

Are Plasticizing Chemicals Contributing to the Worldwide Epidemic of Obesity?

The controversy of bisphenol A (BPA) and BPA alternatives as environmental obesogens



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Introduction

Obesity is a metabolic disease characterized by excessive body fat that is defined clinically as having a body mass index (BMI) over 30. For the first time in human history, the number of obese and overweight people is greater than the number of those who are underweight. An estimated 1/3 of the world's population currently meets the clinical definition of obese, and it is predicted that approximately half the world's population will be obese by 2030. Obesity is a major risk factor for numerous life threatening diseases, including cardiovascular disease, type 2 diabetes, and cancer. In 2014, the global economic burden of obesity was estimated to be 2 trillion US dollars. While genetic predisposition, excess caloric intake and sedentary lifestyle are the main drivers of obesity, these factors cannot fully explain the recent dramatic rise in the global incidence of obesity. Emerging evidence suggests that environmental obesogens, defined as chemicals that interfere with the regulation of metabolism and body weight, may be contributing to the worldwide epidemic of obesity.

One chemical often cited as an environmental obesogen is bisphenol A, more commonly known as BPA. BPA is produced at over 1,000 metric tons per year for use in the manufacture of hard polycarbonate plastics and epoxy resins, as a dye developer in thermal paper, and

as a polymerization inhibitor in the formation of polyvinyl chloride plastics. BPA production exploded in the 1950's following the widespread use of polycarbonate plastics in consumer products including dinnerware and food storage containers, eyeglass lenses and screens for cell phones and laptop computers, toys, pacifiers, impact-resistant safety equipment, and automobile parts. Epoxy resins are widely used in protective linings of canned food and beverages, drinking water storage tanks, wine vat linings, some paints, floorings, and dental sealants, while thermal paper products that contain BPA include cash register receipts and some types of medical technical paper.

The widespread use of BPA in consumer products has resulted in almost universal exposure of humans to BPA. The 2003-2004 United States National Health and Nutrition Examination Survey (NHANES) detected BPA in the urine of 92% of participants surveyed, with the highest levels found in young children aged 1-6 years. Similar findings have been reported for populations around the world. Consumption of food and beverages stored or heated in containers containing BPA is considered the main source and route of human exposure. However, humans can also be exposed through dermal absorption, for example, as a result of handling BPA-impregnated register receipts, and via inhalation of contaminated air and dust.

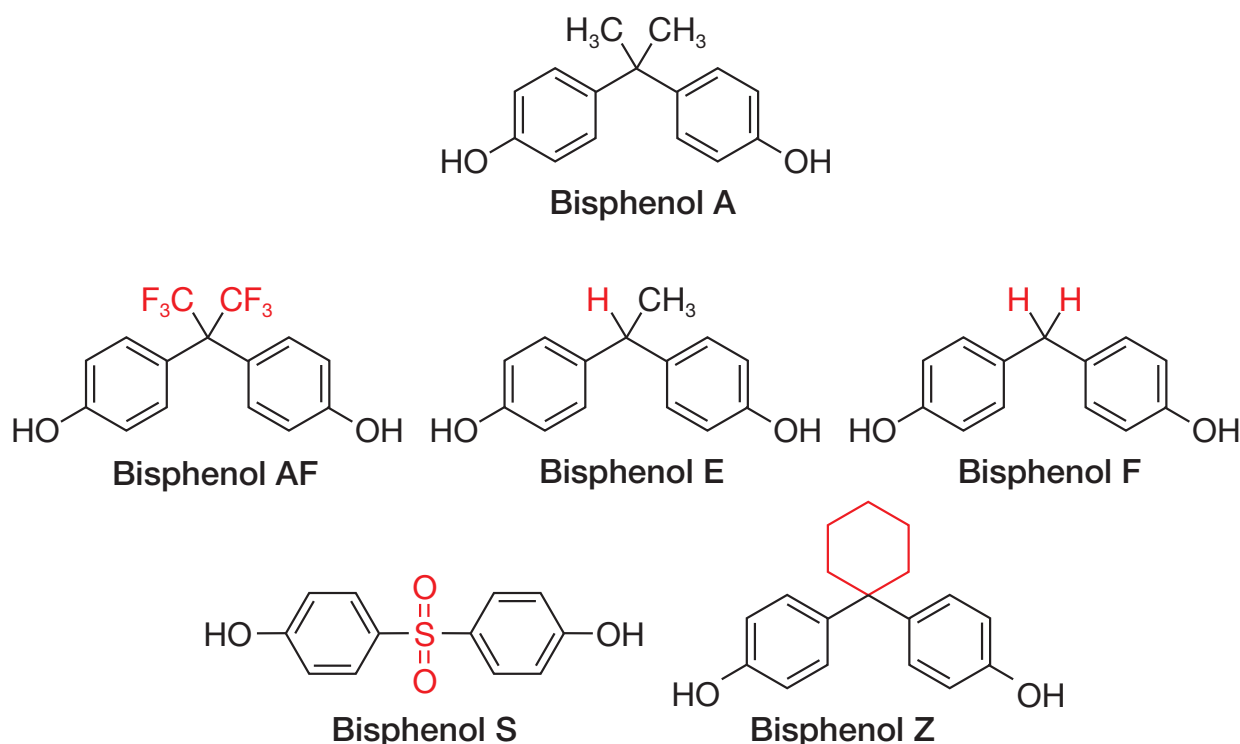


Figure 1. Structure of bisphenol A (BPA) and widely used BPA alternatives.

Observations that BPA is still detected in individuals who are fasting, and that urinary excretion of BPA was elevated 84% in individuals who handled thermal receipts, indicate that non-oral sources of BPA are important contributors to human body burdens of BPA. BPA is rapidly cleared from the body following oral ingestion, but following dermal exposures, body levels of BPA remain elevated for much longer periods of time, suggesting that the route of exposure influences the persistence of BPA in human tissues.

Concerns about adverse health effects associated with BPA exposure began to surface in the 1990s, and data published since then has linked BPA to a variety of health issues, including obesity and comorbidities associated with obesity, such as diabetes, cardiovascular disease and liver disease. However, the case for BPA as an obesogen is controversial, with those who doubt the connection citing a lack of reproducibility in human and animal studies. Despite this controversy, and in response to mounting public health concerns, many countries have promulgated regulations aimed

at decreasing human exposures to BPA. Industry has responded to increasingly restrictive regulations and consumer demands by flooding the market with BPA-free products. This change has significantly decreased human exposure to BPA; however, it is not clear whether this change has translated into reduced human health risks from plasticizing chemicals. This is because industry largely switched to using BPA alternatives, such as BPAF, BPE, BPF, and BPS (Figure 1), as substitutes for BPA in many of the products marketed as BPA-free. These BPA alternatives are structurally and functionally similar to BPA, which raises the question of whether BPA alternatives are environmental obesogens, like BPA. Below, we review the current state of knowledge regarding BPA's link to obesity, and the emerging science regarding the obesogenic potential of BPA alternatives.

Human data linking BPA exposures to obesity

There is epidemiological evidence of a positive association between urinary BPA levels and

obesity in adults, adolescents and children. Studies of NHANES data from 2003-2014 found that urinary BPA levels are positively associated with BMI and waist circumference in children and adults, even after multivariate adjustments. These findings have been replicated in other populations, including Canadian, European, and Chinese children and adults. However, some scientists have questioned the strength of the association between BPA and obesity, largely because some human studies have found no association or a negative association. Early reviews of the epidemiological data concluded that BPA exposure may be involved in the development of obesity, but that the epidemiological data available at the time were not sufficient to establish a positive correlation between BPA and obesity. This ambiguity reflects a number of factors, of which one of the most important has been the challenge of accurately measuring human BPA exposure. BPA is relatively short-lived, thus, urinary levels reflect recent exposures only, and levels of BPA fluctuate significantly over time. Other issues contributing to discrepant epidemiologic findings include differences in how each study defined obesity, the imprecision of evaluating obesity in infants and children, and significant methodological differences across studies. However, the science has improved since the early studies, and a recent systematic review and meta-analysis of 13 published epidemiological studies concluded that children with higher BPA exposures had a significantly greater risk of childhood obesity than their peers with relatively low BPA exposures.

Alternative approaches that have focused on pathophysiologic changes clinically linked to obesity further support the association between BPA and obesity. Tissue levels of BPA are reported to be positively correlated with urinary levels of leptin, a hormone that induces satiety and regulates long-term energy balance. Persistently elevated levels of leptin can lead to leptin resistance, which is linked to increased fat mass. Other hormones that regulate appetite and metabolism of lipids and glucose include

adiponectin, which is secreted by adipose tissue, and ghrelin, which is released from digestive organs and the hypothalamus. Increased BPA levels are correlated with increased adiponectin and decreased levels of ghrelin, both changes associated with obesity in human patients. In a rare study in which volunteers were intentionally administered BPA at a dose below the EU regulatory level for concern, BPA exposure was observed to further impair the insulin response to glucose in individuals with a mild impairment in glucose control, suggesting a gene-environment interaction that increases risk.

Animal evidence that BPA is an obesogen

A key factor in evaluating potential causality is demonstrating that BPA causes obesity in animal models in which exposures can be precisely controlled and documented, and confounding variables can be minimized. Studies using rodent models have reported that exposure to BPA at concentrations within or below levels detected in human tissues significantly increased body weight, fat weight, and both the abundance and size of adipocytes (fat cells). Human-relevant BPA exposures also increased inflammation in adipose tissue, insulin resistance of multiple tissues, lipid accumulation in not only adipose tissue, but also liver, and serum leptin levels, all of which are consequences of and/or accompany obesity. These outcomes were preceded by BPA effects on the expression of genes and signaling pathways involved in the production of adipose tissue or the regulation of amino acid, lipid and glucose metabolism. These altered metabolic profiles were observed well before signs of metabolic disease were apparent in BPA-exposed animals, suggesting that metabolic pathways are an early target of BPA and not a consequence of obesity. The differences in the metabolic fingerprints between control and BPA-exposed offspring persisted throughout life, hinting they may play a causal role in not only childhood but also adult obesity.

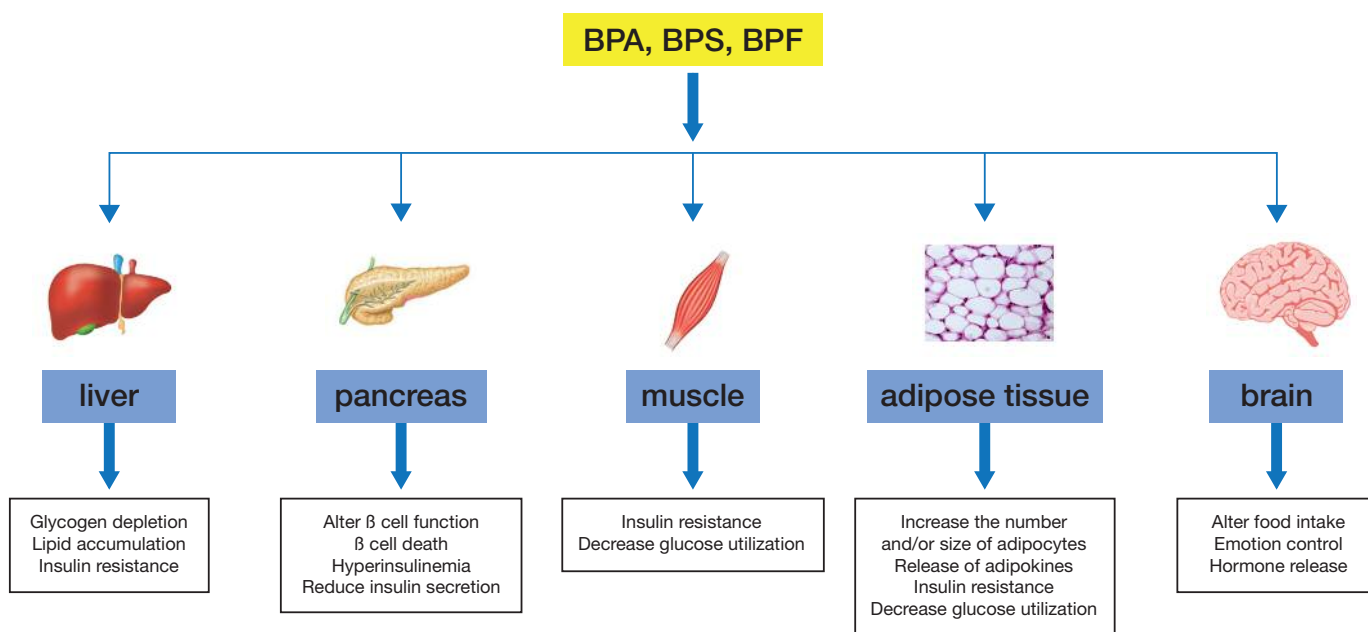


Figure 2. Effects of BPA and BPA alternatives on target tissues that are thought to contribute to the development of obesity.

As is the case in human studies, not all animal studies have found an association between BPA and obesity-related outcomes. As recently reviewed by Rubin, Schaeberle and Soto (2019), there are a number of factors that likely contribute to discrepancies in outcomes across animal studies. Key amongst these are the toxicological properties of BPA itself. BPA effects on obesity exhibit a non-monotonic dose-response relationship, meaning that lower doses of BPA tend to be more obesogenic than higher doses. This is not unusual for endocrine disrupting chemicals such as BPA, but because of this, classic approaches to toxicity testing in which high doses are typically tested are less likely to detect obesogenic effects. An additional confounding factor is BPA-induced hyperactivity, which is not observed in all rodent strains, but when it is, tends to counteract obesogenic effects.

Differences in experimental variables likely also contribute to discrepant findings across animal studies. These factors include differences in (1) the species, strain and sex of the animals used

in the study; (2) the age at the time of BPA exposure (developing animals seem to be more susceptible than adult animals); (3) the age(s) at which the animals were examined (many of the obesogenic effects of BPA manifest later in life, while a few are expressed transiently early in life); (4) the route of exposure (which strongly influences the persistence of BPA in the body); and (5) the environment surrounding the animal, such as the type and condition of plastic cages used to house the animals, and the type of rodent chow fed to the animals (animals fed a soy-based diet were more likely to reveal the obesogenic effects of BPA than animals fed a casein-based diet). Based on their review of the animal literature, Rubin, Schaeberle and Soto concluded that when experimental conditions are similar across studies, the obesogenic effects of BPA are reproducible. In support of their conclusion, a recent systematic review and meta-analysis of the rodent literature concluded that early life exposure to BPA is associated with increased adiposity and circulating lipid levels in rodent models.

How does BPA cause obesity?

Mechanistic studies in rodents suggest that BPA promotes obesity by stimulating adipogenesis (the formation of adipose tissue) and/or dysregulating lipid and glucose metabolism (Figure 2). Adipose tissue is a key target tissue: BPA can act directly on adipose tissue to increase the number of adipocytes and/or to increase their accumulation of lipids, which increases their size. Emerging evidence suggests that these effects may be mediated by binding of BPA to receptors (RXR-PPAR- γ heterodimers) that normally function to promote adipogenesis. BPA has also been shown to interfere with the endocrine function of adipose tissue. Adipose tissue secretes hormones (also referred to as adipokines), such as leptin and adiponectin, which are molecules that signal other tissues to regulate appetite and the metabolism of lipids and glucose. BPA exposure modulates the release of adipokines to promote insulin resistance and increase fat accumulation, leading to obesity.

BPA can also act directly on the liver and skeletal muscle to disrupt lipid and glucose metabolism, potentially via mechanisms involving oxidative stress. Elevated insulin levels are associated with obesity, and BPA can increase insulin secretion from isolated pancreatic islet cells in culture. This effect has been confirmed in vivo. Rats exposed throughout gestation and lactation to BPA in the drinking water at a dose 8 times lower than the European Food Safety Authority's (EFSA) current tolerable daily intake exhibited increased secretion of insulin from pancreatic islet cells. This effect persisted for up to one year after exposure. BPA exposure has also been shown to alter the patterning and function of neural circuits in the hypothalamus that regulate food intake and metabolism. These circuits are established primarily after birth, which may explain why the developing organism is more susceptible to the obesogenic effects of BPA. Emerging evidence suggests that BPA may alter the function of


tissues involved in regulating appetite and metabolism of lipids and glucose via indirect effects that involve changes in the gut microbiota or activation of the immune system.

Likely, BPA promotes obesity by modulating a complex network of molecular pathways. Unraveling this complexity will be important for determining how to prevent or perhaps even reverse obesogen-induced obesity, and may shed important insights on the processes involved in the development of obesity.

Do BPA alternatives pose less risk of obesity?

Evidence of widespread human exposure to BPA and associations between BPA and adverse health effects, particularly in infants, prompted France and Denmark to prohibit BPA in plastic infant bottles as a precautionary measure in 2010. In 2011, this ban was extended to all of Europe, and since 2015, the European Union has banned BPA in all food contact materials. The United States Food and Drug Administration prohibited BPA in products designed for infants and toddlers in 2012, and in 2013, Canada recommended that the general principle of ALARA (as low as reasonably achievable) should be applied to the use of BPA in all consumer products. These regulatory policies, coupled with growing consumer concerns regarding the safety of BPA, resulted in a flood of BPA-free products on the market.

While BPA-free products may seem like a reasonable strategy for reducing health hazards associated with BPA exposure, emerging evidence suggests that at least some of the more than 2 dozen BPA alternatives used in consumer products to replace BPA are similar to or perhaps even more potent than BPA in promoting obesity. Of five human studies investigating a link between BPA alternatives and obesity, two reported that urinary BPF, BPS and/or 4,4-BPF were not associated with obesity, one found that increased levels of BPF



“Avoid plastics with recycling codes 3 or 7 because these often contain BPA or BPA alternatives; instead, look for plastics marked with recycling codes 1, 2, 4, 5, or 6 because they contain negligible levels of bisphenol compounds.”

in brain tissue were associated with a decreased risk of obesity, while two studies of NHANES 2013-2014 data found that urinary BPF and BPS were positively associated with waist circumference and abdominal obesity in adults and children. A case-control study found urinary BPS and BPAF concentrations were associated with increased risk of type II diabetes, and a second study reported a link between serum BPAF concentrations and hypoglycemia in the elderly. Interestingly, oxidative stress is implicated in the development of obesity, and three of four human studies found an association between BPA alternatives and markers of oxidative stress.

Animal studies corroborate the human evidence suggesting that at least a subset of BPA alternatives are similar to BPA in causing obesogenic effects. For example, developmental exposures to BPF and BPS increased body weight and adiposity, altered molecular pathways implicated in the development of obesity, and induced oxidative stress. Exposure to BPA alternatives during development exacerbated obesity in adult animals fed a high fat diet, and changed the expression of genes related to glucose and lipid metabolism.

Whether any BPA alternative is safer than BPA remains a critical public health question that warrants immediate and significant research investment.

Approaches for reducing exposure to BPA and BPA alternatives

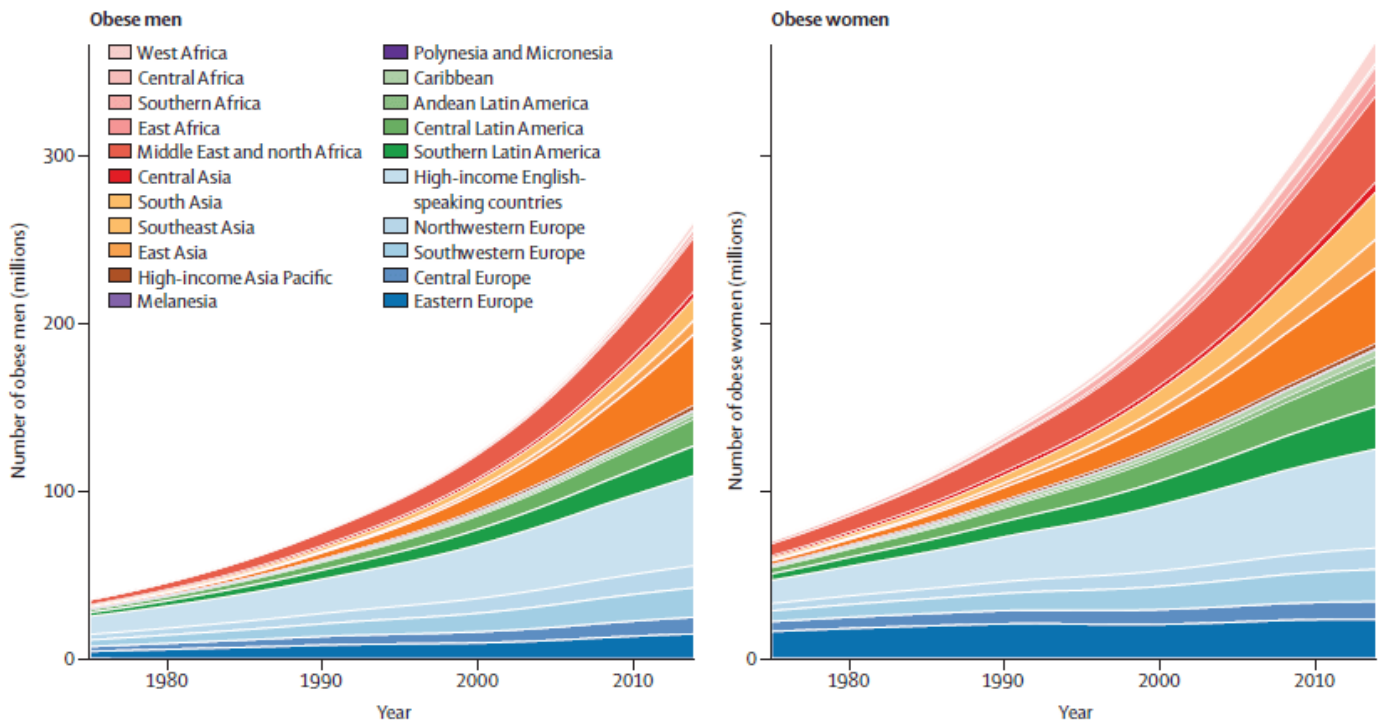
A number of approaches are recommended for reducing personal exposure to BPA and BPA alternatives. Avoid plastics with recycling codes 3 or 7 because these often contain BPA or BPA alternatives; instead, look for plastics marked with recycling codes 1, 2, 4, 5, or 6 because they contain negligible levels of bisphenol compounds. As a general rule, hard clear plastics contain BPA or BPA alternatives while soft or cloudy plastic does not. When possible, replace canned foods with frozen foods or

foods packaged in cardboard cartons made of layers of aluminum and polyethylene plastic (labeled with a number 2 recycling code). Since heating promotes the release of bisphenol compounds from packaging, which can increase their levels in food products by up to 50-fold, avoid microwaving or heating foods or beverages in polycarbonate plastic food containers. Instead, use glass, porcelain, or stainless steel containers for heating and storing food products.

Purchase non-toxic wooden toys or plastic toys free of BPA or BPA alternatives for children. Plastic products that show physical signs of damage or aging should not be considered safe. Dental patients should ask their dentists for BPA-free sealants and fillings. Avoid thermal paper receipts from ATMs, grocery stores and swiping machines, and request an electronic receipt or no receipt when possible. If you work as a cashier or otherwise frequently handle receipts, wear nitrile gloves. BPA released from products can collect in dust, so it is important to wash your and your children's hands often, especially before preparing or eating food, and to clean floors frequently, using a wet mop or HEPA-filtered vacuum if possible, and to dust often using a damp cloth.

Conclusion

Obesity is a global epidemic that affects adults, children and infants, and the rising incidence of obesity and related comorbidities shows no signs of leveling off. A growing body of evidence links exposure to BPA or BPA alternatives to increased risk of obesity across multiple species, including humans. While BPA exposure during all life stages correlates with increased body weight and/or BMI, prenatal, infancy and early childhood appear to increase vulnerability to the obesogenic effects of bisphenol compounds. These data coupled with the documented widespread and continuous human exposure to BPA and BPA alternatives underscore the critical need to invest in research to better understand the obesogenic potential



The rise of obesity (source: Trends in adult body-mass index in 200 countries from 1975 to 2014). © Metrocosm

of these chemicals and to identify safer alternatives.

Additional reading

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