by the hormonees-trogen (17β-estradiol)] [22, 23]. Equally, BPA and TCS have many biological effects mediated via estrogen receptors [24, 25]. Therefore BPA and TCS may source implantation collapse because of their capability to mimic estrogen in humans [26, 27]. In humans, from oocyte maturation to implantation, the organic features of the oocyte and the embryo vary notice-ably. The levels of sex hormones, such as estrogen, progesterone, and androgen, and their receptors also alter significantly. Consequently, consideration of the female reproductive system to BPA and TCS may vary depending on the time of contact. It has been reported that in mice, preimplantation exposure to a similar quantity of BPA or TCS on gestational days 2 and 3 is stronger to induce embryo implantation failure than exposure on gestational days 0 and 1 [28–33]. Thus in mice, gestational days 2 and 3 may be a susceptible window for BPA and TCS. Exposure to these two endocrine disruptors during a susceptible window might lead to implantation stoppage. On the other hand, in humans, the susceptible window for these EDCs still needs further investigation.

In the health center, fertilization can only be established in one way. There is a way to identify embryo implantation collapse in the health center except for patients undergoing in vitro fer-tilization. The most common way to analyze pregnancy is by testing human chorionic gonad-otrophin (HCG) in urine samples. However, HCG is secreted by the syncytiotrophoblast and is noticeable in maternal blood 2 days after implantation of the embryo [30]. Therefore it is possible that many women did not know that they had a fertilized embryo, which subse-quently failed to implant into their endometrium because no HCG was secreted. Yet, if there was vaginal bleeding and a gynecologist was consulted, it will only be seen as ovulation bleed-ing, which is ordinary common occurance in the health center. More often than not, when a woman wants to know if she is pregnant she will perform a urine pregnancy test. On the other hand, a measurable level of HCG in the urine requires the embryo to survive for at least a week after implantation. Since BPA and TCS can be engrossed and excreted rapidly and do not build up in the human body [34–39], a change in habits such as stopping the use

of TCS-containing toothpaste or plastic food containers can result in a variation in the levels of these two chemicals in the human body. This means that if these habits cease for the duration of the susceptible timeframe—for example, the woman no longer uses TCS-containing toothpaste or is using novel TCS-free toothpaste, or no longer uses plastic containers that leak BPA—it could result in a comparatively low level of TCS and BPA in her body and pregnancy could ensue. In the health center, a woman cannot be assessed as infertile unless she has attempted defenseless coitus for at least 1 year without becoming pregnant. This means that maybe BPA and TCS have caused more miscarriages than have been realized. Furthermore, the most susceptible time for BPA and TCS to pursue implantation remains indefinite. Even though the preimplantation period might be a susceptible timeframe for BPA and TCS contact, it might not be the most responsive and significant.

2.5. BPA toxicity in children

Studies have concluded that BPA affects children's health, and shown links between parental urinary BPA concretion and depressive, anxiety, and hyperactive behaviors in children (2–3 years); however, the results were more pronounced for girls than for boys Braun et al. [40]. On the contrary, Perera et al. declared reduced nervous, depressed, and hostile behaviors in girls (3–5 years), but violent and emotionally sensitive behaviors in boys (3–5 years) with prenatal exposure to BPA (measured in pregnant mothers' urine). The BPA variant noncoplanar PCB affects dopamine, serotonin, and acetylcholine, while coplanar PCB affects thyroid hormone and glucocorticoids, and the consequence of these effects are more severe in fetuses, infants, and children [41].

2.6. BPA toxicity in adults

Recently, a number of rare studies have detected the relations between BPA exposure and growth and the reproduction syndrome in humans. Investigations on humans have shown the connection between urine, feces, or blood concentrations of BPA (total/free) and a diversity of health measures including mutation in fetuses, miscarriage, obesity and fertility in women, effect on the uterus lining ("endometrium"), certain hormones that support the control of deoxyribonucleic acid (DNA) damage to reproduction markers, length of gestation, polycystic ovary syndrome, and birth outcomes [42]. Only a small number of studies have summarized the relations between BPA exposure and disorders of reproduction or developmental effects in humans. Studies on humans have looked at the association between urine or blood concentrations of total or free BPA and a variety of incorporated health measures similar to:

  i. hormones that help to control reproduction markers of DNA injury;

 ii. miscarriage or mishandling;

iii. infection in fetuses;

 iv. fertility and obesity in women;

  v. properties of the tissue of the uterus ("endometrium");

 vi. polycystic ovary syndrome, delivery outcomes, and extent of development.

3. Treatment

After ingestion, a metabolic development is excreted by enzymes first and foremost in the liver where the majority of BPA is bound quickly to glucuronic acid to create BPA glucuronide. Because BPA is rapidly solvable in water (H_2O), it is better to get rid of BPA in the urine, which also reduces its capability to interrelate with organic processes in the body. When rats were exposed to BPA in their food with probiotics, their BPA blood concentrations dropped considerably and were defecated 2.7 times more firmly than the nonsupplemented organized collection. In other words, probiotics decreased intestinal amalgamation by boosting BPA secretion and may also repress BPA's unfavorable effects on human health.

A simple and cheap way to increase the probiotic content of energy expenditure is to take supplements such as IVL's Flora Life, the first and only acid-proof, suspended-discharge probiotic accessible on the open market nowadays. One or two capsules a day are all it takes to introduce the digestive zone to 22 billion acceptable bacteria.

Once in the intestine, these suspended free capsules carry the live probiotics essential to vigorously stabilize the gut bacteria and help free the body of poisonous chemicals, along with other numerous health advantages.

4. Preventive measures

4.1. For infants

As investigations continue, concerned parents can take the following preventive actions to decrease infant contact with BPA:

i. avoid pristine plastic infant bottles or containers with the recycling no. 7 and the letters "PC" imprinted on them; a number of these contain BPA;

ii. use licensed or recognized BPA-free synthetic bottles;

iii. use bottles made of opaque plastic, i.e., those made of polyethylene terephthalate (PET) or polypropylene; these do not contain BPA and have the recycling numbers 2 or 5 on them;

   Because heat may be a source of BPA leakage from plastic, the following should be noted:

iv. do not heat or boil polycarbonate bottles;

v. do not wash polycarbonate flasks in the dishwasher;

vi. glass flasks can be an option; however, if the flask is dropped it may break;

vii. breastfeeding is an additional method to decrease probable BPA exposure;

viii. risks connected with giving infants unsuitable (home-based condensed milk) formulas or substitute (soy, goat, or sheep) milk is better than the possible effects of BPA.

4.2. For children and adults

i. before using dental sealants, ask the dentist if the ingredients in the products they use contain BPA;

ii. use glass, stainless steel, paper, cloth, or clay containers for food and beverages;

iii. be aware that "microwave safe and sound" only means that the container or cling wrap will not distort; it has nothing to do with protection;

iv. avoid contact with oily or sour foods and synthetic organisms;

v. recycle any damaged or dented synthetic items;

vi. use ceramic or stainless steel containers;

vii. check the type of plastic a food processor is made from; substitute synthetic coffee filters with clay or metal ones.

5. Conclusion

The current research establishes no proof that BPA is a growing neurotoxicant. Concern is growing regarding the use of BPA products used all over the world. However, it will take a long time to completely prohibit the use of BPA in the synthetics industries, because they are striving to justify and establish that BPA is not that harmful, as shown by a variety of studies and investigations throughout the world. The synthetics industries have a dissimilar viewpoint and as a result much effort is necessary to change methods for the secure elimination of BPA from the environment rather than aiming at banning its use altogether. Interior coverage to free BPA accessible for organic activity within the body is thus probable to be extremely low down. Newborns are susceptible to upper interior BPA standards because of undeveloped glucuronidation movement. Numerous studies in adult women report a relation between BPA exposure and effects on the reproductive system, e.g., recurrent miscarriages, endometrial hyperplasia, and polycystic ovary syndrome. BPA exposure can disturb pubertal timing and cause irregular ovulatory cycles in rodents and these defects result from the abnormal organization of the hypothalamic– pituitary–gonadal axis, the central neuroendocrine corridor that regulates the reproductive process. BPA has also been found to induce apoptosis. As research continues, anxious parents can take preventive measures to diminish infants' exposure to BPA: regular breastfeeding, avoiding the use of dishwashers, and heating or boiling polycarbonate bottles or using BPA-free plastic bottles made of polyethylene, polypropylene, or glass. Children and adults should be encouraged to use glass, paper, cloth, stainless steel, or ceramic packaging/bottles for food and beverages.

There is considerable proof that endocrine disruptors are linked to cancer, childhood development, diabetes, and probably also obesity and metabolic conditions. In addition, it seems extremely possible that endocrine disruptors can add to sterility and associate with fertility. Scientific choices regarding health perils are usually based on what is recognized as the "proof mass." Proof from

the incomplete number of research studies in humans exposed to BPA is insufficient to reach conclusions concerning probable developmental or reproductive risk.

These discrepancies deserve additional investigations for enhanced acceptance of toxic kinetics, class, and interindividual changes, likely for additional sources of contact with BPA and possible confounders impacting on the consequences. An extensive research study can even cover the method for the growth of probiotics, i.e., live microbes that, when administered in sufficient amounts, present a health advantage to the host. Conceivably, these probiotics could be used for the secure elimination of accumulated BPA from live systems.

Abbreviations

BPA	Bisphenol A
EDCs	Endocrine disrupting chemicals
TCS	Triclosan
NRs	Nuclear receptors
PCBs	Polychlorinated biphenyls
HCG	Human chorionic gonadotrophin
DNA	Deoxyribonucleic acid
PET	Polyethylene terephthalate

Author details

Mujtaba Ellahi* and Mamoon ur Rashid

*Address all correspondence to: mujtaba.ellahi@gmail.com

Department of Chemistry, Faculty of Arts and Basic Sciences, Balochistan University of Information Technology, Engineering and Management Sciences (BUITEMS), Quetta, Pakistan

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