REVIEW ARTICLE

Plastic Chemical Bisphenol A Dampens Our Cardiovascular System: Evidence from Clinical and Animal Studies

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Abstract:

The environmental exposure of Bisphenol A (BPA) is a pervasive and growing concern. BPA is a high-volume industrial chemical that possesses estrogen-like properties and functions as an environmental endocrine disruptor. It is used extensively in the production of polycarbonate plastics and epoxy resins for food and beverage packages and hygienic products. An increasing amount of plastic pollution prevalent throughout the world has resulted in the nearly ubiquitous exposure of BPA towards humans and animals alike. Concerns have surfaced accordingly, surrounding the potentially detrimental effects that might result from BPA leaching into foods and beverages. The increase in epidemiological studies related to BPA have since been able to conclude links between BPA-induced oxidative stress, cardiovascular diseases, and hypertension. This review will incorporate current literature examining BPA exposure through clinical and epidemiological trials; these trials will encompass the physiological and toxicological effects that BPA can impose on the human cardiovascular system.

Keywords: bisphenol A, cardiovascular disease, hypertension, clinical studies, preclinical studies, mechanism

Introduction

An estimated 1 million seabirds and over 100,000 marine mammals are dying annually from plastic trash, while an additional eight million metric tons of plastics are compiled on top of approximately 150 million metric tons already circulating throughout the oceans[1,2]. Once plastic enters a waterway, it may turn up in the bodies of whales, or choke fish, turtles, and pelicans alike, thereby leaving bits of microplastics to travel up the food chain. Plastic debris in cities and landfills accumulate as well, at an estimated rate of 2.38-1200 mg of plastic per kg in compost and 1000-24,000 plastic items per kg in sewage sludge [3]. Plastic accumulation within our soil due to litter, flooding, and wastewater may contribute towards plastic concentrations within organic soil to reach the per mil range[3]. Plastic in soil ultimately seeps into groundwater and invades ecosystems, including food intended for human consumption. Meanwhile, the problem is compounded by an exponential increase in plastic production, from 2.3 million tons in 1950 to 448 million tons in 2015; that figure is expected to double by 2050[4]. Single-use plastics, which contribute significantly to plastic pollution, accounting for approximately 40% of all plastic produced each year[5]. The plastic itself, being lightweight, durable, and versatile, is mass-produced inexpensively. Unfortunately, current waste management systems are unable to properly dispose of or recycle plastic waste at the global level, leading to an influx of plastic waste into the environment [5].

Plastic pollution runs rampant in all industrial countries, and some newly industrialized ones typically only have the capacity to mass-produce and consume plastic without proper means of waste disposal [3]. While innovative interventions aimed at reducing plastic pollution currently exist, a practical and concentrated global effort has not yet been orchestrated to implement these technologies at the necessary scale. Furthermore, the overwhelming accumulation of plastic pollution is an immediate cause for concern. Already, plastic pollution has caused drain blockage, polluted ecosystems, endangered wildlife, and provided a breeding ground for infectious disease pathogens[5]. With the exponential increase in worldwide plastic production, we can only expect these problems to intensify.

Besides contributing largely to pollution, components of plastic can be detrimental to human health when ingested. One of the main components of many plastics, especially single-use food and beverage containers, is bisphenol A (BPA). BPA enters the human body by leeching into foods and beverages, seeping into groundwater from plastic landfills, or making its way from plastic-polluted oceans into the fish we consume. BPA is an organic synthetic compound that is structurally similar to estrogen (Figure 1).

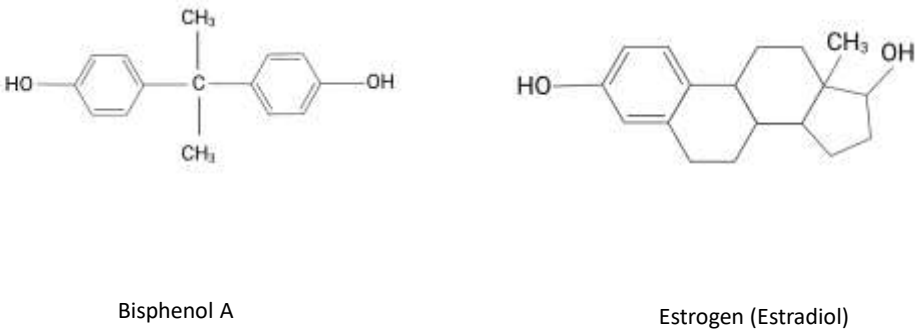

Figure 1: Molecular Structure of Bisphenol A and Estrogen

It has been proven to affect metabolic rates and act as an endocrine disruptor by behaving similarly as the hormone estrogen[6]. Its presence in the body can cause damage to the cardiovascular, immune, and reproductive systems, and lead to the development of metabolic disorders when BPA molecules interfere with signaling pathways[6]. More and more, clinical and preclinical evidence clearly demonstrates that BPA significantly affects our blood pressure (BP).

Hypertension is one important risk factor for almost all different cardiovascular diseases acquired throughout life, including coronary disease, left ventricular hypertrophy, and valvular heart diseases, as well as cardiac arrhythmias, including atrial fibrillation, cerebral stroke, and renal failure[7]. Estimates in 2010 suggested that 31.1% of adults worldwide have experienced symptoms of hypertension[8]. According to the Centers for Disease Control and Prevention (CDC), cardiovascular disease is the leading cause of death, accounting for approximately 1 in every 4 deaths in the US[9]. The correlation between BPA exposure and cardiovascular disease has come into focus due to the high prevalence of this chronic disease on a worldwide scale. In this review, we will focus on the effects of BPA on our cardiovascular system according to previous clinical and experimental studies and summarize our current understanding of the mechanisms underlying BPA-mediated cardiovascular diseases.

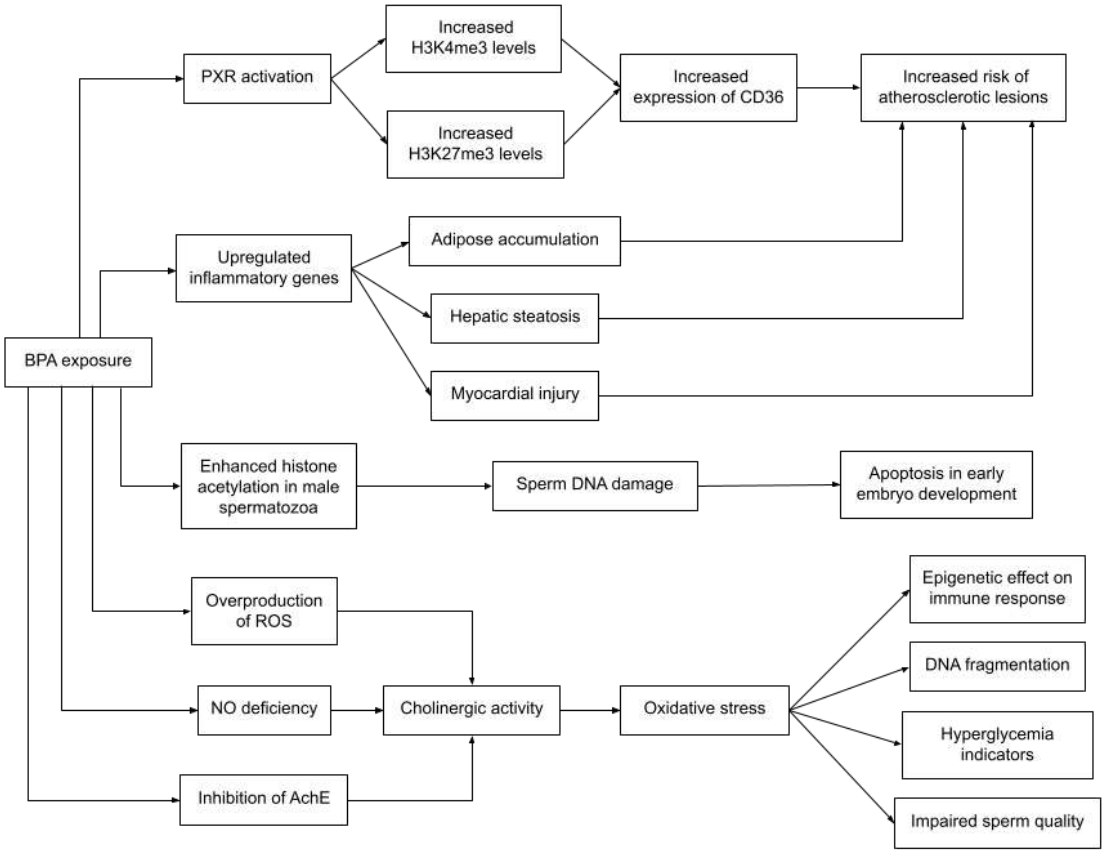

Figure 2: Potential Mechanisms underlining BPA-mediated Cardiovascular Diseases

Clinical Studies

Numerous clinical studies support a positive association between urinary and serum BPA levels and cardiovascular conditions including hypertension and arterial disease. This association has been found in multiple studies of different populations, verifying that the association is independent of covariates, such as age and ethnicity. While the underlying mechanisms involving this association are still unclear, the following clinical evidence demonstrates that increased BPA levels in the body are detrimental to cardiovascular health.

Two groups of authors investigated the connection between BPA exposure and cardiovascular diseases using data from the National Health and Nutrition Examination Survey (NHANES)[10,11]. Using adjusted regression models on the NHANES data, Melzer *et al*. determined that higher BPA concentrations were associated with coronary heart disease in 2005/2006 and in pooled data. Associations with diabetes did not reach significance in 2005/2006, but pooled estimates remained significant[10]. Shankar *et al.* (2012) also conducted an examination on NHANES data and observed a positive association between urinary BPA (uBPA) levels and hypertension in a multiethnic sample of US adults[11]. There was a positive association between increasing levels of uBPA and hypertension independent of confounding factors such as age, gender, race/ethnicity, smoking, body mass index (BMI), diabetes mellitus and total serum cholesterol levels[11]. These studies using NHANES data show a concerning positive correlation between BPA

exposure and heart disease which warrants further research.

Convincing clinical evidence suggests a correlation among urinary and serum BPA concentrations and incidence of hypertension. A study published by Gao *et al.* (2014) revealed through numerous epidemiological studies that increased uBPA concentrations in humans were linked with various types of cardiovascular (CV) diseases[12]. The authors found that environmental exposure to BPA may result in clinically insignificant CV events in healthy individuals, but further insight into the effects on individuals with preexisting CV conditions is needed. A comprehensive review published in 2015 extracted and meta-analyzed thirty-three observational studies (cohort, case-control, and cross-sectional studies) and measured uBPA concentrations[13]. The findings remained consistent with the study published by Gao *et al.* (2014): individuals with elevated uBPA concentrations are more susceptible to diabetes, general/abdominal obesity, and hypertension, opposed to those with lower uBPA concentrations[12].

Evidence is accumulating for possible associations between BPA exposure, increased risk of hypertension and increased BP. In a Korean population, Bae *et al.* (2012) investigated the associations of uBPA with heart rate variability and BP in non-institutionalized elderly (age sixty and older) citizens in Seoul[14]. Their analysis indicated that uBPA was positively associated with BP. Participants in the fourth quartile of uBPA concentration were 1.27x (95% CI, 0.85-1.88) more likely to show hypertension (systolic blood pressure (SBP) ≥ 140 mm Hg or diastolic blood pressure (DBP) ≥90 mm Hg) than participants in the first quartile. When the analyses were restricted to participants who did not report a previous history of hypertension, this odds ratio increased to 2.35 times more likely (95% CI, 1.33-4.17). Bae *et al.* (2015) revealed that the consumption of canned beverages led to an acute increase in uBPA and BP. Sixty noninstitutionalized adults age sixty and older were randomly provided the same beverage either in 2 glass bottles, 2 cans, or 1 can and 1 glass bottle at a time[15]. Two hours after consumption, uBPA concentration increased after consuming canned beverages by >1600% compared with that after consuming glass bottled beverages. SBP adjusted for daily variance increased by approximately 4.5 mm Hg after consuming two canned beverages compared with that after consuming two glass bottled beverages. Another study on a Chinese population observed BP, uBPA concentration, and hypertension diagnoses in eligible individuals without hypertension-related diseases[16]. Compared with the reference group of BPA, individuals in the middle and high exposure groups had an adjusted odds ratio of 1.30 and 1.40 for hypertension and 3.08 and 2.82 mm Hg higher SBP, respectively. Interestingly, some studies highlight an association between BPA levels and hypertension in women. Aekplakorn *et al.* (2015) examined the association between serum BPA and hypertension in a Thai population[17]. Accounting for age, sex, diabetes, BMI, and estradiol level, they found that, compared with the lowest quartile, the adjusted odds ratio (AOR) of hypertension for the fourth quartile of serum BPA was 2.16 (955 CI 1.31, 2.56) in women and 1.44 (0.99, 2.09) in men. Among postmenopausal women, the AOR for the fourth quartile of BPA was 2.33 (95% CI 1.31, 4.15) and, for premenopausal women, it was 2.12 (95% CI 0.87, 5.19). Their findings demonstrated that serum BPA was independently associated with hypertension in women and was likely unaffected by estrogen. Detectable uBPA levels were found in 89% of subjects according to Mouneimne *et al.* (2017) in which they performed a cross-sectional study on a Lebanese population, with females and the elderly being in the highest BPA tertile[18]. There was a positive association between BPA levels and metabolic syndrome,

obesity, type-2 diabetes, hypertension, and dyslipidemia. Although uBPA in the Lebanese population was higher in older women, the levels were similar to world-reported figures.

Multiple studies also show a positive association between prenatal BPA exposure and childhood BP. In a Korean population sample, Bae *et al.* (2017) evaluated the effect of prenatal exposure to BPA at 20 weeks of gestation on BP of children at the age of 4[19]. DBP of children was positively associated with maternal uBPA above the threshold level of 4.5 μg/g creatinine, measured at around 20 weeks of gestation. For 1 log unit increment of prenatal uBPA concentration, DBP was increased by 7.9 mmHg (SE = 2.072; P = 0.0001) after adjusting for potential confounders and pulse pressure was decreased by -8.0 mm Hg (SE = 2.528; P = 0.0015). These findings suggest that prenatal exposure to BPA is associated with higher DBP in children above the 4.5 μg/g creatinine threshold. In a study using the European HELIX (Human Early-Life Exposure) cohort of children aged 6-11, Warembourg *et al*. (2019) found increases in DBP in the children whose mothers had BPA concentrations of 0.7 mm Hg (95% Cl: 0.1 to 1.4 mmHg)[20].

Other research supports an association between BPA exposure and hypertensive disorders during pregnancy. In the Netherlands, a population-based prospective cohort study measured bisphenol concentrations in a spot urine test in early pregnancy among women whose children participated in postnatal follow-up measurements, excluding participants without any BP measurement or preexisting hypertension [21]. Findings showed each log unit increase in bisphenol A was associated with a 0.15 SD (95% CI: 0.03, 0.26) higher intercept, a -0.01 SD (95% CI: -0.01, -0.00) decreasing slope of the umbilical artery PI Z-score, a -1.28 SD (95% CI: -2.24, -0.33) lower intercept, and 0.06 SD (95% CI: 0.02, 0.11) increasing slope of the uterine artery RI Z-score. The observed association of BPA with placental hemodynamics indicates an association of early pregnancy bisphenols with risk for preeclampsia.

Despite the relative abundance of evidence outlining the positive association between BPA exposure and hypertension, other studies have found that BPA exposure is not associated with hypertension. In a Chinese population, Hu *et al*. (2016) reported uBPA concentrations were negatively associated with hypertension, elevated Carotid Intima-Media Thickness (CIMT), and arterial stiffness[22]. These negative associations were stronger among participants age sixty and older compared with participants under 60 and among women compared with men. In a cohort of Spanish participants, Salamanca-Fernández *et al.* (2020) quantified serum concentrations of BPA and four parabens: methylparaben (MP), ethylparaben (EP), propylparaben (PP), and butylparaben (BP)[23]. After a mean follow-up time of twenty-three years, BPA and methylparaben were found in over eighty percent of the study population. However, of the environmental pollutants measured, only PP had an association with arterial hypertension (AHT). No association between serum BPA and AHT were found. In a pilot study conducted in the Czechia, Piecha *et al*. (2016) took twenty-four-hour urine samples and classified patients as dyslipidemic, hypertensive, and type 2 diabetic in order to find a correlation between BPA and phthalate metabolite levels and the metabolic disorders[24]. There was no significant relation of BPA level to diabetes, hypertension, dislipidemia, age, or BMI. Camara *et al*. (2019) also found that BPA exposure is not associated with hypertension in a Canadian population[25]. They measured urinary concentrations of BPA and BP during each trimester in a sample of pregnant women and found that uBPA concentrations were not associated with gestational hypertension or preeclampsia.

Authors/Journals	Diseases	Location	Cohort size	Age (yrs)	Main findings
Melzer et al (2010)	CAD	US population	1455 (2003/04)		NHANES 2003/04: OR (95%CI)=1.60 (1.11, 2.32), P=0.016
Plos One 5(1): e8673		NHANES 2003-2004	1493 (2005/06)	18-74 yrs	NHANES 2005/06: OR (95%CI)=1.33 (1.01, 1.75), P=0.043
		NHANES 2005-2006			NHANES 2003/06: OR (95%CI)=1.42 (1.17, 1.72), P=0.001
Bae et al (2012). Hypertension 60: 786-793	HTN	Seoul, South Korea	All (HTN: NO HTN): 521(138: 383)	70.6±5.2	AOR for SBPA (Q4 vs Q1): 1.27 (0.85, 1.88); (Q3 vs Q1): 1.16 (0.78, 1.72); (Q2 vs Q1): 1.21 (0.80, 1.84)
Melzer et al (2012)		UK	All (CAD: ctr): 1619(758, 861)	Case 64.1 ± 7.5	multivariant AOR for CAD: 1.13 (1.02, 1.24)
Circulation 125: 1482-1490)	CAD		10.8 years follow-up	Control 63.8±7.3 years.	
			ctrs: no CAD, stroke, diabetes		
Shankar & Teppala (2012)	HTN	US population			multivariant AOR for HTN (T3 vs T1): 1.50 (1.12, 2.00)
J Environ Public Health. 2012:481641.		NHANES 2003-2004		18-74 yrs	P-trend = 0.007
Aekplakorn et al (2015).	HTN	Thailand	Men (HTN: NO HTN): 1275(440:835)	Men: 39.58±16.95	AOR for SBPA (Q4 vs Q1): 2.16 (1.31, 3.56) in women;
Int J Hypertens, 594189			Women(HTN: NO HTN): 1283(422:861)	Women: 41.12±16.64	1.44(0.99, 2.09) in men; 1.76 (1.33, 2.33) for all
			All (HTN: NO HTN): 2558(862: 1696)	total: 40.37±16.81	No interaction between sBPA and estradiol level
Bae & Hong (2015). Hypertension 65:313-319.	HTN	Seoul, South Korea	All (HTN: NO HTN): 60(27: 33)	73.1±4.2 years	Canned beverages ↑ [uBPA] >1600% vs glass beverage canned beverage ↑ SBP by 4.5 mmHg vs glass beverage
Hu et al (2016)	HTN	a community in Chongqing	302 patients	65.29 ± 9.78	OR (95%CI) for [sBPA] vs SBP: 1.03 (1.01, 1.05), P=0.018
Journal of Hypertension 34: 332-337		China	(195 men, 107 women)		OR (95%CI) for [sBPA] vs DBP: 1.00 (0.97, 1.04), P=0.719
Piecha et al (2016)	HTN	Prague, Czech Republic	all: 168	Men: 51.2 yrs	OR (95%CI) for [sBPA] vs CKD stage 3 or higher: 4.79 (1.81, 14.25), P=0.004 no significant association between [uBPA] and hypertension and dyslipidemia.
Cent Eur J Public Health. 24(4): 297-301	(T2 diabetes)		Men: 57, women: 111	Women: 65 yrs	
		Seoul and Incheon metropolitan			
Bae et al (2017)	HTN	area	486 mother-child pairs	children: 47.7±1.3 months	For 1 log [uBPA] increase, DBP ↑ 7.9 mmHg (SE 2.072; P=0.0001)
Hypertension. 69(2): 367-374		South Korea	from 13484 enrollers	mothers: 31.2±3.6 years	Pulse pressure ↓ -8.0 mmHg (SE2.528; P=0.0015)
					SBP no significantly associated with prenatal [BPA]
Mouneimne et al (2017)	HTN	Lebanon urban area	501 adults	> 18 yrs	[uBPA] significantly associated with HTN treatment (p=0.004)
Environ Monit Assess. 189(10): 517		in Greater Beirut area			has a trend to be significantly associated with HTN diagnosis (p=0.07)
Camara et al (2019)	HTN	Canada	1,909 pregnant women	N/A	[uBPA] was not associated with GH, but for multiparous women
Am J Perinatol. 36(11): 1127-1135					[uBPA] (0.50-1.30 µg/L) associated with ↓ risk of GH (aOR=0.45; 95% CI: 0.21-0.98)
Philips et al (2019)	HTN	European (766),	1233 pregnant women	30.5±4.8	Association between gestational hypertension & [uBPA]:
Hum Reprod. 34(2): 365-373		Non-European (465), Missing (2)			Basic model OR (95%CI)=1.03 (0.83, 1.27), with adjusted model 1.02 (0.82, 1.26)
					BPA was not significantly associated with BP
Warembourg et al (2019)	HTN	European HELIX cohort	1,277 children	6-11 years	↑ DBP with maternal [BPA] (0.7 mm Hg [95% CI: 0.1 to 1.4 mm Hg])
J Am Coll Cardiol. 74(10): 1317-1328					BPA exposure during pregnancy associated with ↑ DBP & ↑ SBP.
Jiang et al (2020)	HTN	China	All (HTN: NO HTN):	HTN: 60±10	For HTN, AOR (T3 vs T1): 1.40 (1.03, 1.91); (T2 vs T1): 1.30 (0.95, 1.78)
Environmental Pollution 257: 113639			1437(433: 1004)	NON HTN: 55±8	For sBP, AOR (T3 vs T1): 2.82 (0.50, 5.15); (T2 vs T1): 3.08 (0.76, 5.40)
				total: 56±9	
Salamanca-Fernández et al (2021)	HTN	Granada EPIC-Spain center	All: 670	35.2-67.6 yrs	
Environ Res. 193: 110491			Male (AHT): 320 (224)		NO significant association between [sBPA] and hypertension
			Female (AHT): 350 (258)		

Table 1: Summary of Clinical Trials Studies

Current evidence strongly outlines the positive association between BPA levels and the risk of hypertension in humans. In vitro systems should be used in the future to identify the mechanistic link between BPA and specific CV events. Further longitudinal studies and clinical studies investigating the effect of BPA on hypertension in individuals with preexisting conditions are needed. Studies in larger populations with well-defined controls and based in different countries warrant further studies in the near future.

Preclinical Studies

Studies on the pathogenesis of BPA-induced cardiovascular diseases using animal trials have shown fascinating effects. Animal models are frequently used in studies of human diseases so scientists can manipulate adequately large numbers of subjects reach significant results. In the study of BPA-induced cardiovascular diseases, researchers have selected species bearing similarities to the humans in its genome, arterial pathology, metabolism, or the cardiovascular system overall; cost efficiency, lifespan, and abundance of offspring were also considered. These factors contribute to how well a given animal model represents BPA-induced cardiovascular diseases in humans.

Through these animal models, many studies have revealed that BPA exposure is correlated with enhanced atherosclerosis, increased oxidative stress, and whether or not it had an epigenetic effect.

(1) Effect of BPA on atherosclerosis

Atherosclerosis is a chronic inflammatory disorder characterized by lipid deposition in the arteries that eventually develops into atherosclerotic plaque that partially or fully occludes the affected arteries, leading to vascular death. Atherosclerosis is also the leading cause of cardiovascular disease (CVD). Higher BPA exposure has been associated with an increased risk of atherosclerosis and CVD in multiple human population-based studies. The underlying mechanisms for this association and the effect of BPA on the metabolic system are still unclear. Kim *et al.* (2014) investigated a mouse model of atherosclerosis using Apolipoprotein E knockout ($ApoE^{-/-}$) mice fed a high-fat, high-cholesterol diet with or without 50 ug/kg body weight/day BPA for 12 weeks[26]. Their results show that BPA significantly increased atherosclerotic lesions in the aortas of the $ApoE^{-/-}$ mice. Findings also included significantly higher non-high-density lipoprotein (HDL) cholesterol levels in the BPA group than in the control group, indicating that BPA accelerates atherosclerosis in $ApoE^{-/-}$ mice via an increase in non-HDL cholesterol levels. In another study, Sui *et al.* (2014) used a pregnane X receptor (PXR) humanized mouse model to identify the molecular mechanism behind BPA-mediated CVD risk[27]. In the PXR-humanized, ApoE deficient ($huPXR{\cdot}ApoE^{-/-}$) mice, exposure to BPA significantly increased the atherosclerotic legion area in the aortic root and brachiocephalic artery. BPA had no effect on atherosclerosis development in non-PXR-humanized mice. In their second study, Sui *et al.* (2018) also used the $huPXR{\cdot}ApoE^{-/-}$ deficient mouse model and found that perinatal BPA exposure exacerbated atherosclerosis in male offspring but not in female offspring[28]. Perinatal BPA exposure had no effect on plasma lipid levels but increased aortic and atherosclerotic lesion fatty acid transporter CD36 expression in male $huPXR{\cdot}ApoE^{-/-}$ offspring. In the perinatal-BPA-exposed mice, PXR epigenetically regulated CD36 expression by increasing H3K4me3 levels and decreasing H3K27me3 levels in the CD36 promoter in response to perinatal BPA exposure. The findings of both studies by Sui *et al.* support an association between BPA exposure and atherosclerotic risk via the

activation of human PXR, which epigenetically regulated CD36[27,28]. Fang *et al.* (2014) utilized the metabolic and cardiovascular similarities between humans and rabbits to investigate the effect of chronic BPA exposure on metabolism by administering Watanabe heritable hyperlipidemic (WHHL) rabbits with 400-μg/kg BPA per day, orally by gavage, over the course of 12 weeks[29]. Findings show that BPA-treated WHHL rabbits had a much larger gross atherosclerotic legion area in the aortic arch when compared to the vehicle group. Additionally, BPA-treated WHHL rabbits showed increased adipose accumulation and hepatic and myocardial injuries accompanied by up-regulation of endoplasmic reticulum (ER) stress and inflammatory and lipid metabolism markers in livers. In a second study, Fang *et al.* (2015) treated genetically hyperlipidemic Watanabe heritable hyperlipidemic (WHHL-MI) rabbits with BPA at 40 mg/kg/day for 8 weeks by gavage[30]. BPA exposure caused myocardial injury and enhanced atherosclerosis development in the aortic arch, as observed by the significant increase in macrophage number and advanced legion area. BPA-treated rabbits also showed insulin resistance, prominent adipose accumulation, hepatic steatosis, and increased expression of inflammatory genes in the liver. These results identify increased expression of inflammatory genes of the liver, insulin resistance, adipose accumulation, and hepatic steatosis as possible mechanisms by which BPA induces metabolic disorders and enhances atherosclerosis.

(2) Oxidative stress induced by BPA

Oxidative stress is the imbalance between reactive oxygen species (ROS) in the body and the body's ability to detoxify these ROS. In animal studies, BPA exposure has been associated with an increased presence of markers of oxidative stress and decreased ability of the body to protect itself from oxidative stress. The exact mechanisms by which BPA increases ROS and decreases the cardiovascular system's ability to detoxify ROS are unclear at this time. Aboul *et al.* (2015) employed adult male rats to administer daily oral doses of BPA (25 mg/kg for 6 weeks and 10 mg/kg for 6 and 10 weeks)[31]. After 6 weeks, BPA at both doses induced a significant increase in malondialdehyde and a significant decrease in catalase. Both doses resulted in a significant decrease in nitric oxide (NO) levels and in reduced glutathione and acetylcholinesterase (AchE) activity. The results suggest that BPA has cardiotoxic effects which are mediated by oxidative stress resulting from the overproduction of free radicals, the deficiency of NO, and the inhibition of AchE leading to cholinergic activation. They also observed a significant increase in body weight in all BPA-treated animals. Whether BPA promotes obesity is unclear though, as another mouse model by Wang *et al*. (2019) found a decreased body, colon, and liver weight as a result of dietary BPA uptake[32]. The group similarly discovered that dietary BPA uptake increased the levels of oxidative stress indicators such as ROS, reactive nitrogen species, malondialdehyde, and hydrogen peroxide in mouse serum, colon, and liver tissues.

Some studies also cite a connection between BPA-induced oxidative stress and increased prevalence of other disorders such as impaired sperm quality, hyperglycemia, body weight increase, and affected immune response. In one study, Moghaddam *et al*. (2015) intraperitoneally injected mice with control (C), 0.5, and 2 mg/kg concentrations of BPA[33]. After 4 weeks, they found that BPA dose-dependently increased the levels of blood glucose, lipid profile, and malondialdehyde (MDA) and decreased the levels of HDL-C and glutathione (GSH) in the tested groups. BPA injection also increased the level of MDA, decreased the levels of GSH and total antioxidant status (TAS), and decreased the

activities of superoxide dismutase (SOD) and catalase (CAT) in the pancreas of exposed mice. The presence of oxidative stress and hyperglycemia indicators supports an association between BPA-induced oxidative stress and hyperglycemia in adult male mice. In another rat model, male Holtzman rats that were orally gavaged with BPA (0.01 mg and 5.0 mg/kg/bw) over the period of 6 days, and the data shows that BPA caused an increase in lipid peroxidation and a decrease in the activity of various antioxidants in bone marrow cells, blood lymphocytes, and testicular and epididymal tissues[34]. Other studies that have forgone mouse and rat models in favor of fish embryos and spermatozoa have also found intriguing data with regard to immune and reproductive effects resulting from oxidative stress. One such study on zebrafish embryos found valuable insight into the mechanism by which BPA affects the expression of genes related to the immune response in zebrafish embryos following oxidative stress. It revealed a concentration-dependent increase of ROS content and an induced expression of redox-sensitive transcription factors in zebrafish embryos after exposure to various concentrations of BPA for 4 hrs to 168 hrs postfertilization[35]. The researchers found a significant induction of concentrations of proinflammatory mediator, nitric oxide, accompanied by an increase in the activity of nitric oxide synthase (NOS) and upregulation of inducible NOS gene expression in zebrafish embryos on exposures to endocrine-disrupting chemicals (EDC). Another study discovered negative reproductive effects correlated with BPA-induced oxidative stress after investigating the effect of naturally occurring concentrations of BPA[36]. After exposing sterlet spermatozoa to BPA at concentrations possibly occurring in nature (0.5, 1.75, 2.5, 5, and 10 µg/L) for 2 hrs, they observed oxidative stress at concentrations 1.75-10 µg/L, as reflected by significantly higher levels of protein and lipid oxidation and superoxide dismutase activity[36]. BPA significantly decreased spermatozoa motility and velocity at concentrations of BPA 2.5 – 10 µg/L, and there was a significant positive correlation between percent motile spermatozoa and ATP content. Thus, the findings of this study show that naturally occurring concentrations of BPA can induce oxidative stress, leading to impaired sperm quality, DNA fragmentation, and intracellular ATP content in sterlet spermatozoa[36].

(3) Epigenetic effect of BPA

Animal studies have found that BPA exposure during early stem cell and fetal development is associated with impaired offspring cardiovascular function and overall survival. They propose that these negative effects are a result of the effect of BPA on DNA structure, DNA methylation, and DNA histone acetylation. However, there is not yet a consensus on the particular genes that are epigenetically regulated by BPA. Some non-mammal models have been valuable in highlighting the epigenetic effects of BPA by observing population size, chronic toxicity, and apoptosis in early embryonic development. In one such study, Zhou *et al.* (2016) exposed *C. elegans* to BPA (0.0001-10 µM) from L4 larvae to day-10 adults and found that BPA exposure induced significant negative effects on growth, locomotion behaviors, and lifespan[37]. BPA induced strong stress responses *in vivo* and led to significant decreases in population size in BPA-treated groups from 0.1 to 10 µM. Long-term exposure to BPA induced an obvious response, possibly due to cumulative toxic effects, and the Pearson correlation analyses revealed that cep-1 was speculated to play an important role in BPA-induced chronic toxicity in *C. elegans*. Another study exposed male zebrafish to 100 and 2000 µg/L BPA starting during early spermatogenesis and found that histone acetylation of H3K9Ac and H3K27Ac was

enhanced in spermatozoa and embryos from all exposed males[38]. While exposure to 100 µg/L BPA during mitosis slightly increased sperm chromatin fragmentation and enhanced DNA repairing activity in embryos, all other treatments promoted high levels of sperm DNA damage, triggering apoptosis in early embryo development and severely impairing survival. Therefore, it can be concluded that male exposure to BPA jeopardizes embryonic survival and development due to the inheritance of a damaged paternal genome and a hyper-acetylated histone profile.

Other studies using mammal models: rats, mice and monkeys have also observed the epigenetic effects of BPA exposure with more validity which may translate to the effects in humans. Chapalamadugu *et al.* (2014) found that daily, oral exposure of pregnant rhesus monkeys to 400 µg/kg body weight of BPA during early and late gestation led to down-regulation of myosin heavy chain, cardiac isoform alpha (Myh6) in the left ventricle and up-regulation of 'A Disintegrin and Metalloprotease 12', long isoform (Adam12-I) in both ventricles and the right atrium in BPA-exposed fetuses[39]. Their findings support the hypothesis that BPA exposure during fetal development may impact cardiovascular fitness via BPA-induced alteration of the Myh6 and Adam12-I genes. Another study investigated the effects of low-dose developmental BPA exposure on DNA methylation and the expression of Grin2b in adult rat brains and found increased Grin2b mRNA expression and decreased DNA methylation in female (but not in male) rats[40]. In humans, prenatal BPA exposure was associated with increased Grin2b methylation levels in females. Low APGAR (Appearance, Pulse, Grimace, Activity, and Respiration) scores were associated with higher Grin2b methylation levels in females. Therefore, developmental BPA exposure and low APGAR scores can be linked to changes in the epigenetic regulation of Grin2b in a sexual dimorphic fashion. Dolinoy *et al.* (2007) found that maternal exposure to BPA shifted the coat color distribution of viable yellow agouti (Avy) mouse offspring toward yellow, by decreasing cytosine-guanine dinucleotide (CpG) methylation in an intracisternal A particle retrotransposon upstream of the Agouti gene and at another metastable locus, the CDK5 activator-binding protein (CabplAP)[41]. DNA methylation at the Avy locus was similar in all three germ layers, providing evidence that epigenetic patterning during early stem cell development is sensitive to BPA exposure. However, results also showed that maternal dietary supplementation with methyl donors like folic acid or the phytoestrogen genistein negated the DNA hypomethylating effect of BPA. This study provides evidence that changes in offspring phenotypes caused by early developmental exposure to BPA can be counteracted by maternal dietary supplements in yellow agouti mice. Evidence provided by these studies supports a compelling need to continue investigations on the effects of BPA exposure in early embryonic development.

The detrimental effects of BPA must be recognized and the growing prevalence of BPA throughout our world must be acknowledged and confronted. These human and animal studies have concluded a positive association between BPA and reduced cardiovascular health across different species and in different stages of development. We, therefore, cannot afford to be complacent in the growing prevalence of BPA throughout our habitats and environments.

Course of Action

The global proliferation of plastic pollution has tarnished aquatic and terrestrial environments and wrought a ubiquitous exposure to BPA. Unfortunately, current methods of treatment aimed at reducing the presence of BPA in the environment remain inadequate. Clinical evidence and scientific studies correlate clear

detrimental effects of BPA exposure on the cardiovascular system and evidence of invasive plastics in the environments serve as a reminder of a widening problem concerning plastic disposal. Ultimately, if current initiatives remain unchanged, global plastic pollution will continue to grow exponentially and continue to devastate our environments. A working solution requires both a mixture of sustained and aggressive treatments, and greater innovation to provide biodegradable and environmentally friendly substitutes to plastics.

In 2019, Canadian Prime Minister Justin Trudeau announced an initiative to ban all single-use plastics as early as 2021[42]. He joins more than sixty nations that are taking steps towards reducing single-use plastics, through bans or taxes, in hopes of reducing plastic pollution via enacted legislation[42]. Earlier that year, the European Union's Parliament voted to ban the top ten single-use plastic items found on European beaches by 2021 and called for ninety percent of plastic bottles to be recycled by 2025[43]. Most ambitious of all, however, India's Prime Minister Narendra Modi's declaration in 2018 to eliminate all single-use plastic by 2022 for the world's second most populated country[44]. Currently in the U.S., several states have taken key steps toward similar enterprises, with eight states in total having already banned single-use plastic bags[45]. Concentrated action by the federal government, however, is still insufficient. California, in 2014, was the first state to enact such a policy, which took effect in 2016, prohibiting single-use plastic bags at retail stores[45]. Since then, the California Against Waste (CAW) nonprofit that sponsored the bill has reported a substantial reduction in plastic bag litter in the state's rivers, beaches, and landscapes[46]. Therefore, to act against the invasion of plastics in our environments, citizens must call on legislators to enact laws, targeted toward aggressive actions that will bring our global communities one step closer to a standard of zero plastic pollution.

As awareness over the growing pollution crisis has increased, the scientific fields also actively have been engaged in pursuing greener, more environmentally friendly plastic substitutes, and alternatives. A Toronto-based startup, Genecis, shows promising advancements in its mission to innovate and produce greener plastics to replace commonly disposed plastic items, such as straws and certain food packages, at affordable prices[47]. The startup utilizes bacteria that turns kitchen waste into compostable and biocompatible plastics, called polyhydroxyalkanoates (PHAs) that can be molded and sold as plastic products[47]. Already, this plastic is on the market and packaged in a variety of medical applications ranging from heart valves to dissolving sutures. The bioplastic market has also previously seen the introduction of starch-based plastics, cellulose-based plastics, and protein-based plastics, all produced from renewable biomass sources. Starch-based plastics in particular constitute about half the bioplastic market while starch itself is cheap, abundant, and possesses improved mechanical properties, thermal stability, moisture resistance, and gas barrier properties. A persistent switch in household, business, and community policies to such greener, more environmentally friendly alternatives, will be imperative in the fight against the global pollution problem. We advocate and emphasize the importance of individual action to pursue consistent treatments and more biocompatible alternatives. Only then can we reverse the tide of the growing plastic problem and ubiquitous exposure to BPA.

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