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A Review on the Occurrence, Exposure, and Health Impacts of Bisphenol A

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Abstract

Bisphenol A (BPA) is one of the emerging contaminants associated with deleterious health effects on both public and wildlife and is extensively incorporated into different industrial products. BPA is ubiquitously and frequently detected in the environment and has become a serious health issue due to its presence in food organisms and drinking water. The distribution of BPA has recently become an important issue worldwide, but investigations on the toxicity of BPA remain limited. A review of the literature reveals that BPA has a widespread presence in environmental media, such as indoor dust, surface water, sediments, and sewage sludge. In the present review, an overview of the research studies dealing with the occurrence, fate, exposure, and toxicity of BPA is discussed. Recent studies have raised worry over the potentially harmful implications of BPA exposure in humans and wildlife. However, further investigation on the potential risks of BPA to humans and its mechanisms of toxicity should be conducted to better understand and control the risks of such novel chemicals.

Keywords: Bisphenol A, Contaminants, Industrial products, Toxicity, Sewage Sludge

1. Introduction

Bisphenol A (BPA; 2, 2-bis (4-hydroxyphenyl) propane) is one of the highest volume chemicals produced globally[1].It is produced by the condensation of phenol and acetone in the presence of an acid catalyst (hydrogen chloride) and usually a promoter such as a methyl mercaptan. Cation exchange resins can replace the acid catalyst in newer plants. After the reaction and recovery of acid and phenol, the BPA is washed with water, neutralized with calcium hydroxide and distilled under vacuum. Newer processes employ distillation and extractive crystallization under pressure to purify the BPA. Two grades of BPA are produced; one suitable for epoxy resin manufacture and a higher purity grade for polycarbonate production. It is the most commonly detected emerging pollutant in the environment and aquatic ecosystems[2–4]. It is applied in polycarbonate production, metal cans, and as an additive in polyvinyl chloride and many daily plastic products[5]. Not only this, but it has also found its importance in the packaging of food items such as baking powder, cereals, and yeast[6]. BPA has been used as an additive in polycarbonate plastics and epoxy resins to harden the products for their usage as water bottles and food storage containers, due to its cross-linking properties[7]. It is among the most extensively applied synthetic organic substance in the world, surpassing over 6 million tonnes in production annually with Asia being the biggest consumer[8].

Numerous consumer products like facial/body lotions, bar soaps, laundry detergents, shampoo, dishwashing detergents, and toilet bowl cleaners have BPA in varying range of concentrations i.e. between 10 μg g^{-1} and 100 μg g^{-1}[9], however, high BPA levels were seen in thermal receipt papers with a range as high as 20 mg g^{-1}[10]. It has been known that BPA-containing products create a new compound

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Cl*BPA while coming in contact with chlorine-containing water or household cleaning products. Moreover, paper raw material and recycled plastic is also a good source of residual BPA which can yield Cl*BPA[11]. The application of chlorine-based disinfectants to remove the impurities and microorganisms of tap water is an essential process in the present scenario. Nevertheless, it is found to be toxic due to the formation of Cl*BPA in usable water resources[12], thus resulting in the addition of halogens as chlorine atoms to the phenolic aromatic moieties in the structure of BPA by electrophilic substitution reaction on the ortho-position.

The presence of two functional phenolic groups allows this chemical (BPA) to interact with androgen and estrogen receptors as both agonist and antagonist[13], due to which the compound is known as a xenoestrogen or environmental estrogen. Having the capability to stimulate the estrogen receptors it can be classified as an endocrine-disrupting chemical (EDC)[1,14]. The endocrine-disrupting effects of BPA at the estrogen receptor (ER) occur despite the very low affinity of BPA for ERβ, which is 10000 times lower than that of 17-β estradiol[15].

The estrogenic activity of various halogen-derived compounds of BPA has been considered higher as compared to BPA alone[16]. Based on low dose experiments, the higher (about 10-40 times) estrogenic activity of chlorinated BPA compared to BPA alone has been reported[17] which was further found to increase the occurrence of breast cancer[18] and uterine endometrium cancer[19].

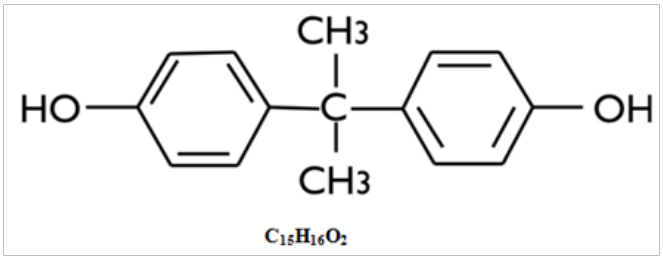
BPA, a familiar endocrine disruptor is intensively toxic to various aquatic organisms (freshwater as well as marine organisms) in the range of 1,000 to 10,000mg/L[20]. Rykowska and Wasiak[21] put forth that a reference dose of oral exposure with a range 0.01 mg/kg/day can be used whereas the United States Environmental Protection Agency (US-EPA) has estimated a reference dose of 50mg of BPA / kg body weight/ day.

2. Literature Search Process

This review was completed by exploring important research and review papers published in journals, books and other online materials. References from some of the identified studies were also reviewed for additional relevant information. The articles for the literature search were mainly collected from Google Scholar, PubMed, Science Direct, Springer, Research Gate and Taylor and Francis. The papers published in the past 20 years were mainly considered for the study. The main keywords that were used to search articles include "sources", "occurrence", "exposure" and "toxicity" of BPA. Most of the papers used for this review were found by searching only the keyword "Bisphenol A", 'BPA" and '2, 2-bis (4-hydroxyphenyl) propane. The papers were checked manually and then filtered based on title, abstract and paper contents. Mendeley software was used to store the bibliography data and add citations.

3. BPA Structure and Physico-chemical Properties

Bisphenol A has been known to be synthesized by a condensation reaction of phenol with acetone in the presence of a strongly acidic ion-exchange resin acting as a catalyst. The molecular structure of BPA can be seen to contain a central tetrahedral carbon atom with 2 phenol groups and 2 methyl groups.



Bisphenol A has low water solubility, comparatively lower range of vapor pressure (5.32×10^{-5} Pa at 25°C), and a low Henery's Law constant of 1.0×10-6 to 1×10^{-5} Pa m3 mol.

Physically, BPA can be seen as a white colorless crystalline solid substance having a mild phenolic odor under suitable conditions. The melting point of the compound ranges from 153-159°C[22,23] and the boiling point is 220°C[23]. The log Kow value of the compound was found out to be 3.32[24], thus showing that the solubility of BPA is good in fats as compared to its solubility in water. The physico-chemical properties of BPA are given in Table 1.

Table 1. Physico-chemical properties of BPA

Molecular formula	$C_{15}H_{16}O_2$
Molecular weight	228.291 g/mol
Density	1.195 g cm^3 (25°C)
Melting Point	153-159°C
Boiling Point	220°C
Solubility in water	Insoluble
Vapour pressure	5.32×10^{-5} Pa (25°C)

4. Occurrence and Environmental Fate

Bisphenol A is not a naturally occurring compound yet it has become ubiquitous in the environment due to its higher production, subsequent environmental introduction, and consumption[25]. Massive utilization of BPA resulted in contamination of all environmental compartments including soil, air, and water[26–29]. Various environmental sources of BPA can be categorized as preconsumer and postconsumer products. Preconsumer sources are those ascribed for the manufacturing of BPA and BPA-containing products, where the initial source of BPA release is obtained from the effluent discharge of manufacturing plants[30–32]. Transport and processing of BPA and BPA-containing products can be considered as an additional source for its pre-consumer release[30,33].

Postconsumer sources of BPA and BPA-containing products are known to include those compounds that are associated with the disposal of waste such as effluent discharge from municipal wastewater treatment plants (WWTP), combustion of domestic waste, leaching of various products from landfills, and degradation of plastics in the environment [26,33–35].Furhacker*et al.*[36] described that removal of 90% of BPA was known to be reported during wastewater treatment in a plant situated in Southern Austria; as such similar reports were obtained in the United States[37]. Despite various efforts regarding the treatment of BPA, its detention in the environment has been reported from time to time[38–42]. For instance, detention of BPA has been reported from Japan with a concentration of 17.2 mg/L in hazardous waste landfill leachates of the country[43] and in the United States, its range in effluents was found out to be 12 mg/l[44].

BPA has been known to be found in various environmental matrices such as air, water, soil sediments, groundwater, etc.[45]and also in food products[46] thus, because of this reason it is found to be accumulated in the population by way of consumption of contaminated food and contaminated water[47].

The various methods for the removal of BPA from wastewater include nanofiltration[48], advanced oxidative processes[49,50], reverse osmosis[51], membrane bioreactors[52,53] and ozone[54]. According to various researchers, adsorption has been proved to be more superior method for providing effective and fast removal of various pollutants with a comparatively simple design, low operating cost, easy to use with less production of harmful byproducts[25,55].

5. Human Exposure

As far as human exposure is concerned, food intake can be considered as the most important among all routes[56,57]. Foods are contaminated with BPA probably in the course of production, handling, packaging, and transportation[58]. Studies also indicated the exposure from drinking water, dental sealants, thermal paper, and, to a smaller extent from inhalation of household dust particles1,[10,59–61]. There are various exposure sources namely canned foods and beverages, polycarbonate water dispensers, medical devices in neonatal intensive care units, vinyl shower curtains and pillow protectors, dish and laundry detergents, tub and tile, beauty care products (such as sunscreen lotions, nail polish, body wash/lotions, bar soaps, shampoo, conditioners, shaving creams, and face lotion/cleanser)[9], thermal paper[62] and toys[63].

The presence of BPA in our environment is indicated by the fact that over 90 % of individuals have detectable levels of BPA in their urine[64], which is the prime route of excretion in humans[65]. The presence of BPA has been detected in neonates, children, and adults,[64] which was measured in a range of body fluids and tissues, including urine, blood, saliva, placental tissue, adipose tissue, and breast milk[64,66].

When the compound is introduced via the oral route, it is absorbed in the gastrointestinal tract and goes through hepatic metabolism which includes oxidation and hydrolysis thus leading to the production of several metabolites together with BPA monosulfate, BPA glucuronide, and BPA disulfate[67]. These metabolites then undergo conjugation and can be excreted in the urine and feces[13].

BPA is reported to be present in the urine of almost all adults and children tested[68–70], and also in the serum of pregnant women71, breast milk[72], follicular and amniotic fluid[73], cord blood and placental tissue[71], and human fetal livers[74].

The presence of BPA and its metabolites can be measured in bodily fluids, along with urine and serum, with the help of combined techniques of solid-phase extraction coupled with isotope dilution high-performance liquid chromatography and mass spectrometry[64]. Studies at a smaller level have evaluated the half-life of excretion of urinary BPA to approximately 4–5 h[75]. It was indicated by successive pharmacokinetic analysis that the excretion rate of BPA is not much affected by fasting, suggesting its excretion slowly from the body[64,75]. Sources and routes of BPA exposure for humans are given in Figure 1.

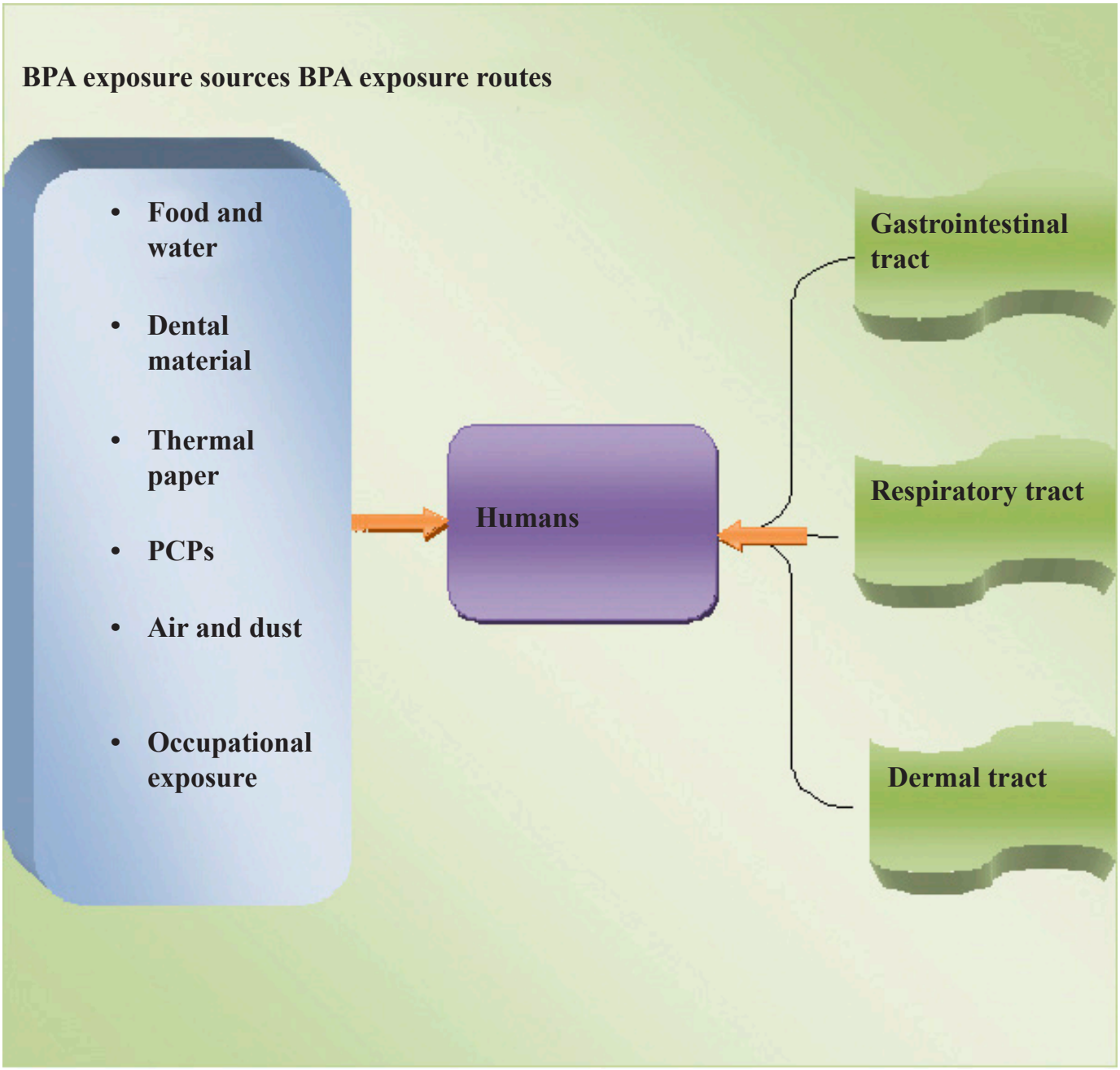


Figure 1. Sources and routes of BPA exposure for humans.

6. Toxicology Studies

Animal experiments have indicated the harmful effects of BPA on different systems and organs, such as the reproductive system, immune system, and nervous system, etc. The molecular mechanism of BPA toxicity explained by Ma *et al.*[76] is given in Figure 2. BPA induces corresponding biological effects through the activation of intracellular signal transduction pathway and regulation of gene expression mediated by cell surface receptors and nuclear receptors (Figure2). Membrane receptors could mediate the activation of SRC and ERK pathways induced by BPA, as well as PI3K/AKT pathway to regulate cell proliferation and migration. Moreover, BPA can regulate the function of the enzyme, such as CYP450 family and antioxidant enzyme. Aromatase can catalyze androgen conversion to estrogen to affect endocrines. BPA can also affect the antioxidant system, lead to ROS and LPO accumulation, and impair cell activity with mitochondrial dysfunction. Moreover, BPA causes genetic toxicity including DNA strand break, oxidative DNA damage, and chromosome mutation, etc. Besides, epigenetic changes play an important role in

gene expression induced by BPA without DNA sequence alternation. Different toxicological effects of BPA have been explained under the following headings:

6.1 Endocrine-disrupting Activity

BPA is a well-known endocrine disruptor that has been found to bind to estrogen receptors having estrogenic effects in laboratory studies. BPA resembles the natural thyroid hormone triiodothyronine and has the potential to disrupt the hypothalamus-pituitary-thyroid axis in humans and wildlife[77]. Even though BPA has a lower affinity for nuclear estrogen receptors relative to 17-beta estradiol (E2), the estrogenic potency of BPA is equivalent to E2 for responses mediated by non-nuclear estrogen receptors[78]. Moreover, BPA can act as an antiestrogen, which blocks the estrogenic response by competing with endogenous E2[79,80]. BPA can bind to androgen receptors directly and is considered as antiandrogenic which blocks endogenous androgen action[81,82]. It has been indicated that BPA can bind to thyroid receptors, having both agonistic and antagonistic effects on thyroid function[82,83]. The interaction of BPA with various other organs as well as physiological systems namely the developing central nervous system, the endocrine pancreas, and the immune system were also reported[82].

In humans, thyroid function is measured by thyroid hormone concentrations, which is disrupted by BPA in humans. The pituitary gland releases Thyroid-Stimulating Hormone (TSH) in response to brain signaling, which acts on the thyroid gland producing thyroxine (T4) and tri-iodothyronine (T3). T3 is also generated in the peripheral organs from the deiodination of T4. The production of thyroid hormones is regulated by negative feedback to the brain[84]. Meeker *et al.*[85] stated that the higher urinary BPA in males of sub-fertile couples was considerably associated with lower circulating TSH. It was found by Meeker and Ferguson[86] in anNHANES (National Health and Nutrition Examination Survey) population, that urinary BPA was inversely related to total T4, whereas some evidence supported the inverse relationship with TSH[87]. A study by Wang *et al.*[87]on a cross-sectional population of workers in epoxy resin plants in China stated that higher total urinary BPA was significantly associated with higher free T3.

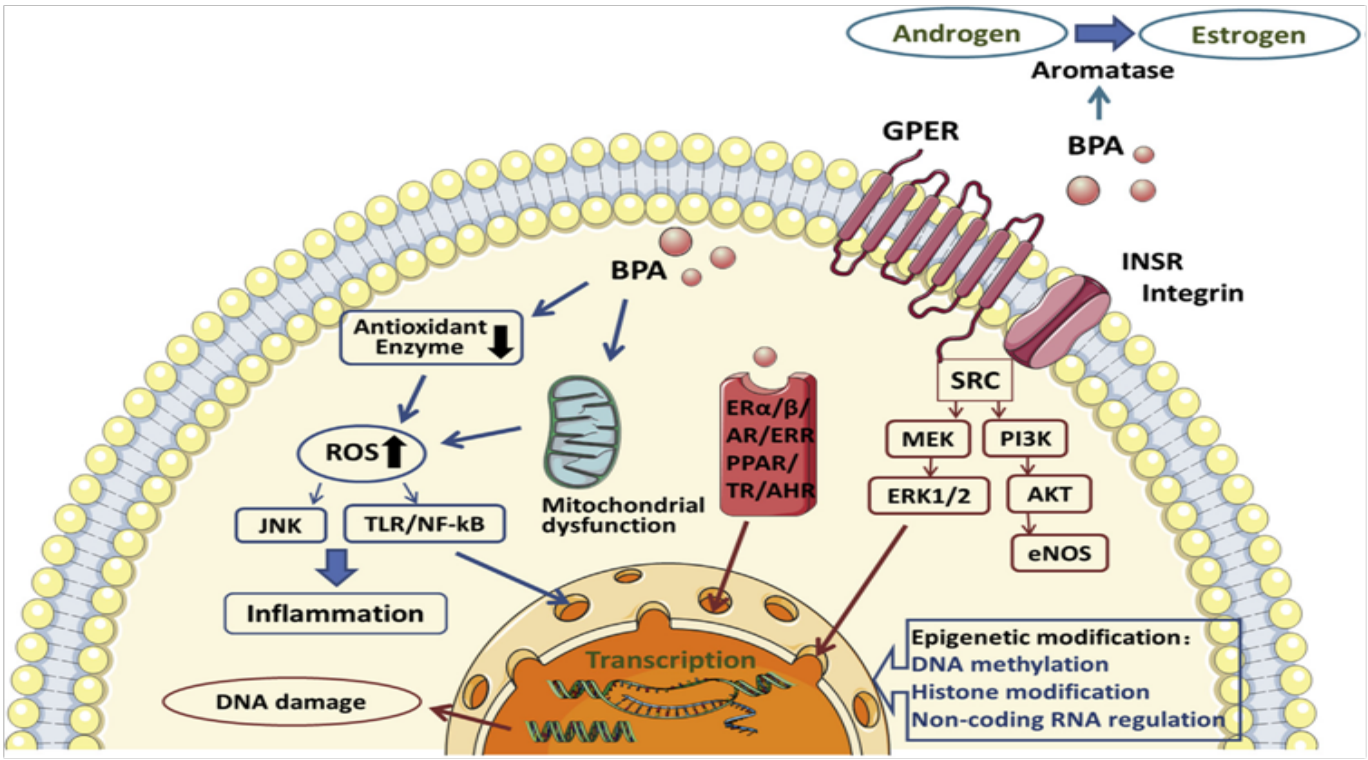


Figure 2. The mechanisms of BPA toxicity76. BPA: Bisphenol A; INSR: Insulin receptor; ER: Estrogen receptor; AR: Androgen receptor; ERR: Estrogen related receptor; PPAR: Peroxisome proliferator-activated receptor; TR: Thyroid hormone receptor; AHR: Aryl hydrocarbon receptor; ROS: Reactive oxygen species; JNK: c-Jun N-terminal kinase; TLR: Toll-like receptors; SRC: Proto-oncogene tyrosine-protein kinase; MEK: MAPK/ERK kinase; ERK: Extracellular regulated protein kinases; PI3K: Phosphatidylinositol-3-kinases; AKT: Protein kinase B; eNOS: Endothelial nitric oxide synthase

6.2 Reproductive Toxicity

BPA has aromatase-like activity and can convert testosterone to estrogen to activate the aryl hydrocarbon receptor which is involved in the synthesis and degradation of steroid hormones[80]. Generally, BPA could impair the normal reproductive function by disturbing the sex hormone excretion and activity, and also induce the occurrence of infertility.

BPA has also been reported to affect various endpoints of fertility. The correlation of higher urinary BPA with lower serum E2 and oocyte yield was revealed by Ehrlich *et al.*[88]. The higher urinary BPA corresponded to reduced maturation of the oocytes was also reported which was further measured by the number and percentage of mature oocytes at metaphase II on the day of egg retrieval. There were also a very small number of fertilized oocytes in women with higher urinary BPA which was measured by the number and percentage of oocytes with two pronuclei. Fertilized embryos were also assessed for normal cell cleavage. There was a trend ($p = 0.08$) for increased urinary BPA to be associated with decreased blastocyst formation on the 5th day of fertilization[88]. Minguez-Alarcon *et al.*[89] gave a relationship between the changes in endometrial wall thickness and BPA levels in urine. They found that the endometrial thickness of women (< 37 years old) had a positive correlation with urinary BPA levels, on the other hand, the endometrial thickness of women (>/=37 years old) was negatively correlated to BPA concentrations in urine. Furthermore, higher serum BPA levels were detected in polycystic ovary syndrome (PCOS) patients in comparison to healthy women[90] and adolescents[91]. These results revealed the potential role of BPA in the occurrence of PCOS. BPA was reported to be associated with adverse pregnancy outcomes, like miscarriage and premature delivery. Shen *et al.*[92] concluded that BPA could increase the risk of Recurrent Miscarriage (RM). Besides, spontaneous preterm births (PTB), preterm premature rupture of membranes (pPROM) were also reported to be associated with BPA levels[93,94]. The harmful effects of BPA on oocyte progression and quality, chromosome segregation, along oocyte apoptosis were demonstrated both in vitro and in vivo studies[95,96]. BPA can impair fertility by disrupting the physiological germ cell nest breakdown, which was shown by the multiple transgenerational toxicities after in utero exposure in mice[97]. The capability of BPA to induce oxidative stress and inflammatory mediators in human endometrial cells has also been demonstrated by Cho *et al.*[98] BPA decreased the 17β-estradiol level in medaka (*Oryziaslatipes*)[99] and reduced ovarian maturation in goldfish (*Carassius auratus*)[100].

BPA can exert detrimental effects on the male reproductive system and is also reported to cause prostate cancer[101]. Sperm quality in the men was also reported to be affected by BPA exposure[102]. Higher urinary BPA was found to be remarkably correlated with lower sperm quality measures (i.e. concentration, count, vitality, and motility). BPA could increase estradiol (E2), progesterone, serum luteinizing hormone (LH), and testosterone (T) levels and could decrease serum cortisol concentrations also[103]. In addition, the higher BPA levels in urine and plasma of infertile males have been observed by Vitku *et al.*[104].Studies by Peretz *et al.*[105] and Prins *et al.*[106] suggested that BPA is a testicular toxicant in animal models. Castellini *et al.*[107] reported that exposure of BPA to rat negatively interfered with the regulation of spermatogenesis throughout the hypothalamus-pituitary gonadal axis. BPA was also known to cause reproductive dysfunction in seahorses accompanied by apoptosis of follicular cells and up-regulation of pro-apoptotic genes[108]. BPA also impaired vitellogenesis in male *Acanthopagrus latus* and gonadal steroidogenesis in *Sparus aurata*[109,110]. The genotoxic effect of BPA was also observed in prostate epithelial cells after 24h treatment with increasing concentrations, which showed that BPA down-regulated the expression of p53[111]. De Flora *et al.*[112] assessed the persistence of DNA adducts in prostate cells treated with high or low concentrations of BPA.

6.3 Other Adverse Health Effects Induced by BPA

Chen *et al.*[113] described that BPA levels in school-aged girls were associated with Idiopathic Central Precocious Puberty (ICPP). However, higher BPA concentrations were known to be associated with delayed puberty in girls and earlier puberty in boys, showing a gender-dependent effect[114]. Chen *et al.*[115] investigated the effects of BPA exposure caused during pregnancy on the mental and behavioral problems of preschool children. They put forth that a higher level of maternal BPA exposure to be a potent risk factor for unusual behavior in preschool children, especially boys. Perera *et al.*[116] studied that prenatal BPA exposure was associated significantly with depression and anxiety in boys, whereas postnatal BPA exposure had nearly no effect and was not associated with any such symptoms. Nor *et al.*[117] provided evidence that prenatal exposure of BPA could be an important factor for neurodevelopmental disorders like autism. Moreover, BPA has also been shown to be associated with hyperactivity disorder, prosocial behavior, various insomnia-related problems, and language development[114,118,119].

Gascon *et al.*[120] reported that prenatal BPA exposure might also affect normal respiratory function and also showed a marked effect on the increased level of asthma symptoms and a high incidence rate of respiratory infections occurring throughout childhood. In addition to the above findings, a considerable amount of research in the said field has proved that the level of BPA is significantly associated with the risk that is associated with various neurodevelopmental diseases, like autism spectrum disorder[121]. At the same time, BPA has also proved to be a potent risk factor for the development of various cancers such as cervical cancer, breast cancer, prostate cancer, ovarian cancer, lung cancer, etc.[122–124].

Cuomo *et al.*[125] showed strong evidence that higher BPA exposure in humans not only induces epigenetic mutations but also found to be carcinogenic. Del Pup *et al.*[126] described the vulnerability of humans and some invertebrate species to BPA-based risks. The exposure of BPA in the body could be affected by multiple routes of diverse sources. For example, the intake of more than 100g of beverages in Korean women was reported to increase the urinary level of BPA[127]. The effect of BPA has not been limited only to humans but also investigated on other aquatic organisms such as fish. For example, a short-term exposure of BPA at 100mM level was found to induce oxidative stress in the Atlantic salmon fish kidney cell line[128]. In contrast, several long-term exposures of BPA have been seen to cause the transcriptional response of the immune genes. Not only this, the exposure of BPA at concentration 50mg/l can induce several harmful effects on the gill tissue of fishes[129]. It has been proved that BPA exposure during the gestation period in mice affected the ambient glucose metabolism[130]. The treated mice were also found to be susceptible to diabetes-based complications in the later stages of life. Not only animals, but plants have also shown detrimental effects after exposure to BPA. For instance, Soybean seedlings when exposed to BPA at a concentration of 1.5 mg/l have shown to decrease the overall chlorophyll content, thus affecting the rate of photosynthesis[131].

BPA exposures were also shown to be negatively associated with the general immune response while studying a strong cross-sectional study of adults and children (age 6 and above). BPA has proved to be a potent chemical that can disrupt the immune function and also promote the occurrence of some of the known allergy-related diseases such as bronchial hyper-responsiveness, asthma, diabetes mellitus type 1 (T1D), and autoimmune diseases[132,133]. Rees Clayton *et al.*[134] while examining the data from National Health and Nutrition Examination Survey (NHANES) 2003–2006 found that urinary BPA was known to show a significant correlation with antibody titers to cytomegalovirus (CMV). Further, an increase in this antibody indicated a depressed immune response and thus can be the early marker of dysfunction in immune response in humans. In adults, a higher level of BPA was shown to be associated with an increased level of antibody titer of CMV. This discrepancy was justified by authenticating the correlation between the response and time of exposure to BPA and BPA exposure was proved to adversely affect the immune function from time to time. Studies by Yang *et al.*[135], Qiu*et al.*[136] and Qiu*et al.*1[37] suggested that multiple signaling pathways like nuclear factor κB (NF-κB), Estrogen Receptors (ERs), and peroxisome proliferator-activated receptor were involved in BPA or its analog induced immunotoxicity in Head Kidney (HK) macrophages of *Cyprinus carpio*.

The correct pathway by which BPA increases the susceptibility of disease to immune deregulation as allergy has not yet been elucidated, only a little knowledge of such direct mechanisms has been gathered so far. For instance, two independent *in vitro* and *in vivo* studies examined the ability of BPA to variously activate the response of proallergic T helper (TH) cytokines. The *in vitro* study found that BPA was associated with a response characterized by an upregulation in the TH2 pathway and synthesis of interleukin (IL)-4[138]. Whereas in the *in vivo* study, the effect on the dendritic cells after exposure to BPA versus 17 β estradiol was examined both with the administration of tumor necrosis factor (TNF) alpha BPA was shown to induce a higher production of proallergic TH2 chemokines and cytokines, including various CC chemokine ligand (CCL)-1, IL-3, IL-5, and IL-10. This immune response was seen to be associated with a higher expression of TH2 transcription GATA-binding protein (GATA3)[139].

BPA has been known to play a significant role in the development of diabetes, Cardiovascular Disease (CVD), and obesity also. The structure of BPA is similar to 17β-estradiol and thus show binding to estrogen-related (ER) receptors such as ERα, ERβ, ERγ, peroxisome proliferator-activated receptor gamma (PPAR-γ) and G-protein coupled estrogen receptor GPR30[140,141]. Still, the mechanism of action has not been fully understood, yet binding of BPA to these receptors have been associated to induce insulin resistance, adipogenesis, oxidative stress, and pancreatic beta-cell dysfunction[142–145]. At concentrations that are typically seen in humans, BPA act either via extranuclear ERα [146] or ER β[147]. These two studies made use of whole Islets of Langerhans and β- cells from mice lacking ERα, ERβ, and also in humans to demonstrate that estrogen receptors mediate this low dose effect of BPA. Hugo *et al.*[148] also demonstrated that BPA at environmentally relevant doses could be a potent inhibitor for the release of adiponectin, an

adipokine that can protect humans from various obesity-related metabolic syndromes. Andersson and Brittebo[149] described that it may also have a direct proangiogenic effect on the primary endothelial cells, thus demonstrating that human endothelium can be an important target for BPA. Marmugi *et al.*[150] put forth that BPA exposures for eight months in adult mice resulted in a sufficient increase in adipose tissue mass, glucose intolerance, increased cholesterol biosynthesis, hyperglycemia, and hypercholesterolemia. However, the relevance of these animal studies to humans remains unclear due to an extra enterohepatic recirculation in rodents, thus resulting in a decreased rate of BPA excretion compared to humans[65].

Cell signaling has been known to be widely associated with various body processes, both beneficial and adverse. Several alkyl phenols, including BPA, are potent activators of signal response such as Ca signaling and ERK[151]. Increased exposure of BPA resulted in permanent and long-lasting alteration in the DNA methylation patterns of various cell-signaling genes[152]. BPA induced oxygen radical formation and changed the activity of mitochondria that ultimately led to the activation of different signal transduction pathways.[153,154] Overall health effects associated with BPA exposure has been summarised in Figure3.

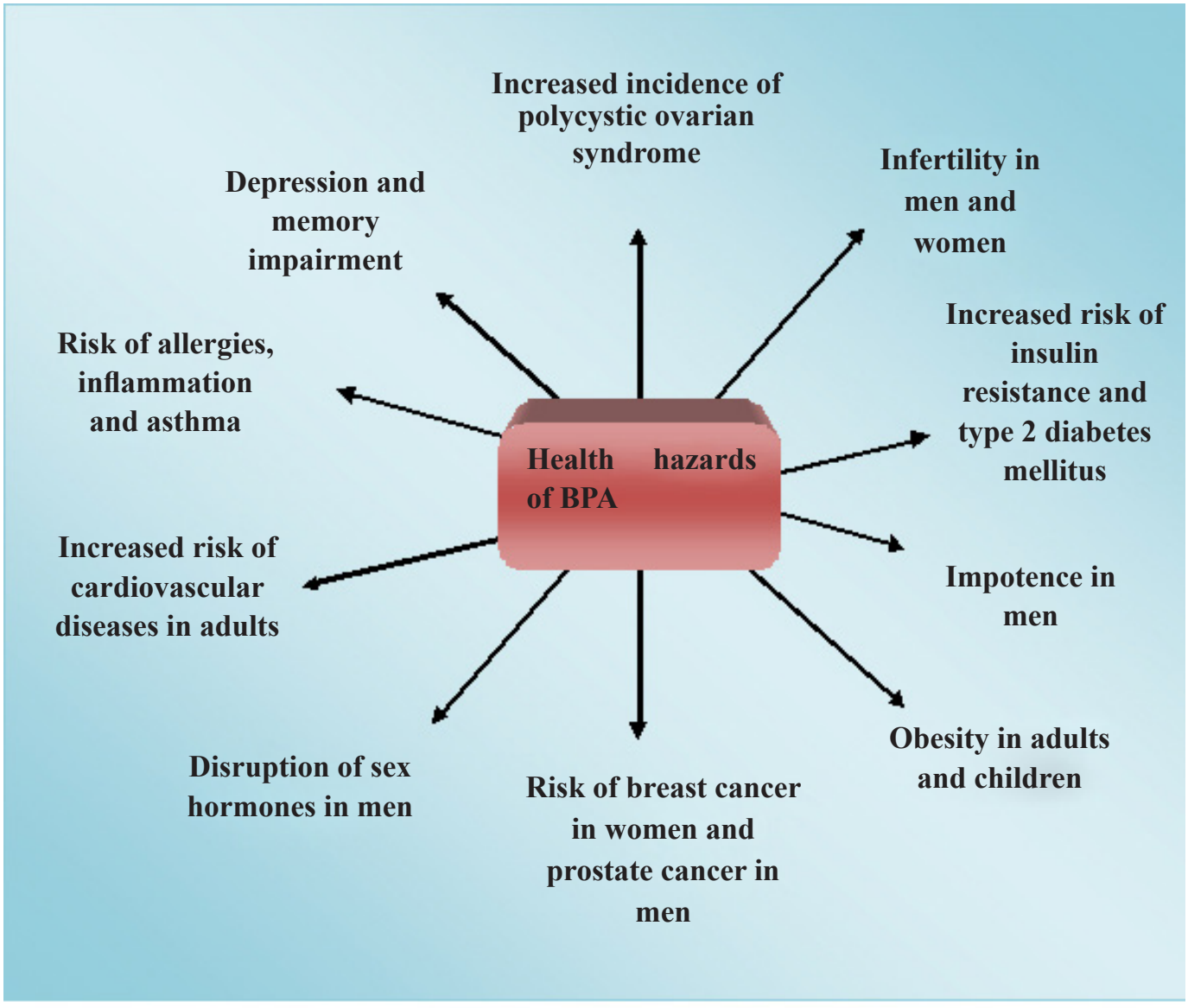


Figure 3. Negative health effects associated with BPA exposure.

6.4 Genotoxicity

BPA has been proved to be non-mutagenic in various assays like Ames test, mammalian gene mutation assay, and lymphoma sister chromatid exchange[155,156]. Still, a controversy regarding mutagenicity has been reported by various authors showing its potential to induce point mutation, double-stranded DNA breaks, and aneuploidy[157–159]. Tsutsui *et al.*[160] worked on the induction of aneuploidy and DNA adduct formation in Syrian hamster embryo cells exposed to BPA. Ochi[161] and Can *et al.*[162] further confirmed that this has led to not only disruption of the organization of cytoplasmic microtubular complex, but also that of mitotic and meiotic spindle formation. BPA has been known to induce a marked effect on the aneuploidy and chromosome aggression failure in the oocytes of mice when they are exposed to its low concentration[163]. BPA has also been observed to induce the formation of micronuclei in organisms like mussel gills[164] and fish erythrocytes[165] Allard and Colaiacovo[166] put forth that BPA could be of significant importance in impairing the chromosomal synapsis and also disrupting the progression of meiotic Double-Strand Break Repair (DSBR) and resulted in impaired integrity of genome during meiosis, which can be arbitrated via inhibition of DNA- dependent protein kinase (DNA-PK) activity[167]. Kim *et al.*[168] confirmed that submicromolar concentration of BPA has been known to be associated with DNA damage and proliferation associated with prompting DNA synthesis and also elevating the expression of various cell-cycle proteins in human hepatocyte cell lines.

BPA has also been known to cause DNA damage by inhibiting telomerase activity thus affecting chromosome stability and cell variability in various species. Herz *et al.*[169] confirmed that BPA in human Peripheral Blood Mononuclear Cells (PBMC) could play a potent role in inhibiting the telomerase activity in a non-monotonic manner. In addition to these findings, they also mentioned that the inhibition of telomerase activity was due to the rapid activation of the ER/GPR30-ERK transduction pathway. The mechanism of genotoxicity induced by BPA included chromosome mutation which occurs in the stage of meiosis and is known to severely influence the organism and offspring development. BPA concentrations were described to be positively correlated with sperm sex chromosome disomy which can be a major cause for male infertility[170] After oral administration of BPA to the mouse, disruption of normal spindle assembly, kinetochore-microtubule attachment, and chromosome alignment can be prominently studied with a marked effect on the first polar body extrusion[96]. Moreover, a lower concentration of BPA has shown increased spindle abnormalities and variously misaligned chromosomes that affect the maturation of oocytes in a non-monotonic way[171].

7. Prevention and Control of BPA

BPA is migrated into the environment mainly through the processing of BPA during manufacturing, incomplete removal during wastewater treatment, landfill leachates, and leaching from discarded BPA-based materials (e.g., hydrolysis of polycarbonate, recycled paper)[35].BPA has been known to be found in various environmental matrices such as air, water, soil sediments, groundwater, etc.[45]and also in food products [46] thus, because of this reason it is found to be accumulated in the population by way of consumption of contaminated food and contaminated water[47].

The various methods for the removal of BPA from wastewater include nanofiltration[48], advanced oxidative processes[49,50], reverse osmosis[52], membrane bioreactors[52,53] and ozone[54]. According to various researchers, adsorption has been proved to be more superior method for providing effective and fast removal of various pollutants with a comparatively simple design, low operating cost, easy to use with less production of harmful byproducts[25,55].

Some countries have banned the use of BPA in some types of consumer products. The Canadian government was the first country to declare BPA as a 'dangerous substance' 172 and prohibited the sale, import, and advertisement of baby bottles that contained BPA[173,174] European Commission in 2011 decided to forbid the BPA used in polycarbonate infant feeding bottles[13,173]. BPA-based baby bottles, sippy cups in 2012 and BPA-based resins in the coatings of infant formula packaging in 2013 were also restricted by FDA (Food and Drug Administration) in response to American Chemistry Council petition, respectively[173,175,176].

The public concern and governmental regulations on BPA stimulated the development and production of alternative substances to replace BPA in a myriad of applications. A number of chemicals that are structurally similar to BPA have already been used in the manufacture of polycarbonate plastics and epoxy resins. These chemicals share a common structure of two hydroxyphenyl functionalities and are collectively referred to as bisphenol analogs. A total of 16 bisphenol analogs have been documented for industrial applications. With emerging BPA substitutes, their toxic potential Health and health threats have attracted a great deal of interest from scientists and the Audience. Figure 4 illustrates various alternatives to prevent BPA exposure in humans.

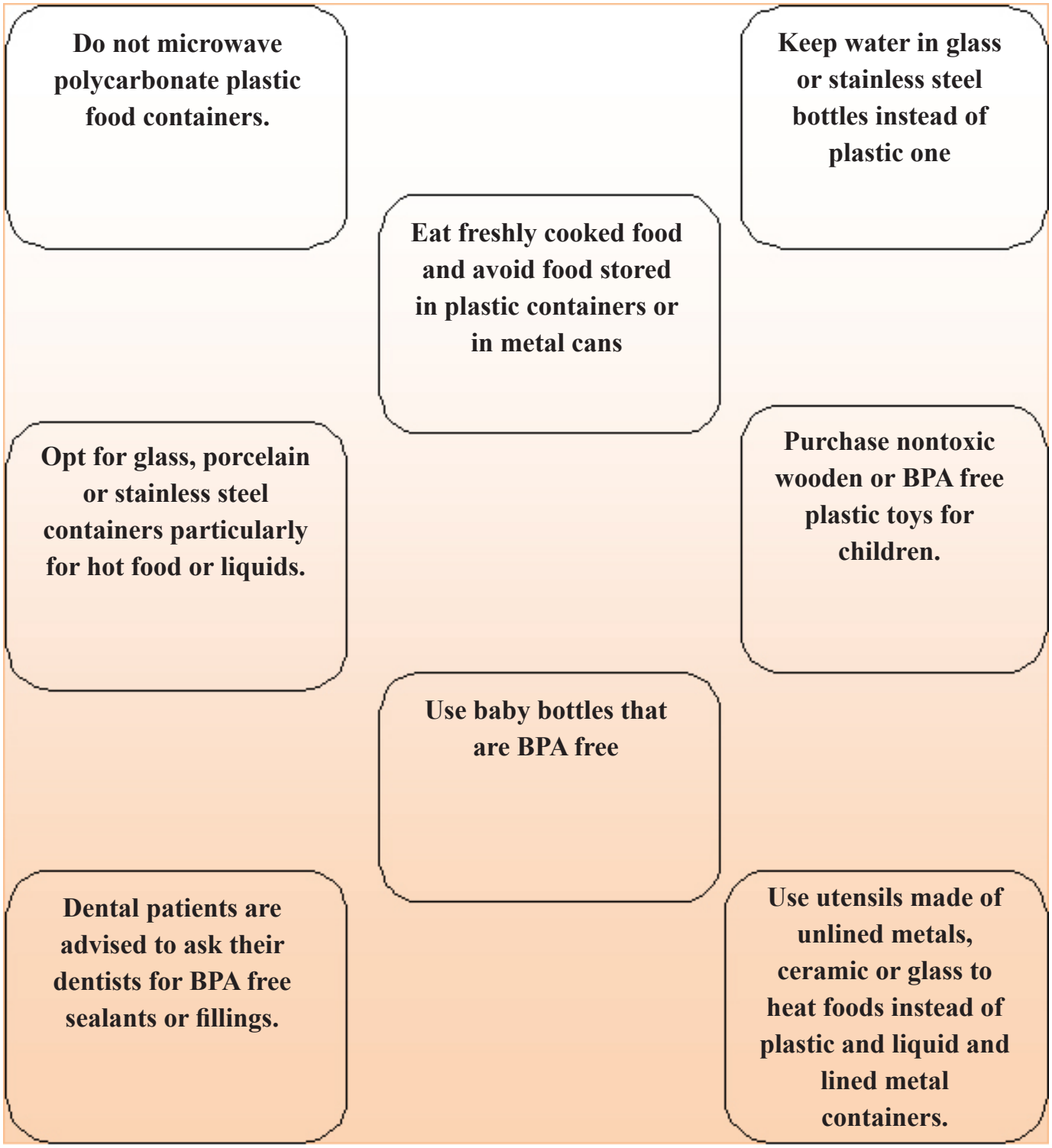


Figure 4. Alternatives to prevent BPA exposure in humans.

8. Conclusion

The wide use of BPA is still practiced despite the evidence of adverse health impacts associated with exposure to this endocrine disruptor. Studies on laboratory animals showed adverse health effects even at low dosages. Early exposure to BPA has resulted in the alteration of hormones, thereby affecting the immune system and body functions. Compared with numerous studies on BPA, the adverse effects of

BPA substitutes, especially chronic exposure, should be further investigated. Further investigations are needed to give a clearer description of BPA analogues' health effects. And further risk assessment of BPA substitutes should be conducted for better regulation and health protection.

9. Conflict of Interest

The authors declare no conflict of interest.

10. Acknowledgment

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