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Bisphenols as Human Health Hazard: A Systematic Review on Potent Sources, Route of Exposure, Harmful Effects and Safe Alternatives

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Abstract

Bisphenols (BPs), as components of polycarbonates and laquer-coatings, are used for day to day household purposes, and frequent exposure has potential negative effects on each organ of the body, mostly evident by genetic changes and mitochondrial dysfunction. Children are at high risk due to higher accumulation per kg body weight which explicit toxic effect. Present strategies are to downsize exposure by replacing polycarbonates with wood, glass, stainless steel or green substitutes like bisguaiacol-F, soy protein isolate etc. At present, biodegradation by bacteria and fungus would be a great help to fight environmental bisphenols. It is necessary to come up with strong and functionally equivalent alternative to bisphenols which can safeguard future generations from further harmful effects.

Keywords: Bisphenols, Bisphenol A, Bisphenol B, Bisphenol S, Bisphenol Toxicity

1. Introduction

Plastics have permeated every aspect of modern life and are used in a variety of utility items *viz.* utensils, food packages, water pipes, tin cans, medical devices and reusable containers. According to Plastics Europe Market Research Group, the world production of plastics has increased by more than 200 times from 1950s to 2015. Plastics have polycarbonate as their important components and 'Bisphenol A (BPA) and its derivatives' are major components of these. BPs are extensively used as monomers for the production of polycarbonate plastics, non-polymer additives, epoxy resins and as an antioxidant in the end of polymerization reaction[1]. It is used as colour developer in carbonless copy paper and thermal receipt paper[2]. The thermal paper is heated by laser light, and as a result, BPA reacts with thermal paper dye and produces a colour-developing complex. Use of bisphenols (BPs) in the production process makes a plastic clearer, colourable, tough, easy to thermoform, resistant to changing environmental factors like exposure to temperature and chemicals.

BPA, either in its free form or on exposure to factors like heat and chemicals leach out and find an entry into human bodies through air, water, food, and skin contact[3]. Human and animal-based studies have proven BPs' negative effects on health, even in low concentrations[4]. Several analogues of BPs came in light as its competent substitutes but recent evidences place doubts on their health impacts as well. It is necessary to comprehend about BPs, and their routes to seep in to food and body, pathophysiology of disease and preventive mechanism to prevent humans from these toxic compounds. In this regard, present review tries to explore different studies conducted worldwide and document under one heading. This review also tries to explore different solution options available to minimise BPs exposure to human population.

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2. Major BPs of Health Significance

BP represents a group of compounds containing two hydroxyphenyl functionalities, of which, one is always phenol from which it has derived its name 'bisphenol'. More than sixteen different types of BPs have been reported. Bisphenol A (BPA), Bisphenol B (BPB) and Bisphenol S (BPS) (Figure 1) are of utmost importance due to their wide applications and health hazards[5]. This section gives a brief account of the nomenclature, chemistry, history and usage of different types of BPs.

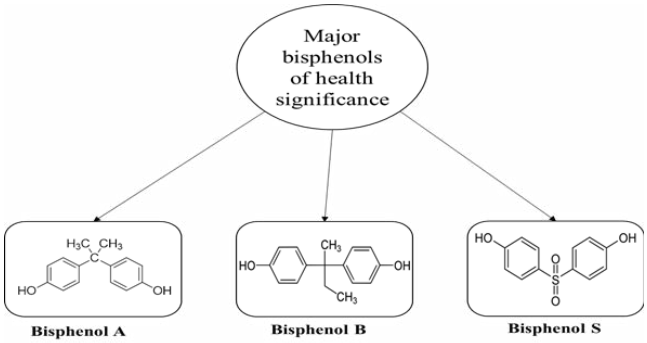


Figure 1. Major BPs of health significance

2.1 Bisphenol A [2,2-(4,4'-dihydroxydiphenyl) propane]

BPA is a symmetrical aromatic molecule and its production involves the condensation of phenol with acetone in the presence of a strongly acidic ion-exchange resin. It is moderately water soluble with a solubility of 300 mg/L at room temperature but dissociates in an alkaline environment (pK_a 9.9–11.3)[6]. The use of BPA in the commercial production of polycarbonates began in the 1950s. Amongst all the types of BPs, BPA is of most usage and concern. Its estrogenicity was first reported by Edward Charles Dodds and Wilfrid Lawson in 1936. BPA has an ability to replace natural estrogen in medical therapy but its use as a drug was banned in 1971, after its discovery as potential carcinogenic compound especially in case of vaginal cancers[7]. Presently, it has become a key component of plastic industry and is widely used chemical in the structure of epoxy resins, as anti-corrosive agent and lacquers of metal cans. In the production process of polycarbonate, BPA reacts with phosgene and forms an ester linkage. Figure 2 shows how polycarbonate is synthesised from BPA and phosgene.

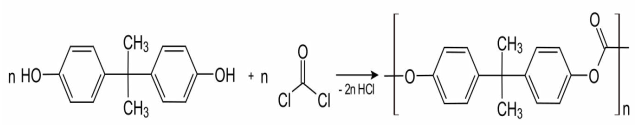


Figure 2. Synthesis of polycarbonates from BPA and phosgene

This linkage is not stable at high temperature and pH changes. Increase in temperature or deviation in these conditions results increased hydrolysis and release of BPA as shown in Figure 3.

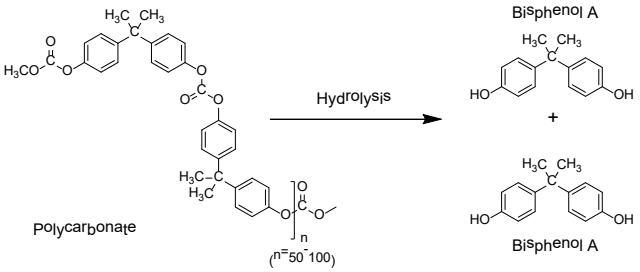


Figure 3. Hydrolysis of polycarbonate into BPA

2.2 Bisphenol B [4-(2-hydroxyphenyl)-butan-2-yl)] phenol

BPB has a crystalline or tan granular structure. The compound has a molecular formula of $C_{16}H_{18}O_2$, molecular weight of 242.32 g/mol and melting point of 120.5°C[8]. BPB is soluble in organic solvents like acetone, benzene, ether, and methanol but is insoluble in water. It is mainly used in the manufacture of phenolic and polycarbonate resins. BPB has been found to exert similar androgenic effects and estrogenic activity as shown by BPA and interferes with cellular processes, like proliferation, by using MCF-7 breast carcinoma cells, and murine bone marrow dendritic cells[9]. The human exposure may occur through dermal contact or by ingestion of food containing BPB.

2.3 Bisphenol S [bis(4-hydroxyphenyl) sulfone]

BPS is an important member of the family of BPs. It has a molecular formula of $C_{12}H_{10}O_4S$, molecular weight of 250.27 g/mol and boiling point of 240.5°C[8]. It was introduced as a substitute of BPA and has been used extensively in the development of BPA-free plastic products

and thermal receipts. Hence, a large content of BPS has been reported from thermal receipts as compared to BPA[10]. However, later it was also reported to have same endocrine properties similar to BPA but in lesser degrees[11]. BPS levels of below detection limit to more than 100 mg/kg has been reported in "BPA free" samples[12].

3. Exposure to BPs

Major source of BPs exposure are plastics as they are made up of polycarbonate which contains BPs as one of the important component in its structure. Plastics have been widely used to store food and improper handling of reheating of stored food at high temperature results in the leaching of BPs from these packages to the food. One of the other major causes of food contamination with BPs is lacquer coatings used in canned foods. Infants are exposed to BPs through milk and water bottles and sippy cups[13] while adults are exposed majorly through canned foods and beverages[14]. The non-food sources of BP exposure are currency notes, thermal receipts, contaminated water and dust. BPA has been used as heat activated developer to the printing surface in thermal papers like tickets for airlines, trains and buses, cash register receipts[15]. These paper coatings may contain up to milligrams of free BPA[15-18]. Exposures through thermal receipts are of major concern as they contain BPA in free form and hence, large exposures occur through them[19].

The risk of bisphenol exposure is more among infants and children as compared to adults, because the exposure to the same content of BPs may result in more concentration in children's body in terms of per Kg body weight. Through the food, water and air, BPs enters into the human body and hence have been detected in human urine as well as serum samples. Table 1 summarises the detection of different types of BPs in various food samples, environmental sources and human fluid samples.

4. Effect of Environmental Conditions on the Migration of BPS

A decrease in pH of the contact solution results in an increase in BPA migration (Mercea, 2009). Ethanol–water mixture allows faster release of BPA from polycarbonate (PC) in comparison to water. Heating has been also reported to increase the migration of BP[5]. The leaching of BPA at low concentrations has been found even when the storage and usage of the product is in accordance with the manufacturer's instructions. Brede *et al.*[30] tested BPA migration in twelve PC baby bottles which were subjected to hot water treatments like dishwashing, boiling and brushing. Average concentration of BPA in every bottle was found to be 0.23 mg L^{-1}. Similar results were reported by Sun et al.[31] who reported increased BPA migration from PC bottles on exposure to hot water. The migration rates further increased with repeated exposure to water. However, in a study conducted by Maia et al.[32], it was found that washing, brushing or soaking of PC bottles with water containing detergent retarded BPA migration from the polymer.

The epoxy resins applied to tin cans as inner coating contains BPA diglycidyl ether as the main component[14]. The release of BPA from lacquers was estimated to range from 4 to 23 g per tin[33]. Cao et al.[34] conducted a study in which 78 canned food products, *viz.* tuna fish, condensed soup, ready to serve (RTS) soup, vegetables, pasta and tomato paste were analysed for the detection of BPA. The bisphenol was found in almost all the samples and the concentration of BPA ranged up to 534 ng/g. BPA concentration was below MDL (minimum detectable limit) in only one sample, i.e. tomato paste (up to 2.1 ng/g)[34]. In a study conducted in England, BPA was detected in 61.29% of the canned food samples (n=62)[22] whereas, 70% contamination from BPA was reported in Portugal (n=30) in canned beverages[28]. BPB was also detected in 50% of samples in a concentration ranged of 0.06 to 0.16 µg/kg[28].

When cans containing water were heated to 100°C, the BPA concentrations were found to increase by 1.7-55.4 times as compared to that of unheated containers[33]. Takao et al.[35], showed that the exposure of tins to the temperature of 100°C, which is the temperature of boiling water, can cause 18 times faster release of BPA from the polymer. Low BPA concentrations (0.06 ng cm^{-2}) were found in epoxy lined-tinned food, which was not pasteurized. On the other hand, when tins were heated at 80°C and 100°C, significantly higher BPA in range of 21 and 32 ng cm^{-2}, respectively was released. It was also reported that the BPA release was dependent on two factors, i.e. degree of epoxy resin polymerization and the use of BPA as a first-order component in its production. Use of ethanol-based hand sanitizers can increase the transmission of BPA from the receipt surface to the surface of the hand[15].

Table 1. Country-wise data of bisphenol exposure through different food and environmental sources

Bisphenol type	Countries	Sample type	Total no. of samples	Detection rate	Level of detection	References
BPA	Canada	Beverage cans	69	100 %	0.03–4.5 ng/ ml	19
	China	Municipal sewage sludge	52	76.9 %	0.42 to 152 ng / g DM	20
	Denmark	Household waste paper	100 houses for 1 week	100%	0.4 to 8100 µg / g DM	21
	England	Different canned foods	62	61.29 %	2 µg /kg	22
	Germany	Urine	30	96.7 %	0.1 to 14.5 µg / L	23
	Greece	House dust	28	100 %	27 to 4400 ng / g	24
	Hong Kong	Blood	153	94.4 %	0.16 to 3.38 ng / ml	25
	Japan	Amniotic fluid	32	100 %	1.1 to 8.3 ng/ ml (depending upon gestation time)	26
		Blood	30 (premenopausal, non-pregnant women)		2.0 ± 0.8 ng/ ml	
			37 (women with early pregnancy)		1.5 ± 1.2 ng/ ml	
			37 (women with late pregnancy)		1.4 ± 0.9 ng/ ml	
		Ovarian follicular Fluids	36		2.4 ± 0.8 ng/ ml	
		Umbilical cord blood samples	32		2.2 ± 1.8 ng/ ml	
	New Zealand	Different canned foods	80	100 %	Up to 191 µg / kg	27
	Portugal	Canned beverages	30	70 %	0.03 to 4.70 µg/L	28
	USA	Urine sample	2517	92.6%	0.4 to 149 µg/L	29
BPB	China	House dust	34	6 %	<1 to 4.6 ng / g	24
	Denmark	Household waste paper	100 houses for 1 week	100%	0.4 to 8100 µg / g DM	21
	Italy	Canned peel tomatoes	42	21 %	27.1 to 85.7 µg / kg	2
	Portugal	Canned beverages	30	50 %	0.06 to 0.16 µg/kg	28
	USA	House dust	22	5 %	<1 to 8.4 ng / g	24
BPS	China	Municipal Sewage Sludge	52	82.7 %	1.57 to 143 ng/g DM	20
	Colombia	House dust	42	62 %	<2 to 35 ng / g	24
	Denmark	Household waste paper	100 houses for 1 week	73%	0 to 170 µg/g DM	21
	Greece	House dust	28	86 %	<2 to 21000 ng / g	24
	Pakistan	House dust	22	50 %	<2 to 66 ng / g	24
	Romania	House dust	23	100 %	6.2 to 4900 ng / g	24
	USA, China, India, Japan, Korea, Quwait, Malaysia, Vietnam	Urine sample	315	81%	0.02 to 14 ng/ml	18
	USA, Japan, Korea, Vietnam	Thermal receipts	112	100%	22 mg/g	17
		Currency	52	90%	Traces (µg/g)	
		Other paper products	105			
		• Flyer		80 %		
		• Magazine		40 %		
		• Food cartons		57 %		

DM = dry matter.

5. Migration of BPs into Human Body

BPs seeps in to food and water from contact materials like coverings, coatings and containers. In the manufacturing of polycarbonate (PC) products, during diffusion and hydrolysis of polymers some of the BPA may remain unreacted and can migrate to the food during storage through various routes (Figure 4). Regulatory agencies assume oral route as the major source of human exposures[36]. According to a research, human exposure to BPA from oral route is estimated in range from 0.48-1.6 g/kg body weight per day[33]. BPA exposure has also been reported from direct exposure of skin to BPA containing cosmetics and thermal paper receipts[37]. Other mode of entry of BPs in the human body is through inhalation. Study of dust samples collected from 120 homes in US revealed the occurrence of BPA at concentrations ranging from 0.2 to 17.6 mg/kg in 86% of collected samples[38]. Another study conducted by Geens et al.[19] in Belgium showed that BPA was found at a higher average concentration of 6.53 mg/Kg in office dust as compared to home dust. As dust can easily penetrate through air passages, it is a potential source of BPA exposure. Nevertheless, the exposure is substantially less than that of food sources[19].

6. Health Hazards and Mode of Action

Recent studies on the usage of BPs have reported its consequential effects on human body (Figure 4), which may be long lasting. Several toxic effects have been reported in animal studies, which are due to endocrine-disruption activity, oxidative potential and mutagenic potential[39].

6.1 Genetic Effects

BPs impart genetic effects on human body by direct interaction with genetic material at the chromosome and deoxyribonucleic acid level. Changes in chromosomal aberration, deletion or rearrangement of chromosomal segment brings about structural changes in DNA and

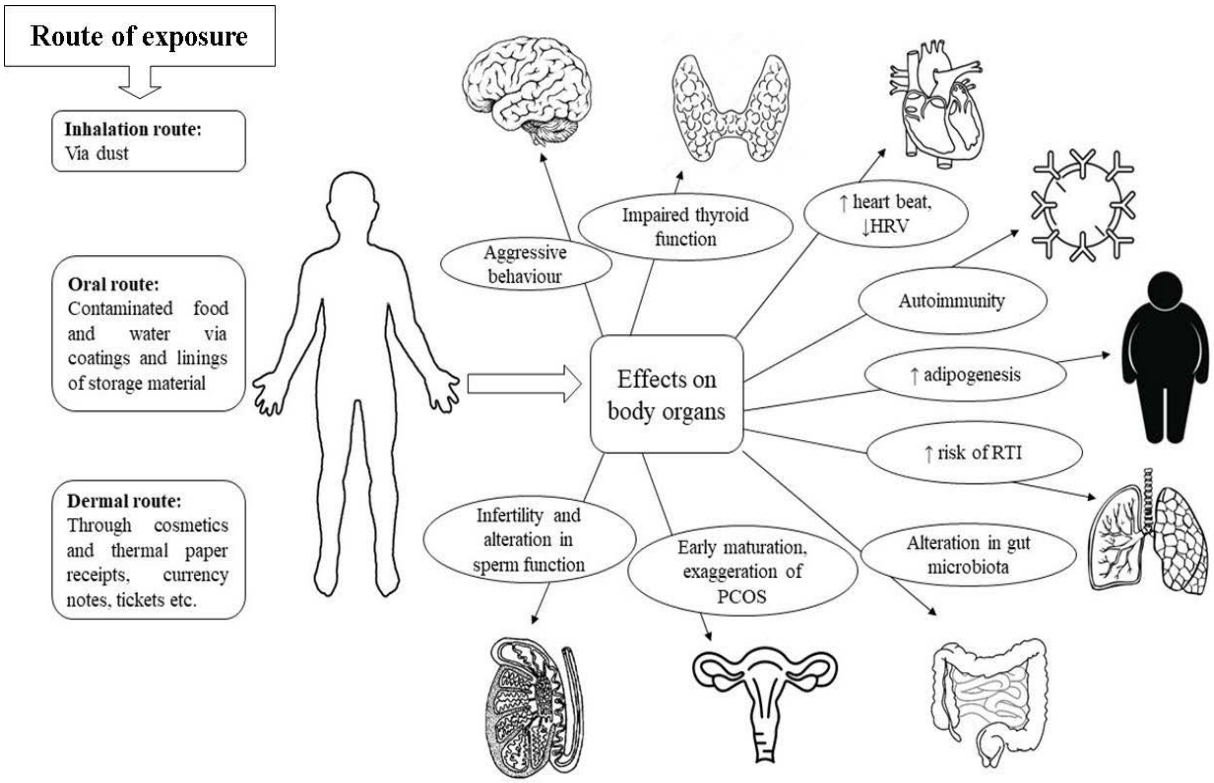


Figure 4. Routes of human exposure to bisphenols and its impact on different body organs
HRV = Heart Rate Variability; RTI = Respiratory Tract Infections; PCOS = Polycystic Ovarian Syndrome

results in broken strands, alters scheduled DNA synthesis and gene mutations letion of whole chromosome and/or rearrangement of chromosomal segments. Alterations in DNA results in broken strands, changes in scheduled DNA synthesis and gene mutations. These alterations has specifically been studied for BPA, however other analogues have also been reported to have such effects[40]. These alterations can lead to a wide range of health impacts like infertility, miscarriages and birth defects in humans[41].

6.2 Epigenetic Effects

Epigenetic mechanisms produce permanent changes through mitotically or meiotically heritable changes in gene expression. These do not entail changes in the DNA sequence. Recent studies have reported the association of BPA exposure with induction of epigenetic defects like altered developmental pathways and cell processes visible by modifications in epigenetic markers. The mechanisms include DNA methylation, non-coding ribonucleic acid (RNA) expression and histone modification. Hypermethylation of estrogen receptor, observed in rat testis, is one of the examples of epigenetic changes resulting in ill effects on sperm production process and fertility issues. Weng et al.[42] reported that exposure of human primary breast epithelial cells to BPA increases DNA methylation in lysosomal-associated membrane protein-3 gene and inhibits its expression. This repression indicates an increased risk of breast cancer in later life. In addition, BPA exposure has been shown to alter micro RNA (miR-146a) expression, which is a biomarker of sepsis, in human placental cell lines[43] suggesting potential influences in developmental pathways of the fetus.

6.3 Oxidative Stress and Mitochondrial Dysfunction

Oxidative balance refers to the number of free radicals. It can be disrupted by either increase in Reactive Oxygen Species (ROS) production or decrease in the capacity of antioxidant defense, or both the factors. Various studies suggest that BPs can disturb oxidative homeostasis through direct or indirect pathways, including disruption in mitochondrial function[44] and variation in antioxidant enzymes[45]. Administration of ascorbic acid is found to reverse the effects of oxidative stress in rat liver occurred due to BPs[46]. BPA-induced oxidative stress can accelerate toxic aggregation of human islet amyloid polypeptide (hIAPP), resulting in damage to β-cells and hence increasing the chances of development of type 2 diabetes[47].

BPA exposure has been found to impair mitochondrial function in the liver even within doses below the no - observed - adverse - effect level (NOAEL) [39]. In rat insulinoma (INS-1) cells, BPA exposure can lead to alterations in gene expression involved in mitochondrial function and metabolism, thus also leading to pancreatic dysfunction[48].

6.4 Endocrine Disruption

Disruption of endocrine system can occur at different physiological levels by different mechanism that lead to either change in the amount of hormones released (hypo or hypersecretion of hormones), interference with hormonal receptors, and modification in hormonal metabolism. All these effects end up with wide range of health adversities to the host ranging from developmental disturbances to birth defects, reproductive abnormalities, immunological alterations, neurobehavioral and metabolic disorders. BPA acts as a xenoestrogen. The xenoestrogenic property is attributed to its ability to bind with either the nuclear (classical method) or membrane estrogen receptors. Other non-classical pathways of action include G-protein-coupled receptor 30 or other non-genomic pathways[49-51]. BPs bind receptors associated with endocrine hormones like estrogen receptors and androgen receptors as well as those of other body systems like peroxisome proliferator-activated receptor[52, 53]. It is effective even at a concentration of 1 ng L^{-1} [26]. This results in altered biosynthesis, secretion, action and metabolism of hormones in the body[54].

6.5 Reproductive Dysfunction

The endocrine disrupters alters embryonal development and impairs reproduction[55]. In adult human males, BPA increases the occurrence of low sperm count, early puberty etc., whereas in women, increased everyday exposure can increase the risk of miscarriages, breast cancer, polycystic ovarian syndrome and ovarian cysts[56]. Detection of BPA in gestational tissues have verifiedits potential to pass from mother to foetus[37]. Animal-based studies have provided a firm base for possible reproductive abnormalities in human beings. Deformities in reproductive organs,

decline in sperm quality, and hindrance of sperm maturity were reported in fishes[57-58]. Increased prostate weight, decrease in daily sperm production, reduced size of seminal vesicle and general obesity was detected in laboratory mice when exposed to BPA[59]. Increased ova production and abnormalityin reproductive organs was also observed in snails on exposure to BPA[60].

6.6 Impaired Nutrient Metabolism

Recent studies have suggested increased risk of obesity, diabetes and heart disease on exposure to BPA[51, 61]. BPA is found to influence glucose metabolism through insulin resistance, adipogenesis, pancreatic β-cell dysfunction and/ or increase in oxidative stress, which can induce obesity and also result in diabetes type 2[51]. The estrogen-like effect of BPS was detected even at the extremely low concentrations of 10^{-15} M. BPA and BPS induce lipid accumulation in preadipocytes, moderate specific regulatory pathways for adipogenesis and lipid metabolism, and a signature of gene, which results in adiposity and insulin sensitivity[62-63]. BPS is more potent adipogen than BPA[3].

6.7 Errors in Cell Signalling

BPA exposure has been shown to alter cell signalling pathways that can be induced by ROS, contribute to the generation of ROS, or promote cell proliferation and pro survival[64-65]. BPA exposure in particular leads to over-activation of mitogen-activated protein kinase (MAPKs), PI3K/AKT, and NF-jB pathways. This has been linked to increased cell proliferation, up-regulation of pro-survival proteins, and increased migration and invasion in a number of cells, including breast, colorectal, ovarian, and prostate[66-67]. Knockdown of c-Myc during BPA exposure was shown to reverse the induction of ROS and DNA damage[69]. Studies that noted a reduction of ROS after BPA exposure observed an increase in nuclear respiratory factor (NRF) proteins[69-70] and mRNA levels of heme oxygenase-1 (ho1) and nicotinamide adenine dinucleotide phosphate (NADPH) Quinone Dehydrogenase 1 (NQo1)[69]. These changes indicated that BPA, when proposed to act as an antioxidant, stimulated antioxidant response elements in the genome to protect cells from oxidative stress[69]. Very low doses of BPA stimulate human seminoma cell proliferation. BPS has been found to disrupt the membrane initiated E2-induced cell signalling which in turn can lead to death of cells. Further, release of prolactin can cause various adverse health effects by interfering with the normal activity of hormones. The effect of BPs on human organ system has been discussed in Table 2.

6.8 Other Effects

Hormone disrupting properties of BPA have been found to result in hepatotoxic, immunotoxin, mutagenic and carcinogenic effects[105]. Neurotoxic and teratogenic properties have also been exhibited by BPA, although the results are in consistent[106-107].

Table 2 gives detailed information on effect of BPs on various organ systems and their mode of action.

7. Minimizing Exposure to BPs

In light of significant adverse health effects of BPs on humans, it is imperative to search for alternative strategies (Figure 5). However, finding an alternative is challenging, given its widespread applications and incorporation in commonly used plastic products. It is of utmost importance that we find replacements for the most potent bisphenol - BPA. Various health agencies and plastic manufacturing industries are working to find alternative bisphenol-free chemicals.

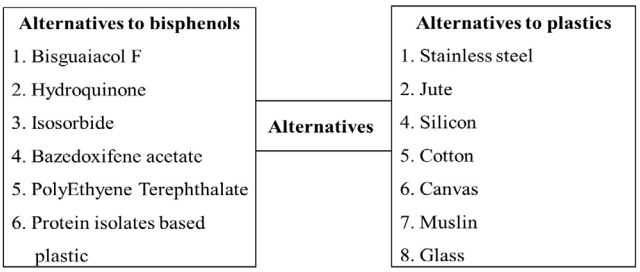


Figure 5. Alternatives to BPs and plastic

In this regard, nineteen alternative chemicals were examined by Environmental Protection Agency, EPA to find potential replacements for BPA and BPS, as a developer in thermal paper and established that most of the alternatives to BPA are at least moderately hazardous to human health as well as aquatic toxicity[108]. The report identified that "decision makers may wish to consider alternative printing systems". The use of BPA or BPS in thermal paper production have been unable to find any safe alternatives, thus supporting the EPA's recommendation that thermal paper should be replaced with other safer technologies[108].

Table 2. Effect of bisphenols on various organ systems and their mode of action

Organ system	Effect	Pathway / Mechanism of action	References
Muscular system	Cachexia in cancer patients	• Via the activation of those cytokines, which are transcriptional targets of the oestrogen-related receptors (ERRs).	71
Nervous system	Aggressive behaviour	• During sexual differentiation, male patterning is induced in Central Nervous System due to conversion of estrogen from testosterone.	72-73
Endocrine system	• Impaired thyroid function • Thyroid resistance syndrome • Attention-deficit hyperactivity disorder (ADHD) like syndrome	• By binding with T3 and antagonizing T3 activation of thyroid hormone receptor. • By inhibition of thyroid hormone receptor (TR) mediated gene activation • BPA inhibition of negative feedback mediated by β isoform of thyroid hormone receptor, i.e. TRβ	74-76
	• Obesity	• Bisphenols are obesogenic chemicals and these can direct the differentiation of stem cells into adipocytes, further promoting the accumulation of triglycerides (TGs) in mature adipose cells.	77
Circulatory system	• Increased blood pressure and decreased heart rate variability	• By affecting the autonomic nervous system. • By altering cardiac Ca2+ handling protein expressions.	78-79
Immune system	• Alteration in T and B cell homeostasis, which favours weakening of immune system and can also result in autoimmunity • Alter other important cytokines of autoimmune diseases such as TNF-α and interleukins IL-6, IL-4 and	• By increased interferon-gamma (g-INF) promoter activity in lymphoid cells. • Due to increased g-INF mRNA and increased secretion of g-interferon, which is associated with autoimmune diseases • By inhibiting adherence of macrophages.	80-82
	• Alteration in gut microbiota • Decrease in bifidobacteria	• BPA evokes decrease in interluekin (IL)-17-producing T helper cells (T_H17) and T helper type 1 (T_H1) in the small intestine, which is associated with intestinal dysbiosis at adulthood.	83
Respiratory system	• Increased bronchial inflammation • Allergen induced airways hyperreactivity • Increased chances of asthma and respiratory tract infections	• High concentrations of BPA (10^{-5} to 10^{-4} M) induce interleukin (IL)-4 and allergen specific IgE production from CD_{4+} T cells to promote eosinophilic inflammation In the airways	84-86
Digestive system	• Impaired glucose homeostasis and insulin sensitivity; • Elevated levels of plasma triglycerides, glycerol, and hormone leptin	• Alteration in pancreatic β-cell function. • Alterations of estrogen signalling.	51, 87
Reproductive system	• Oxidative stress damage during spermatogenesis • Impairment of the quality of spermatogenesis	• Massive reactive oxygen species (ROS) production in the testis of BPA-exposed animals, like 8-Oxo-2'-deoxyguanosine (8-OHdG), one of the major products of DNA oxidation and γH2AX, a novel biomarker for DNA double-stranded breaks, in germ cells. • BPA exposure in neonates significantly reduces crossover and meiotic recombination, affects the pool of spermatogonial stem cell of the developing testis, thus permanently reducing sperm production. • Through the modulation of sirtuin-1 (SIRT1), a NAD^+-dependent deacetylase, involved in the progression of spermatogenesis	88-89

	• Increased chances of benign prostatic hyperplasia (BPH)	• By inducing epithelial–mesenchymal transition (EMT), which refers to conversion of polarized and immotile epithelial cells into motile mesenchymal cells which results in benign prostrate hyperplasia.	90
	• Infertility in males, low spermatozoa count, sperm protein alteration, inhibition of sperm motility, alteration in sperm function	• Alter hormonal signal through binding to ERs on male germ cells • Decreasing ATP levels in spermatozoa. • Increase in the phosphorylation of tyrosine residues on sperm proteins involved in protein kinase A-dependent regulation • Induction of an advanced acrosome reaction, resulting in poor fertilization and compromise in embryonic development.	57-60, 91-93
	• Erectile dysfunction	• Due to a peripheral effect on penile corpora cavernosa and a central effect at brain level.	94
	• Prostate cancer	• Due to androgen receptor mutation (T877A) which results in androgen-independent prostate cancer cell proliferation.	14, 95
	• Earlier age at menarche among girls • Enhances ovarian androgen production	• Not reported	60, 96-98
	• Breast cancer	• ERRα exhibits increased recruitment to the promoter of prognostic marker gene of breast cancer, viz. Trefoil factor 1 (TFF1), present on chromosome 21. • Similarly, abnormal expression of ErbB2 receptor tyrosine kinase, and activation of ErbB2 signalling in breast cancer cell lines increases the expression of ERRα target genes[18]	71, 99-101
	• Exaggerate the severity of the PCOS	• Owing to the decreased hepatic clearance that arises from androgen excess	102-104

Even products labelled as "BPA free" are found to contain its analogues, viz. BPS, BPF which are equally hazardous[109]. BPA analogues i.e., BPS and BPF have reported similar effects from both these chemicals as from BPA[62]. Other materials like acrylics or polyesters do not cater to the purpose of unique properties as exhibited by BP. Szafran et al[110] have characterized the properties of potential bisphenol substituents like 2, 2' BPA, Bisguaiacol F (BGF), CHDM 4-hydroxybuyl acrylate, hydroquinone (HQ), and tetra methyl bisphenol F. It was found that these chemicals have very low estrogenic properties as compared to endocrine disrupter BP, when selective estrogen receptor modulators (SERMs) 4HT and bazedoxifene acetate (BZA) were used as antagonist controls. "Green" alternatives like bisguaiacol-F (BGF) and soy protein isolates based plastic sound economic and safer alternatives to BPs. BGF is a by-product of paper industry and is synthesised from plants, whereas soy protein isolates can replace BPs in plastic film coatings due to adhesive properties[110-111]. Bio-sourced products from pine bark and polyphenol derivatives from other forestry by-products can be used to replace BPA. The FDA (Food and Drug Administration) has authorized the use of GRIMALID line for applications in contact with food. GRIMALID is a line of semi-crystalline polyamides, i.e., amorphous homopolyamide- and copolyamide-type polyamides that can be used to replace polycarbonate itself. In epoxy resins, bio-sourced di-alcohol isosorbide is used in place of BPA. Poly ethylene terephthalate (PET), a synthetic polymer, is a BPA free polycarbonate, which has important application in manufacturing water bottles, jars and jugs. PET is produced by polycondensation of glycol ethylene with terephthalic acid. Hence, some worthwhile substitutes like BGF, HQ, BZA, isosorbide, PET etc. which, on further investigation can replace BPs for its use in polycarbonate or plastic industry.

Since the scientists have yet been unable to find a chemical, which can effectively replace BPs fully, it is important that we consider replacement of polycarbonates and plastic itself. Stainless steel, glass, acrylics, porcelain, glass, wood, cotton, silicon etc. are such compounds, which have the ability to replace plastic in manufacturing of bags, utensils, machineries, equipment, bottles, boxes etc.

Investigations have shown that plants and microorganisms are capable of transforming BPs into compounds that can be used as a sole carbohydrate substrate and source of energy. Microbes like fungi can also degrade BPs into metabolites that exhibit lower toxicity and estrogenicity than BPA. BP degrading fungi species include *Irpexlacteus*, *Trametes versicolor*, *Ganodermastipitaion*, *Lentinusswartzii, Schizophyllum commune*, *Pleurotuseryngii*, etc. (Shin, Choi & Song, 2007; Arboleda et al. 2013). Several proteobacteria strains including *Pseudomonas* sp. SU1, NAR11, FU12, NO14, SU19, FU20; *Klebsiella* sp. NE2, SU5; *Enterobacter* sp. HI9, HA18, etc. have been found to effectively degrade BPA into less toxic metabolites (Matsumura et al. 2009). Indigenous microflora of water can be used to remove these compounds from polluted environment however they have a limited efficiency and alternative methods are required to remove these chemicals[115].

8. Regulation of BPs

Several regulatory steps have been taken to prevent the health hazards which may occur on exposure to BPs. In 2015, US Senator, Dianne Feinstein introduced a bill, BPA in Food Packaging Right To Know Act, to protect Americans from BPA, a synthetic estrogen. The act mandates to carry a warning label on products containing BPA. According to various world health agencies, the NOAEL for BPA is 5mg/kg body weight per day[116-117]. This level is about five hundred times above conventional estimates of human exposure. The Environmental Working Group (EWG) constantly argues that FDA has always denied that the presence of BPA in epoxy containing plastics is more than safer limit for humans, despite massive evidence that exposes the dangers of BPs. The agency has also denied the petition to ban BPA, although it continues to urge the replacements of BPA in manufacturing processes. The EWG has come up with a database of around 16000 food products that involve the use of BPA. Usage of BPA in the manufacturing of baby bottles was bannedby European Food Safety Authority (EFSA) and others food safety agencies in 2010. Canada was the first country to replace BPA by BPS and banning BPA in baby bottles[118], however toxicity of BPS is no less. Recently, Food and Drug Administration also banned the use of BPA in packaging materials of baby formula. EFSA has fixed the maximum migration limit of BPA from food packages to 0.6 ppm while the tolerable daily intake is set to 0.05 mg/kg body weight/day. These contradictory numbers between the global health agencies indicate the need to revise the regulations in lieu of increasing health hazards due to BPs. Indian data on regulation of use of BPs is scarce.

9. Conclusion

BPs and its analogues have evolved as an irreplaceable component of modern accessories. Its outstanding properties give it a definite place in production of polycarbonates, lacquer coating and printing ink (thermal receipts and currency notes). Worldwide occurrence of BPs has been detected in food, water and air. Leaching is one of common mechanism through which BPs find their way into the food system and finally to the human body. The health hazards caused by BPs even in minute quantities cannot be overlooked. From contaminating food to disrupting endocrine functions, the health hazards are numerous. BPA, the most hazardous of all, needs immediate attention by regulatory agencies as well as manufacturers. Although, various studies and reports have documented the use of alternatives to BPs, but present investigations have found similar health effects from them also. At the same time, researchers can investigate some of the economic and environment friendly potential BP substitutes from plants sources and industrial by-products. Use of materials like glass and porcelain, which have been tested for ages, should be promoted. Technologies must be developed for minimal use of BPs in manufacturing and to remove BPs from already contaminated products and sources.

10. References

1. Le HH, Carlson EM, Chua JP, Belcher SM. Bisphenol A is released from polycarbonate drinking bottles and mimics

the neurotoxic actions of estrogen in developing cerebellar neurons. Toxicol Lett. 2008 Jan 30;176(2):149–56.
2. Grumetto L, Montesano D, Seccia S, Albrizio S, Barbato F. Determination of bisphenol A and bisphenol B residues in canned peeled tomatoes by reversed-phase liquid chromatography. J Agric Food chem. 2008 Oct 30;56(22):10633–7.
3. Ahmed S, Atlas E. Bisphenol S-and bisphenol A-induced adipogenesis of murine preadipocytes occurs through direct peroxisome proliferator-activated receptor gamma activation. Int J Obese. 2016 Oct;40(10):1566.
4. Thompson RC, Moore CJ, Vom Saal FS, Swan SH. Plastics, the environment and human health: current consensus and future trends. Philos Trans R Soc Lond B: Biol Sci. 2009 Jul 27;364(1526):2153–66.
5. Albercht C. Fact sheet on Bisphenol S *(BPS)*, Cancer Association of South Africa. Available at https://www.cansa.org.za/files/2008/06/Fact-Sheet-BPS-Dr-Carl-Albrecht-Final-4-10.pdf.
6. O'Neil MJ, Heckelman PE, Koch CB, Roman KJ. The Merck Index: An Encyclopedia of Chemicals, Drugs, and Biologicals, 14th Edition. Whitehouse Station, NJ: Merck and Company; 2006.
7. Herbst AL, Ulfelder H, Poskanzer DC. Adenocarcinoma of the vagina: association of maternal stilbestrol therapy with tumor appearance in young women. N Engl J Med. 1971 Apr 22;284(16):878–81.
8. Haynes WM. Handbook of Chemistry and Physics 91st ed. Boca Raton, FL: CRC Press; 2010-2011.
9. Rosenmai AK, Dybdahl M, Pedersen M, Alice van Vugt-Lussenburg BM, Wedebye EB, Taxvig C, Vinggaard AM. Are structural analogues to bisphenol a safe alternatives?. Toxicol Sci. 2014 Feb 27;139(1):35–47.
10. Thayer KA, Taylor KW, Garantziotis S, Schurman SH, Kissling GE, Hunt D, Herbert B, Church R, Jankowich R, Churchwell MI, Scheri RC. Bisphenol A, Bisphenol S, and 4-Hydro xyphenyl 4-Isopro oxyphenyl sulfone (BPSIP) in Urine and Blood of Cashiers. Environ Health Perspect. 2015 Aug 25;124(4):437–44.
11. Maćczak A, Cyrkler M, Bukowska B, Michałowicz J. Bisphenol A, bisphenol S, bisphenol F and bisphenol AF induce different oxidative stress and damage in human red blood cells (in vitro study). Toxicol in Vitro. 2017 Jun 1;41:143–9.
12. Becerra V, Odermatt J. Detection and quantification of traces of bisphenol A and bisphenol S in paper samples using analytical pyrolysis-GC/MS. Analyst. 2012;137(9):2250–9.
13. Li X, Ying GG, Zhao JL, Chen ZF, Lai HJ, Su HC. 4-Nonylphenol, bisphenol-A and triclosan levels in human urine of children and students in China, and the effects of drinking these bottled materials on the levels. Environ int. 2013 Feb 1;52:81–6.
14. Sun C, Leong LP, Barlow PJ, Chan SH, Bloodworth BC. Single laboratory validation of a method for the determination of bisphenol A, bisphenol A diglycidyl ether and its derivatives in canned foods by reversed-phase liquid chromatography. J Chromatogr A. 2006 Sep 29;1129(1):145–8.
15. Hormann AM, Vom Saal FS, Nagel SC, Stahlhut RW, Moyer CL, Ellersieck MR, Welshons WV, Toutain PL, Taylor JA. Holding thermal receipt paper and eating food after using hand sanitizer results in high serum bioactive and urine total levels of bisphenol A (BPA). PloS One. 2014 Oct 22;9(10):e110509.
16. Mendum T, Stoler E, VanBenschoten H, Warner JC. Concentration of bisphenol A in thermal paper. Green Chem Lett Rev. 2011 Mar 1;4(1):81–6.
17. Liao C, Kannan K. Widespread occurrence of bisphenol A in paper and paper products: implications for human exposure. Environ Sci Tech. 2011 Oct 5;45(21):9372–9.
18. Liao C, Liu F, Alomirah H, Loi VD, Mohd MA, Moon HB, Nakata H, Kannan K. Bisphenol S in urine from the United States and seven Asian countries: occurrence and human exposures. Environ Sci Tech. 2012 Jun 7;46(12):6860–6.
19. Geens T, Goeyens L, Kannan K, Neels H, Covaci A. Levels of bisphenol-A in thermal paper receipts from Belgium and estimation of human exposure. Sci Total Environ. 2012 Oct 1;435:30–3.
20. Song S, Song M, Zeng L, Wang T, Liu R, Ruan T, Jiang G. Occurrence and profiles of bisphenol analogues in municipal sewage sludge in China. Environ Pollut. 2014 Mar 1;186:14–9.
21. Pivnenko K, Pedersen GA, Eriksson E, Astrup TF. Bisphenol A and its structural analogues in household waste paper. Waste Manage. 2015 Oct 1;44:39–47.
22. Jordakova I, Dobias J, Voldrich M, Poustka J. Determination of bisphenol A, bisphenol F, bisphenol A diglycidyl ether and bisphenol F diglycidyl ether migrated from food cans using gas chromatography-mass spectrometry. Czech J Food Sci. 2003;21(3):85–90.
23. Koch HM, Kolossa-Gehring M, Schröter-Kermani C, Angerer J, Brüning T. Bisphenol A in 24 h urine and plasma samples of the German Environmental Specimen Bank from 1995 to 2009: a retrospective exposure evaluation. J Expo Sci Environ Epidemiol. 2012 Nov;22(6):610.
24. Wang W, Abualnaja KO, Asimakopoulos AG, Covaci A, Gevao B, Johnson-Restrepo B, Kumosani TA, Malarvannan G, Minh TB, Moon HB, Nakata H. A comparative assessment of human exposure to tetrabromobisphenol A and eight BPs including bisphenol A via indoor dust ingestion in twelve countries. Environ Int. 2015 Oct 1;83:183–91.
25. Wan HT, Leung PY, Zhao YG, Wei X, Wong MH, Wong CK. Blood plasma concentrations of endocrine disrupting

chemicals in Hong Kong populations. J Hazard Mater. 2013 Oct 15;261:763–9.
26. Ikezuki Y, Tsutsumi O, Takai Y, Kamei Y, Taketani Y. Determination of bisphenol A concentrations in human biological fluids reveals significant early prenatal exposure. Hum Reprod. 2002 Nov 1;17(11):2839–41.
27. Thomson BM, Grounds PR. Bisphenol A in canned foods in New Zealand: an exposure assessment. Food Addit Contam. 2005 Jan 1;22(1):65–72.
28. Cunha SC, Almeida C, Mendes E, Fernandes JO. Simultaneous determination of bisphenol A and bisphenol B in beverages and powdered infant formula by dispersive liquid–liquid micro-extraction and heart-cutting multidimensional gas chromatography-mass spectrometry. Food Addit Contam 2011 Apr 1;28(4):513–26.
29. Calafat AM, Weuve J, Ye X, Jia LT, Hu H, Ringer S, Huttner K, Hauser R. Exposure to bisphenol A and other phenols in neonatal intensive care unit premature infants. Environ Health Perspect. 2008 Dec 10;117(4):639–44.
30. Brede C, Fjeldal P, Skjevrak I, Herikstad H. Increased migration levels of bisphenol A from polycarbonate baby bottles after dishwashing, boiling and brushing. Food Addit Contam. 2003 Jul 1;20(7):684–9.
31. Sun Y, Wada M, Al-Dirbashi O, Kuroda N, Nakazawa H, Nakashima K. High-performance liquid chromatography with peroxyoxalate chemiluminescence detection of bisphenol A migrated from polycarbonate baby bottles using 4-(4, 5-diphenyl-1H-imidazol-2-yl) benzoyl chloride as a label. J Chromatogr B: Biomed Sci Appl. 2000 Nov 10;749(1):49–56.
32. Maia J, Cruz JM, Sendón R, Bustos J, Sanchez JJ, Paseiro P. Effect of detergents in the release of bisphenol A from polycarbonate baby bottles. Food Res Int. 2009 Dec 1;42(10):1410–4.
33. Vandenberg LN, Hauser R, Marcus M, Olea N, Welshons WV. Human exposure to bisphenol A (BPA). Reprod Toxicol. 2007 Aug 1;24(2):139–77.
34. Cao XL, Corriveau J, Popovic S. Bisphenol A in canned food products from Canadian markets. J Food Prot. 2010 Jun;73(6):1085–9.
35. Takao Y, Lee HC, Kohra S, Arizono K. Release of bisphenol A from food can lining upon heating. J Health Sci. 2002;48(4):331–4.
36. Vandenberg LN, Hunt PA, Myers JP, Vom Saal FS. Human exposures to bisphenol A: mismatches between data and assumptions. Rev Environ Health. 2013 Apr 1;28(1):37–58.
37. Dodson RE, Nishioka M, Standley LJ, Perovich LJ, Brody JG, Rudel RA. Endocrine disruptors and asthma-associated chemicals in consumer products. Environ Health Perspect. 2012 Jul;120(7):935.
38. Rudel RA, Camann DE, Spengler JD, Korn LR, Brody JG. Phthalates, alkylphenols, pesticides, polybrominated diphenyl ethers, and other endocrine-disrupting compounds in indoor air and dust. Environ Sci Tech. 2003 Oct 15;37(20):4543–53.
39. Moon MK, Kim MJ, Jung IK, Koo YD, Ann HY, Lee KJ, Kim SH, Yoon YC, Cho BJ, Park KS, Jang HC. Bisphenol A impairs mitochondrial function in the liver at doses below the no observed adverse effect level. J Korean Med Sci. 2012 Jun 1;27(6):644–52.
40. Rochester JR, Bolden AL. Bisphenol S and F: a systematic review and comparison of the hormonal activity of bisphenol A substitutes. Environ Health Perspect. 2015 Jul;123(7):643.
41. Bromer JG, Zhou Y, Taylor MB, Doherty L, Taylor HS. Bisphenol-A exposure in utero leads to epigenetic alterations in the developmental programming of uterine estrogen response. FASEB J. 2010 Jul;24(7):2273–80.
42. Weng YI, Hsu PY, Liyanarachchi S, Liu J, Deatherage DE, Huang YW, Zuo T, Rodriguez B, Lin CH, Cheng AL, Huang TH. Epigenetic influences of low-dose bisphenol A in primary human breast epithelial cells. Toxicol Appl Pharmacol. 2010 Oct 15;248(2):111–21.
43. Avissar-Whiting M, Veiga KR, Uhl KM, Maccani MA, Gagne LA, Moen EL, Marsit CJ. Bisphenol A exposure leads to specific microRNA alterations in placental cells. Reproductive Toxicol. 2010 Jul 1;29(4):401–6.
44. Tiwari D, Kamble J, Chilgunde S, Patil P, Maru G, Kawle D, Bhartiya U, Joseph L, Vanage G. Clastogenic and mutagenic effects of bisphenol A: an endocrine disruptor. Mutat Res-Gen Tox En. 2012 Mar 18;743(1):83–90.
45. Kabuto H, Amakawa M, Shishibori T. Exposure to bisphenol A during embryonic/fetal life and infancy increases oxidative injury and causes underdevelopment of the brain and testis in mice. Life Sci. 2004 Apr 30;74(24):2931–40.
46. Bindhumol V, Chitra KC, Mathur PP. Bisphenol A induces reactive oxygen species generation in the liver of male rats. Toxicol. 2003 Jun 30;188(2-3):117–24.
47. Gong H, Zhang X, Cheng B, Sun Y, Li C, Li T, Zheng L, Huang K. Bisphenol A accelerates toxic amyloid formation of human islet amyloid polypeptide: a possible link between bisphenol A exposure and type 2 diabetes. PloS one. 2013 Jan 23;8(1):e54198.
48. Angle BM, Do RP, Ponzi D, Stahlhut RW, Drury BE, Nagel SC, Welshons WV, Besch-Williford CL, Palanza P, Parmigiani S, Vom Saal FS. Metabolic disruption in male mice due to fetal exposure to low but not high doses of bisphenol A (BPA): evidence for effects on body weight, food intake, adipocytes, leptin, adiponectin, insulin and glucose regulation. Reprod Toxicol. 2013 Dec 1;42:256–68.

49. Thomas P, Dong J. Binding and activation of the seven-transmembrane estrogen receptor GPR30 by environmental estrogens: a potential novel mechanism of endocrine disruption. The J Steroid Biochem Mol Biol. 2006 Dec 1;102(1-5):175-9.
50. Vandenberg LN, Maffini MV, Sonnenschein C, Rubin BS, Soto AM. Bisphenol-A and the great divide: a review of controversies in the field of endocrine disruption. Endocr Rev. 2009 Feb 1;30(1):75–95.
51. Alonso-Magdalena P, Vieira E, Soriano S, Menes L, Burks D, Quesada I, Nadal A. Bisphenol A exposure during pregnancy disrupts glucose homeostasis in mothers and adult male offspring. Environ Health Perspect. 2010 Sep;118(9):1243.
52. Wetherill YB, Hess-Wilson JK, Comstock CE, Shah SA, Buncher CR, Sallans L, Limbach PA, Schwemberger S, Babcock GF, Knudsen KE. Bisphenol A facilitates bypass of androgen ablation therapy in prostate cancer. Mol Cancer Ther. 2006 Dec 1;5(12):3181–90.
53. Iso T, Watanabe T, Iwamoto T, Shimamoto A, Furuichi Y. DNA damage caused by bisphenol A and estradiol through estrogenic activity. Biol Pharm Bull. 2006;29(2):206–10.
54. Diamanti-Kandarakis E, Bourguignon JP, Giudice LC, Hauser R, Prins GS, Soto AM, Zoeller RT, Gore AC. Endocrine-disrupting chemicals: an Endocrine Society scientific statement. Endocr Rev. 2009 Jun 1;30(4):293–342.
55. Damstra T, Barlow S, Bergman A, Kavlock R, Van Der Kraak G. Global assessment of the state-of-the-science of endocrine disruptors. Geneva: WHO. 2002.
56. Devi GP, Kumari MC, Madhavi B. Adverse effects of plastic on environment and human beings. J Chem Pharm Sci. 2014;974:2115.
57. Shioda T, Wakabayashi M. Effect of certain chemicals on the reproduction of medaka (*Oryzias latipes*). Chemosphere. 2000 Feb 1;40(3):239–43.
58. Metcalfe CD, Metcalfe TL, Kiparissis Y, Koenig BG, Khan C, Hughes RJ, Croley TR, March RE, Potter T. Estrogenic potency of chemicals detected in sewage treatment plant effluents as determined by in vivo assays with Japanese medaka (Oryzias latipes). Environ Toxicol Chem. 2001 Feb 1;20(2):297–308.
59. Vom Saal FS, Nagel SC, Coe BL, Angle BM, Taylor JA. The estrogenic endocrine disrupting chemical bisphenol A (BPA) and obesity. Mol Cell Endocrinol. 2012 May 6;354(1-2):74–84.
60. Duft M, Schulte-Oehlmann U, Weltje L, Tillmann M, Oehlmann J. Stimulated embryo production as a parameter of estrogenic exposure via sediments in the freshwater mudsnail Potamopyrgus antipodarum. Aquatic Toxicol. 2003 Sep 10;64(4):437–49.
61. Shankar A, Teppala S. Urinary bisphenol A and hypertension in a multiethnic sample of US adults. J Environ Public Health. 2012.
62. Boucher JG, Ahmed S, Atlas E. Bisphenol S induces adipogenesis in primary human preadipocytes from female donors. Endocrinology. 2016 Mar 22;157(4):1397–407.
63. Boucher JG, Gagné R, Rowan-Carroll A, Boudreau A, Yauk CL, Atlas E. Bisphenol A and bisphenol S induce distinct transcriptional profiles in differentiating human primary preadipocytes. PloS one. 2016 Sep 29;11(9):e0163318.
64. Watson CS, Bulayeva NN, Wozniak AL, Finnerty CC. Signaling from the membrane via membrane estrogen receptor-α: estrogens, xenoestrogens, and phytoestrogens. Steroids. 2005 May 1;70(5-7):364–71.
65. Rochester JR. Bisphenol A and human health: a review of the literature. Reproductive Toxicol. 2013 Dec 1;42:132–55.
66. Koong LY, Watson CS. Rapid, nongenomic signaling effects of several xenoestrogens involved in early-vs. late-stage prostate cancer cell proliferation. Endocr Disruptors. 2015 Jan 1;3(1):e995003.
67. Song H, Zhang T, Yang P, Li M, Yang Y, Wang Y, Du J, Pan K, Zhang K. Low doses of bisphenol A stimulate the proliferation of breast cancer cells via ERK1/2/ERRγ signals. Toxicol in Vitro. 2015 Dec 25;30(1):521–8.
68. Pfeifer D, Chung YM, Hu MC. Effects of low-dose bisphenol A on DNA damage and proliferation of breast cells: the role of c-Myc. Environ Health Perspect. 2015 Dec;123(12):1271.
69. Chepelev NL, Enikanolaiye MI, Chepelev LL, Almohaisen A, Chen Q, Scoggan KA, Coughlan MC, Cao XL, Jin X, Willmore WG. Bisphenol A activates the Nrf1/2-antioxidant response element pathway in HEK 293 cells. Chem Res Toxicol. 2013 Feb 13;26(3):498-506.
70. Ponniah M, Billett EE, De Girolamo LA. Bisphenol A increases BeWo trophoblast survival in stress-induced paradigms through regulation of oxidative stress and apoptosis. Chem Res Toxicol. 2015 Aug 18;28(9):1693–703.
71. Deblois G, Giguère V. Oestrogen-related receptors in breast cancer: control of cellular metabolism and beyond. Nat Rev Cancer. 2013 Jan;13(1):27.
72. Kawai K, Nozaki T, Nishikata H, Aou S, Takii M, Kubo C. Aggressive behavior and serum testosterone concentration during the maturation process of male mice: the effects of fetal exposure to bisphenol A. Environ Health Perspect. 2003 Feb;111(2):175.
73. Gorski RA. Sexual differentiation of the endocrine brain and its control. Brain Endocrinol. 1991; 71–104.
74. Zoeller RT. Environmental chemicals impacting the thyroid: targets and consequences. Thyroid. 2007 Sep 1;17(9):811–7.
75. Seiwa C, Nakahara J, Komiyama T, Katsu Y, Iguchi T, Asou H. Bisphenol A exerts thyroid-hormone-like effects on

mouse oligodendrocyte precursor cells. Neuroendocrinol. 2004;80(1):21–30.
76. Moriyama K, Tagami T, Akamizu T, Usui T, Saijo M, Kanamoto N, Hataya Y, Shimatsu A, Kuzuya H, Nakao K. Thyroid hormone action is disrupted by bisphenol A as an antagonist. J Clin Endocrinol Metab. 2002 Nov 1;87(11):5185–90.
77. Heindel JJ, Newbold R, Schug TT. Endocrine disruptors and obesity. Nat Rev Endocrinol. 2015 Nov;11(11):653.
78. Gao X, Wang HS. Impact of bisphenol A on the cardiovascular system—epidemiological and experimental evidence and molecular mechanisms. Int J Environ Res Public Health. 2014 Aug 15;11(8):8399–413.
79. Mendelsohn ME. Estrogen actions in the cardiovascular system. Climacteric. 2009 Jan 1;12(sup1):18–21.
80. Ahmed SA. The immune system as a potential target for environmental estrogens (endocrine disrupters): a new emerging field. Toxicol. 2000 Sep 7;150(1-3):191–206.
81. Haas C, Ryffel B, Le Hir M. IFN-γ receptor deletion prevents autoantibody production and glomerulonephritis in lupus-prone (NZB× NZW) F1 mice. J Immunol. 1998 Apr 15;160(8):3713–8.
82. Schwarting A, Wada T, Kinoshita K, Tesch G, Kelley VR. IFN-γ receptor signaling is essential for the initiation, acceleration, and destruction of autoimmune kidney disease in MRL-Faslpr mice. J Immunol. 1998 Jul 1;161(1):494–503.
83. Malaisé Y, Menard S, Cartier C, Gaultier E, Lasserre F, Lencina C, Harkat C, Geoffre N, Lakhal L, Castan I, Olier M. Gut dysbiosis and impairment of immune system homeostasis in perinatally-exposed mice to Bisphenol A precede obese phenotype development. Sci Rep. 2017 Nov 3;7(1):144–72.
84. Gascon M, Casas M, Morales E, Valvi D, Ballesteros-Gómez A, Luque N, Rubio S, Monfort N, Ventura R, Martínez D, Sunyer J. Prenatal exposure to bisphenol A and phthalates and childhood respiratory tract infections and allergy. J Allergy Clin Immunol. 2015 Feb 1;135(2):370–8.
85. Midoro-Horiuti T, Tiwari R, Watson CS, Goldblum RM. Maternal bisphenol a exposure promotes the development of experimental asthma in mouse pups. Environ Health Perspect. 2009 Oct 5;118(2):273–7.
86. Lee MH, Chung SW, Kang BY, Park J, Lee CH, Hwang SY, Kim TS. Enhanced interleukin-4 production in CD4+ T cells and elevated immunoglobulin E levels in antigen-primed mice by bisphenol A and nonylphenol, endocrine disruptors: involvement of nuclear factor-AT and Ca2+. Immunol. 2003 May;109(1):76–86.
87. Wozniak AL, Bulayeva NN, Watson CS. Xenoestrogens at picomolar to nanomolar concentrations trigger membrane estrogen receptor-α–mediated Ca2+ fluxes and prolactin release in GH3/B6 pituitary tumor cells. Environ Health Perspect. 2005 Apr;113(4):431.
88. Chianese R, Viggiano A, Urbanek K, Cappetta D, Troisi J, Scafuro M, Guida M, Esposito G, Ciuffreda LP, Rossi F, Berrino L. Chronic exposure to low dose of bisphenol A impacts on the first round of spermatogenesis via SIRT1 modulation. Sci Rep. 2018 Feb 13;8(1):2961.
89. Hulak M, Gazo I, Shaliutina A, Linhartova P. In vitro effects of bisphenol A on the quality parameters, oxidative stress, DNA integrity and adenosine triphosphate content in sterlet (Acipenser ruthenus) spermatozoa. Comp Biochem Physiol C: Toxicol Pharmacol. 2013 Aug 1;158(2):64–71.
90. Huang DY, Zheng CC, Pan Q, Wu SS, Su X, Li L, Wu JH, Sun ZY. Oral exposure of low-dose bisphenol A promotes proliferation of dorsolateral prostate and induces epithelial–mesenchymal transition in aged rats. Sci Rep. 2018 Jan 11;8(1):490.
91. Karmakar PC, Kang HG, Kim YH, Jung SE, Rahman MS, Lee HS, Kim YH, Pang MG, Ryu BY. Bisphenol A affects on the functional properties and proteome of testicular germ cells and spermatogonial stem cells in vitro culture model. Sci Rep. 2017 Sep 19;7(1):11858.
92. Li J, Mao R, Zhou Q, Ding L, Tao J, Ran MM, Gao ES, Yuan W, Wang JT, Hou LF. Exposure to bisphenol A (BPA) in Wistar rats reduces sperm quality with disruption of ERK signal pathway. Toxicol Mech Methods. 2016 Mar 23;26(3):180–8.
93. Rahman MS, Kwon WS, Lee JS, Yoon SJ, Ryu BY, Pang MG. Bisphenol-A affects male fertility via fertility-related proteins in spermatozoa. Sci Rep. 2015 Mar 16;5:9169.
94. Kovanecz I, Gelfand R, Masouminia M, Gharib S, Segura D, Vernet D, Rajfer J, Li DK, Kannan K, Gonzalez-Cadavid NF. Oral Bisphenol A (BPA) given to rats at moderate doses is associated with erectile dysfunction, cavernosal lipofibrosis and alterations of global gene transcription. Int J Impot Res. 2014 Mar;26(2):67.
95. Maeda T. Prostate News. Prostate Cancer and Prostatic Diseases. 2005;8:2-6.
96. Lupien SJ, McEwen BS, Gunnar MR, Heim C. Effects of stress throughout the lifespan on the brain, behaviour and cognition. Nat Rev Neurosci. 2009 Jun;10(6):434.
97. Zhou W, Liu J, Liao L, Han S, Liu J. Effect of bisphenol A on steroid hormone production in rat ovarian theca-interstitial and granulosa cells. Mol Cell Endocrinol. 2008 Feb 13;283(1-2):12–8.
98. Denham M, Schell LM, Deane G, Gallo MV, Ravenscroft J, DeCaprio AP. Relationship of lead, mercury, mirex, dichlorodiphenyldichloroethylene, hexachlorobenzene, and polychlorinated biphenyls to timing of menarche among Akwesasne Mohawk girls. Pediatrics. 2005 Feb 1;115(2):e127–34.

99. Ariazi EA, Kraus RJ, Farrell ML, Jordan VC, Mertz JE. Estrogen-related receptor α1 transcriptional activities are regulated in part via the ErbB2/HER2 signaling pathway. Mol Cancer Res. 2007 Jan 1;5(1):71–85.
100. Badache A, Gonçalves A. The ErbB2 signaling network as a target for breast cancer therapy. J Mammary Gland Biol Neoplasia. 2006 Jan 1;11(1):13–25.
101. Barry JB, Giguère V. Epidermal Growth Factor–Induced Signaling in Breast Cancer Cells Results in Selective Target Gene Activation by Orphan Nuclear Receptor Estrogen-Related Receptor α. Cancer Res. 2005 Jul 15;65(14):6120–9.
102. Goodarzi MO, Dumesic DA, Chazenbalk G, Azziz R. Polycystic ovary syndrome: etiology, pathogenesis and diagnosis. Nat Rev Endocrinol. 2011 Apr;7(4):219.
103. Takeuchi T, Tsutsumi O, Ikezuki Y, Takai Y, Taketani Y. Positive relationship between androgen and the endocrine disruptor, bisphenol A, in normal women and women with ovarian dysfunction. Endocr J. 2004;51(2):165–9.
104. Takeuchi T, Tsutsumi O, Nakamura N, Ikezuki Y, Takai Y, Yano T, Taketani Y. Gender difference in serum bisphenol A levels may be caused by liver UDP-glucuronosyltransferase activity in rats. Biochem Biophys Res Commun. 2004 Dec 10;325(2):549–54.
105. Rees Clayton EM, Todd M, Dowd JB, Aiello AE. The impact of bisphenol A and triclosan on immune parameters in the US population, NHANES 2003–2006. Environ Health Perspect. 2010 Nov 29;119(3):390–6.
106. Ryan KK, Haller AM, Sorrell JE, Woods SC, Jandacek RJ, Seeley RJ. Perinatal exposure to bisphenol-a and the development of metabolic syndrome in CD-1 mice. Endocrinol. 2010 Mar 29;151(6):2603–12.
107. Yang YJ, Hong YC, Oh SY, Park MS, Kim H, Leem JH, Ha EH. Bisphenol A exposure is associated with oxidative stress and inflammation in postmenopausal women. Environ Res. 2009 Aug 1;109(6):797–801.
108. EPA (2014) Bisphenol A alternatives in thermal paper. United States Environmental Protection Agency. Available at https://www.epa.gov/sites/production/files/2014-05/documents/bpa_final.pdf. Accessed on March 25, 2018.
109. Christensen et al. 2014. Available at https://www2.mst.dk/Udgiv/publications/2014/03/978-87-93178-20-5.pdf. 2014. Accessed on February 25, 2018.
110. Szafran AT, Stossi F, Mancini MG, Walker CL, Mancini MA. Characterizing properties of non-estrogenic substituted bisphenol analogs using high throughput microscopy and image analysis. PloS one. 2017 Jul 13;12(7):e0180141.
111. Kumar R, Choudhary V, Mishra S, Varma IK, Mattiason B. Adhesives and plastics based on soy protein products. Ind Crops Prod. 2002 Nov 1;16(3):155–72.
112. Shin E, Choi HT, Song H. Biodegradation of endocrine-disrupting bisphenol A by white rot fungus Irpex lacteus. J Microbiol Biotechnol. 2007 Jul 1;17(7):1147.
113. Arboleda C, Cabana H, De Pril E, Jones JP, Jiménez GA, Mejía AI, Agathos SN, Penninckx MJ. Elimination of bisphenol A and triclosan using the enzymatic system of autochthonous Colombian forest fungi. ISRN Biotechnol. 2012 Sep 18;2013.
114. Matsumura Y, Hosokawa C, Sasaki-Mori M, Akahira A, Fukunaga K, Ikeuchi T, Oshiman KI, Tsuchido T. Isolation and characterization of novel bisphenol-A-degrading bacteria from soils. Biocontrol Sci. 2009;14(4):161–9.
115. Saiyood S, Inthorn D, Vangnai AS, Thiravetyan P. Phytoremediation of bisphenol A and total dissolved solids by the mangrove plant, Bruguiera gymnorhiza. Int J Phytorem. 2013 May 1;15(5):427–38.
116. FAO/WHO. Bisphenol A (BPA)- Current state of knowledge and future actions by WHO and FAO. INFOSAN information note no. 5/2009; November 2009.
117. FDA. Advancing regulatory science for public health. US Food and Drug Administration, Silver Spring, MD; 2010.
118. Moghadam ZA, Mirlohi M, Pourzamani H, Malekpour A. Bisphenol A in "BPA free" baby feeding bottles. J Res Med Sci. 2012 Nov;17(11):1089.