

Human Bisphenol A Exposure and the “Diabetes Phenotype”

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Abstract

Bisphenol A (BPA), a known endocrine disruptor, is a food contaminant suspected of being a contributing factor to the present-day increase in obesity, diabetes, and cardiovascular disease. This issue is of increasing interest in the field of diabetes research and has become a matter of concern for regulatory agencies and food industries. Recently, the number of studies involving BPA has increased exponentially, but there are still many gaps in the knowledge of the relationship between actual BPA exposure and cardiometabolic risk and of the modalities of food intake exposure, all of which prevents sound judgments concerning the risks to human health. This review focuses on the association between human exposure to BPA and obesity, thyroid function, diabetes, insulin resistance, metabolic syndrome, cardiovascular diseases, and BPA content in food. Many cross-sectional studies support, sometimes contradictorily, an adverse effect of BPA exposure on obesity, diabetes, and cardiovascular diseases. Few prospective studies support an adverse effect of BPA exposure on such pathologies. Moreover, no intervention studies have been conducted to evaluate the causality of such associations. This is mainly due to lack of an appropriate database of BPA content in foods, thus hindering any estimation of the usual dietary BPA intake.

Keywords

bisphenol A, obesity, diabetes, cardiovascular disease, metabolic syndrome, food

Introduction

The prevalence of obesity, diabetes, and cardiovascular disease (CVD) has reached epidemic proportions worldwide and is continuing to increase. Data from different regions throughout the world suggest that more than 1 adult in every 5 adults has metabolic syndrome, a predisposition of the above-mentioned diseases.^{1,2} Although the pathogenesis is multifactorial, excess visceral fat and defective insulin action are the cornerstones to the disease. The “big two” causes are considered to be over-eating and a sedentary lifestyle, so most research and therapeutic effort has been focused on the control of food intake, the increment of energy expenditure, and improvement in insulin action. The failure of these efforts to slow down the increasing rate of the epidemic has led to the most authoritative researchers turning their attention to alternative hypotheses.³ Indeed, the epidemic has been associated with a worldwide increment in exposure to environmental chemical pollutants, which are collectively termed endocrine disruptors (EDs) that interfere with the production, release, transport, metabolism, binding action, and elimination of natural hormones regulating homeostasis and development. Also food and beverages have changed within this same time frame, having become susceptible to

ED contamination through processing and packaging and being subsequently shared across the globe. One of the best studied and most prevalent EDs is bisphenol A (BPA).

Like other EDs, BPA acts by mimicking the action of estradiol. The exposure to BPA in inappropriate concentrations, and during an improper time window, can affect multiple organ system development and function, including control of energy balance and glucose homeostasis.

In the 1950s, polymer chemists discovered that BPA molecules could be polymerized to make polycarbonate plastic, and it soon became a basic compound in the manufacture of the resin lining food and beverage cans and of the polycarbonate used in food and beverage storage containers. The leaching of

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BPA out of such products is increased by heating, contact with alkaline/acid substances, and repeated use and exposure to microwaves. Indeed, contact with food is thought to be a major contributor to the mean values of 2 to 4 ng mL⁻¹ of unconjugated BPA detected in adult and foetal serum.^{4,5} Currently, a daily dose of 50 µg kg⁻¹ d⁻¹ is considered “safe” for human consumption,⁶ but recent findings suggest that the current levels of human exposure to BPA exceed the daily dose. Bisphenol A is highly glucuronidated in the liver and is primarily excreted into the bile. However, unconjugated (bioactive) BPA can be found in the blood and, in its glucuronidated form, in urine.⁵ Unconjugated BPA circulating in blood indicates an internal exposure to the compound, as does its presence in urine, but in this latter case it also suggests a failure of first-pass conjugation and removal or deconjugation. Furthermore, age, sex, liver function, and physiological status (eg, pregnancy) could influence BPA metabolism. Being lipophilic, BPA can also be stored in adipose tissue. In animal models, the tissue/serum concentration ratios range from 0.7 in liver to 5 in adipose tissue, reflecting differences in tissue perfusion, composition, and metabolic capacity. One study detected unconjugated BPA accumulation in half the studied women.⁷

Bisphenol A endocrine disruption is relevant both in early-life than in life-time, interfering with the production, release, transport, metabolism, binding, action, or elimination of natural hormones, producing the so called “diabesity phenotype.”

Given the mounting of so much evidence on the effect of BPA on human health, there is now harsh debate among scientists, industry, and regulatory agencies on whether BPA should be banned from use in food packaging.⁸ In March 2010, Canada banned BPA from plastic baby bottles and formulas and in September declared it as a toxic substance harmful to health and environment. In April 2010, Denmark was the first European country to ban BPA from materials in contact with food for children older than 0 to 3 years. In November 2010, a joint World Health Organization and Food and Agriculture Organization (FAO) panel stated that it would be “premature to conclude that these evaluations provide a realistic estimate of the human health risk.” However, in January 2011, the European Commission (EC) prohibited the use of BPA for the manufacture of polycarbonate infant feeding bottles. In 2011, the French Agency for Food, Environmental and Occupational Health & Safety rated the BPA relationship with diabetes and CVD in humans as “suspected,” and in the animal rated the effects on lipid and glucose metabolism “confirmed” and “controversial,” respectively. In 2014, the European Food Safety Authority (EFSA) launched 2 Web-based public consultations calling for scientific opinion on public health risks in relation to BPA presence; however, the results remained inconclusive.

The purpose of this manuscript is to review the available knowledge of epidemiologic evidence on BPA exposure and obesity, diabetes, and CVD. However, the review of the state of the art reveals that all evidence has been produced relating single measurements of urinary, and rarely plasma, BPA concentrations to clinical end points, but the quantification of BPA intake is still far from being possible due to the large gaps in the

present-day knowledge. We also explored this issue by analyzing the information available on BPA amounts in foods.

Human BPA Exposure and Obesity

The prevalence of obesity has increased steadily over the last 5 decades, reaching epidemic proportions in both developed and developing countries.⁹ Furthermore, overweight and obesity are major contributors to several noncommunicable diseases such as metabolic syndrome, type 2 diabetes mellitus, coronary heart disease, stroke, some forms of cancer, and serious social and psychological sequels. The commonly adduced causes of obesity, for example, behavioural factors like excessive food intake associated with erroneous food habits, sedentary lifestyle, and genetic predisposition, do not completely explain the increment in obesity prevalence. For this reason, there is strong interest in researching obesity pathogenesis, looking for new possible causes, since the challenge to effectively treat obesity is still open. In 2002, Baillie-Hamilton suggested, for the first time, a potential role of chemical toxins in the etiology of obesity by showing that the present obesity epidemic has coincided with the marked increment in industrial chemicals in the environment over the past 40 years.¹⁰ Following the proposal of the Baillie-Hamilton hypothesis, several studies investigated the effect of environmental chemical exposure on nutritional status. This led to the very strong suspicion that EDs could induce obesity.^{11,12} Indeed, EDs can interfere with normal endocrine system functioning by affecting the endocrine apparatus and, consequently, the serum levels of hormones that regulate several human metabolism pathways. These compounds have been termed “obesogens,” based on the idea that they can downregulate lipid metabolism and adipogenesis.

On considering the ED compounds, it is to be noted that there is a growing evidence that BPA can act as an obesogen environmental agent, interfering with physiological weight control patterns. It seems to downregulate adipose tissue metabolism, endocrine hormone systems, and the central hypothalamic–pituitary–adrenal axis.^{13,14} Bisphenol A may play a role in the development of obesity not only when exposure occurs after birth but also when it occurs “in utero”. Specifically, it has been hypothesized that the obesogenic effect of BPA may be modulated by the availability of methyl donors (eg, folates) for DNA methylation, this could mean that the programming of adipogenesis, appetite, and energy metabolism may be permanently damaged and, consequently, increase risk in later life obesity.¹⁵ The epigenetic effects of BPA exposure during development could interfere with complex differentiating endocrine signalling pathways and cause adverse consequences later in life, leading to the concept of “developmental origins of adult disease.”¹⁶

Most of the studies concerning the relationship between BPA and obesity have been conducted in vitro or in vivo on animal models^{17,18} and present conflicting results most likely due to the wide range of BPA doses applied.

On adipocytes, in vitro studies have shown disruptive effects of BPA on normal adipocyte development as well as

on the homeostatic control of adipogenesis and early energy balance.^{19,20} Specifically, it has been observed that low concentrations of BPA induce lipid accumulation mediated by the production of reactive oxygen species in the mitochondria of HepG2 cells.²¹ Moreover, BPA seems to promote adipogenesis, stimulating glucocorticoid receptors in the 3 T3-L1 Cell Line (mouse fibroblasts that can differentiate into adipocytes) and, in combination with insulin, promoting adipocyte formation.^{22,23} Recently, BPA effects on human adipocytes, taken from breast, subcutaneous, and visceral adipose tissues, were investigated on more than 20 participants. The authors reported that BPA between 1 and 10 nmol/L concentrations interfered with adipocyte metabolism by inhibiting adiponectin release and stimulating the release of 2 inflammatory cytokines, interleukin (IL-6) and tumor necrosis factor α (TNF- α), showing a 'U' shaped dose-response curve and suggesting that BPA can also act at low dosage.²⁴ Adiponectin is one of the most abundant circulating adipokines, exerting an effect on glucose and lipid metabolism and modulating insulin sensitivity by stimulating glucose utilization and fatty acid oxidation.²⁵ Moreover, it also has an anti-inflammatory activity, which together with the effect on the proinflammatory cytokines TNF- α and IL-6, may be the link between several noncommunicable diseases (CVD and type 2 diabetes mellitus) and BPA exposure.^{24,26}

In vivo studies on animal models resulted in controversial results on the effect of BPA accumulation in adipose tissue, suggesting that the magnitude of the effect depends on the timing of exposure and dose; Nunez et al²⁷ showed that, in rats, high doses of BPA for 15 days led to a reduction in body weight and lower feeding efficiency, while Seidlova-Wuttke et al²⁸ found that feeding BPA to rats for 3 months did not alter the body weight, fat depots, or triglyceride levels. During prenatal and neonatal periods, it was demonstrated that low doses of BPA, in the human exposure range, in both mice and rats resulted in increased body weight of the offspring, particularly the females.^{29,30}

From an epidemiological point of view, there are several published studies primarily designed to assess the association between BPA exposure and obesity. Most use a cross-sectional design,³¹⁻³⁴ in children, adolescents, and adults. On the contrary, there are very few prospective cohort studies that have examined early-life BPA exposure effects, and these report contradictory findings, and only one study has investigated the effect of weight loss on BPA exposure.³⁵

Cross-sectional studies in children and adolescents. The association between BPA exposure and nutritional status was explored in 259 Chinese school children (older than 8-15 years).³⁶ The authors found that high urine BPA concentration and a daily intake estimate of BPA were significantly associated with an increment in body mass index (BMI) in all the participants. Interestingly, they estimated a geometric mean daily intake of 8.2 ng kg⁻¹ day BPA, much lower than the tolerable daily intake of 50 μ g kg⁻¹ day recommended by EFSA in 2007. These findings reinforce the concept that not only hormones and neurotransmitters, but also endocrine disrupting

substances, exert effects at very low exposure levels. Similarly, in 1326 Chinese students (older than 4-12 years), high urine BPA levels were associated with overweight, but only among female students older than 9-12 years (most likely in pubertal developmental stages)³⁷; this confirms findings in experimental animal studies where exposure to high BPA levels led to weight gain in females but not in males.²⁹ The association between BPA exposure and obesity was also examined in the United States on 2200 children older than 6-18 years who participated in the National Health and Nutrition Examination Survey (NHANES) in 3 study cycles, 2003-2004, 2005-2006, and 2007-2008, analyzing gender and race/ethnicity separately. The authors found a positive association between increasing levels of urinary BPA and obesity, independent of age, sex, race/ethnicity, and other social and life style variables like education and physical activity level. Children in the highest quartile of BPA (>5.4 ng mL⁻¹) had a multivariable odds ratio for obesity of 2.55.³⁸ These results confirmed the conclusion of the study previously conducted on 6- to 19-year-olds recruited in the same nationally representative survey.³² Moreover, Wells et al³⁹ observed a significant positive association between BPA exposure and waist-to-hip ratio, suggesting a relation with central obesity that is a better overall predictor of cardiometabolic risk, particularly among normal weight or overweight children.^{40,41}

Cross-sectional studies in adults. In 3390 Chinese adults older than 40 years and older, a positive and significant association between urinary BPA concentration and the prevalence of generalized obesity, abdominal obesity, and insulin resistance has been reported. The BPA concentration was higher in participants with a higher BMI than in those with lower BMI.³³ Similar results were also found in a contemporary general population sample of US adults. The BPA exposure appeared to be associated to obesity independently of confounding factors including age, education, smoking, alcohol intake, physical activity, and other factors, in both genders and in all major racial/ethnic groups. Interestingly, as occurs in children and adolescents, also in adults BPA exposure is associated not only with BMI but also with waist circumference. Among the 2104 adults recruited, waist circumference was found to be significantly higher in those with urinary BPA concentrations in the highest tertile compared to those in the lowest tertile.⁴² Waist circumference is a strong indicator of obesity and is significantly associated with the risk of future cardiovascular events in healthy men and women and with all-cause mortality⁴³ in middle-aged men and women.⁴⁴ These findings are corroborated by the results of a cross-sectional study conducted on 1030 Korean adults, in which a positive association between urinary BPA concentrations and BMI, body fat and waist circumference was found. Waist circumference was higher among participants with urinary BPA concentrations in the highest quartile compared to those with urinary BPA concentrations in the first and second quartile.⁴⁵ Recently, the association of BPA serum level and fat mass, fat distribution and circulating levels of adiponectin, leptin, and ghrelin was explored in 890

men and women older than 70, showing that BPA was positively associated with adiponectin and leptin, negatively with ghrelin, and unrelated to adipose tissue measurements.⁴⁶ The relationship between BPA and ghrelin was stronger in women than in men. Our previous data indicated that ghrelin concentration in the elderly patients, both basal and after meal suppression, is unrelated to fat mass but is negatively correlated with fat free mass after statistically adjusting for androgen levels.⁴⁷ The effect of BPA on ghrelin plasma levels needs to be evaluated both at the basal level and after meal suppression, because ghrelin's effect on hunger and satiety depends not only on its basal level but also on its post prandial level and, possibly, the worsening anorexia of aging. The results on circulating levels of adiponectin and BPA confirm the findings obtained in the cellular model²⁴ and support the hypothesis that BPA may interfere with adipocyte metabolism and the hormonal control of hunger and satiety.

Prospective cohort studies in children and adolescents. In a Spanish study, Valvi et al⁴⁸ examined the effects of prenatal BPA exposure on postnatal growth and obesity on 402 pregnant mothers and their children, measuring BPA concentrations in the first and third trimesters of pregnancy from mothers and during the rapid child growth of the first 6 months of life. Bisphenol A was not associated with obesity-related outcomes at earlier ages, but at 4 years both waist circumference and BMI were positively related to BPA exposure. Similarly, Harley et al⁴⁹ evaluated the association of urinary BPA concentrations with BMI, central obesity, and body fat of 402 pregnant mothers and their children up to 9 years, and participants recruited in the Salinas Valley, California. They found that prenatal urinary BPA concentrations were associated with decreased BMI and body fat at 9 years in girls, partially confirming the results of Nunez et al²⁷ in the animal model. Urinary BPA concentrations at 5 years were not associated with any anthropometric parameters at 5 or 9 years, whereas BPA concentrations at 9 years were positively associated with BMI, waist circumference, fat mass, and overweight/obesity at 9 years in boys and girls confirming other cross-sectional studies.⁴⁹ These results suggest that the duration of BPA exposure may be an important determinant in its effect on human nutritional status. Finally, in 297 mother-child pairs recruited in the Cincinnati area, the urinary BPA concentrations of the pregnant women were measured during the second and third trimesters and in their children at 1, 2, and 5 years. The BPA exposures were not associated with increased BMI at 2 to 5 years of age whereas higher early childhood BPA exposures were associated with accelerated growth during this period.⁵⁰

Prospective cohort studies in adults. Longitudinal studies covering the time range from "in utero" exposure to adulthood are not yet available as the first prospective cohort studies started only in 1999. However, one study involving BPA exposure followed the effects of significant changes in food intake on 151 obese participants sampled in Belgium and carried out a follow-up assessment of the effects of significant changes in food intake over a period of 1 year. The time course of the urinary BPA

levels throughout the year of dietary treatment for weight loss was assessed and compared with lean participants. The authors did not find any significant correlation of the urinary BPA levels and BMI or any differences within the obese individuals themselves during the weight loss program at 3, 6, and 12 months, independently of the strategy applied (dietary planning and lifestyle counselling vs bariatric surgery) for weight loss.³⁵

In conclusion, cross-sectional human studies in children, adolescents, and adults suggest that urinary BPA concentrations are associated with increased BMI, body fat, and central obesity, but these findings could result from confounding or reverse causation because diet is an important source of BPA exposure and obesity is linked to uncorrected dietary patterns, for both quality and quantity of foods. Prospective studies have reported contrasting results and fail to shed light on any possible link between early exposure and the risk of obesity in adulthood because, currently, the follow-up period is too short. Furthermore, more information about exposure sources is needed to evaluate BPA exposure, not only by urinary excretion measurements but also by food intake assessment. Nutritional knowledge would allow a better understanding of both BPA metabolism (potentially different in obese patients) and BPA intake (certainly higher in obese patients). The assessment of BPA dietary intake is a key element to the creation of opportunities to reduce BPA exposure.

Human BPA Exposure and Thyroid Hormones

Thyroid hormones regulate energy homeostasis by acting on both peripheral tissues and the central nervous system.⁵¹ Overt hypothyroidism is associated with decreased resting energy expenditure (REE) and weight gain, while hyperthyroidism is associated with increased REE and weight loss. Recently, Spadafra et al⁵² did not find any association between REE and Thyroid-stimulating hormone (TSH) in euthyroid participants, confirming results obtained in severely obese patients where REE was not associated with TSH in the presence of euthyroidism.⁵³ These results taken together suggest that only an increment or decrement in thyroid hormones beyond the physiological range can affect REE.

It has been supposed that BPA influences thyroid hormone metabolism, acting either as an agonist or antagonist on the thyroid hormone receptor.⁵⁴ In the perinatal period, BPA-exposed rats had elevated T4 levels during development, and upregulation of a thyroid hormone-responsive gene in the brain, without significant changes in TSH levels.⁵⁵

The relationship between urinary BPA concentrations and serum thyroid hormones was evaluated in 1346 adults and 329 adolescents (older than 12-19 years) from the NHANES 2007 to 2008.⁵⁶ In adults, an inverse relationship between urinary BPA and total T4 and TSH was observed, supporting previous reports concerning the association between BPA and altered thyroid hormones.⁵⁷

In conclusion, human exposure to BPA may be associated with alterations in circulating thyroid hormone levels, as demonstrated in cross-sectional studies. However, additional

longitudinal studies to assess the effects of BPA exposure and endocrine function, with an eye to clinical implications, are needed.

Human BPA Exposure and Type 2 Diabetes Mellitus

Initially, the possible association of type 2 diabetes mellitus and BPA was studied cross-sectionally, implying the tested hypothesis that diabetes is concomitant, but not necessarily consequent to BPA exposure.

Since 2003, various NHANES cohorts in the United States have been studied repeatedly to confirm this hypothesis, but the results have often been discrepant. Lang et al⁵⁸ were the first to report a positive association with self-reported diabetes, whose odds were 1.4 per 1-standard deviation increment in urinary BPA concentration in the 2003 to 2004 cohort: 1455 adult participants older than 18 to 74 years. They further supported their findings when they repeated the study on 1493 patients in the 2005 to 2006 cohort. Note that in this cohort (2005 to 2006), the association with diabetes did not reach significance, but the pooled estimates of the 2003 to 2008 cohorts remained significant.⁵⁹ The authors reported that in the second cohort, urinary BPA was 30% lower, with a geometric mean value of 1.79 compared with the earlier mean of 2.49 ng mL⁻¹. The greater range of the patients' BPA exposure in the first NHANES cycle could have influenced the detection of BPA association with diabetes. It was argued that self-reported diabetes could underestimate the true prevalence of diabetes.⁶⁰ This modality of diabetes recognition could have subtracted statistical power from the former investigations. Thus, in 2011 a new study included a third cycle (2007-2008) in the analysis and defined diabetes according to glycated hemoglobin (HbA1c) measurements. Overall, urinary BPA and HbA1c were significantly associated in 4389 adult participants, though when the analysis was replicated within each of the 3 cycles, it was recognized that it was the first NHANES cycle that drove the correlation.⁶¹ In the same year, another analysis⁶² was conducted in the same 3 cohorts using recent guidelines of the American Diabetes Association (ADA)⁶³ for diabetes criteria, that is, a serum glucose greater than 126 mg dL⁻¹ after fasting for a minimum of 8 hours, a serum glucose greater than 200 mg dL⁻¹ for those who fasted less than 8 hours before their NHANES visit, an HbA1c value greater than 6.5% or self-reported current use of oral hypoglycemic medication or insulin. Using the full spectrum of the possibilities to diagnose diabetes, this study found that there was a positive association between serum BPA levels and diabetes mellitus in this nationally representative sample of US adults. In subsequent stratified analyses, the observed association was found to be present among both normal weight and overweight/obese adults.

A strong objection to the validity of the previous analyses on NHANES was raised by LaKind et al⁶⁴ at the end of 2012. They claimed that using scientifically and clinically supportable exclusion criteria and outcome definitions, they consistently found no associations between urinary BPA and heart disease or diabetes.⁶⁴ They concluded that, in principle, it is

inappropriate to use cross-sectional data sets like NHANES to draw such conclusions about short-lived environmental chemicals and chronic, complex diseases.

The work of LaKind et al⁶⁴ soon drew replies and comments, ranging from acknowledgment of support from the Polycarbonate/BPA Global Group of the American Chemistry Council, thus possibly endangering scientific independence of judgement in this delicate matter that is very susceptible to the influence of relevant economical interests, to comprehensive reviews supporting the methodological approaches of the former works challenged by these authors.⁶⁵

The NHANES saga was finally enriched by Sabanayagam et al whose study examined the association between urinary BPA levels and prediabetes in 3516 participants from the 3 cycles between 2003 and 2008.⁶⁶ Again, prediabetes was defined according to ADA criteria (fasting glucose concentration 100-125 mg dL⁻¹ or 2-hour glucose concentration of 140-199 mg dL⁻¹ or an HbA1c value of 5.7%-6.4%). This work associated BPA with prediabetes, more strongly for women and obese patients. In summary, with the exception of one study, all the investigators who evaluated the association of BPA and diabetes or prediabetes in the NHANES cohorts between 2003 and 2008 found at least some evidence of positive association.

The association of BPA and diabetes has drawn attention also in nonwestern countries, where the current diabetes epidemic is of major concern. In a cross-sectional study from China, there was no detection of a clear association between urinary BPA concentrations and objective measures of impaired glucose regulation, including type 2 diabetes mellitus. The study, involving 3423 participants selected from 10 185 candidates, was a representation of normotolerant, impaired glucose regulation, and diabetes subjects. Caution is raised by the authors because the study did not assess diet or treatment of existing diabetes.⁶⁷ A cross-sectional study of 1210 middle-aged Koreans failed to detect an association between self-reported diabetes and urinary BPA.⁶⁸ The BPA urinary concentrations in Korean patients were comparable to these in the US samples; nonetheless, as noted above, the methodology to assess diabetes may have underestimated its prevalence. More recently, higher BPA exposure, reflected in higher urinary concentrations of BPA, was associated with diabetes in the Iran general adult population in a small study of 119 cases of type 2 diabetes mellitus controlled with 120 nondiabetic participants.⁶⁹ Finally, 2581 patients from the Thai National Health Examination Survey (2009) were investigated for the association between serum BPA concentrations and impaired fasting glucose or diabetes, the latter being defined on the basis of either fasting plasma glucose or a physician's diagnosis. Serum BPA concentrations were associated with diabetes and not with impaired fasting glucose.⁷⁰

Most studies were cross-sectional in nature, with an inherent limitation in the possibility of detecting a temporal relationship between exposure and subsequent clinical manifestations that support a causal relationship. Indeed, only through longitudinal studies could stronger evidence be found to support the theory

that BPA exposure contributes to the development of diabetes, and the first of such studies in this field was published only recently.⁷¹ The study involves 2 cohorts of the Nurses Health Study (NHS): one composed of postmenopausal women (average age 66 years—NHS1), the other of younger, premenopausal women (average age 46 years—NHS2). From the 2 cohorts, the authors measured BPA and 8 major phthalate metabolites among 971 incident type 2 diabetes mellitus case-control pairs. Interestingly, a clear association was found between BPA and incident diabetes in the premenopausal women but not in the post-menopausal women. The authors speculated that this difference in susceptibility to diabetes from exposure to BPA, according to menopausal status, could be explained according to the hypothesis that the BPA endocrine interference of estrogen receptors of pancreatic β cells would be enhanced in premenopausal women. Thus, the findings of this first longitudinal study strengthen the idea that BPA exposure could increase diabetes risk, despite the often discrepant results from the many cross-sectional studies conducted worldwide.

Association with insulin resistance. It could be that BPA contributes to type 2 diabetes mellitus by increasing insulin resistance. This led to a Korean study of 950 individuals living in urban areas, and such an association was supported by the study reporting a significant positive relationship of urinary BPA with plasma glucose concentrations.⁷² In 2012, a large cross-sectional study included 3390 adults aged 40 years or older in China.³³ After adjusting for BMI, waist circumference, smoking, alcohol intake, education levels, systolic blood pressure, high-density lipoprotein, low-density lipoprotein, total cholesterol, triglycerides, highly sensitive C-reactive protein, alanine transaminase, and γ -glutamyl transferase, the fourth quartile of urinary BPA concentration significantly increased the prevalence of insulin resistance by 37% compared with the first quartile. Interestingly, this association was driven by the normal-weight individuals rather than by the overweight ones, suggesting that the effect of higher BMI may overwhelm that of BPA on insulin resistance in participants with higher BMI. More recently, in overweight or obese Ohio children aged 3 to 8 years, the BPA levels were associated with insulin resistance,⁷³ providing further evidence for the potentially diabetogenic effects of BPA starting at a young age.

Human BPA Exposure, Metabolic Syndrome Components, and Coronary Disease Risk Factors

Among the many risk factors for coronary disease, there appears to be strong evidence of an association between BPA and hypertension. In their analysis of the first NHANES cycle (2003-2004) Shankar et al⁷⁴ found a positive association between the increasing levels of urinary BPA of 1380 participants and hypertension, independent of confounding factors such as age, gender, race/ethnicity, smoking, BMI, type 2 diabetes mellitus, and total cholesterol levels. The odds of blood pressure-reducing medication use and/or blood pressures >140/

90 mm Hg increased by 1.50 between the extreme tertiles of BPA exposure. The same positive association was found in 560 elderly citizens from Korea even though the odds of being hypertensive significantly increased, more than doubled, only in the individuals without previous history of hypertension.⁷⁵

In 2014, the participants in NHANES 2003 to 2008 showed increasing levels of urinary BPA positively associated with metabolic syndrome.⁷⁶ In contrast, in the Prospective Investigation of the Vasculature in the Uppsala Seniors study, weaker associations were observed for coronary risk assessed by the Framingham Risk Score together with circulating serum levels of BPA.⁷⁷

Human BPA Exposure and CVD

The NHANES cohorts support much of the evidence for an association of urinary BPA and coronary disease, as was found in the earlier work on the 2003 to 2004 cohort⁵⁸ and confirmed in the subsequent work of Meltzer et al,⁵⁹ though attenuated in the 2005 to 2006 cohort. Peripheral artery disease was also associated with urinary BPA in an analysis of 745 participants from the 2003 to 2004 cycle of NHANES, with odds increased by 2.69 between the extreme tertiles of exposure.⁷⁸ Similar findings were also found in a European investigation of 591 patients participating in The Metabonomics and Genomics in Coronary Artery Disease (MaGiCAD) study.⁷⁹ The BPA exposure was higher in those with severe coronary artery stenoses compared to those with no vessel disease.

The incidence of coronary disease after BPA exposure was also studied prospectively in NHANES 2003 to 2006 participants during the 10 years of follow-up and showed trends similar to previously reported cross-sectional findings in the more highly exposed participants, providing stronger support for the hypothesis of adverse cardiovascular effects of BPA exposure.⁸⁰

Human Food Exposure to BPA

Humans are continuously exposed to BPA due to its presence in food and the environment. Foods, especially canned food, are the predominant means of human exposure to BPA,⁸¹ which is a key component of the epoxy resins used in the internal coating of cans to prevent direct contact between the metal wall of the container and the food or beverage content, and to protect cans from rusting and corrosion.^{82,83} However, due to an incomplete polymerization process, significant amounts of BPA residues in this coating can migrate from the cans to the food and beverage contents.⁸¹

Heat treatment, storage conditions, and the presence of damage are the principal factors influencing BPA migration. Goodson et al⁸⁴ filled empty epoxyphenolic coated cans with 4 different foods and a simulated food. After filling, the cans were sealed and processed using the usual conditions (90 minutes at 121°C or 30 minutes at 121°C). To evaluate the effect of damage on BPA migration, half the cans were dented and then all the cans (damaged and undamaged) were stored at 5°C, 20°C, and 40°C and analyzed at 1, 3, and 9 months. The authors

found that 80% to 100% of the BPA present in the coating migrated into the food during the sterilization process, this level remaining unchanged for extended storage and damaged cans. Instead, Errico et al⁸⁵ found different results for canned tomatoes: in this study, the cans were stored at 25°C, 37°C, and 45°C and, in order to simulate poor preservation, some cans were dented. This study showed that the BPA migration level increased with increasing storage temperature (at 37°C and 45°C, the concentrations were about 3 to 10 times those measured at 25°C) and the presence of damage increased the BPA migration by more than 30% to 40%. The controversial results of these 2 studies can be explained by the different time/temperature conditions employed during the sterilization process. In fact, the drastic heat process used by Goodson et al⁸⁴ determined an almost total release of BPA from the internal coating of the cans, therefore the subsequent storage and presence of damage proved inconsequential. However, in the second study,⁸⁵ where the tomato products have a low pH, the sterilization of the product was achieved under milder heat processing conditions (generally 6 minutes at 115°C). In this case, part of the residual BPA remained in the coating after the sterilization process and, therefore, the BPA concentration in the food increased during storage and in the presence of damage. These findings are supported by the findings of Munguia-Lopez and Soto-Valdez and Munguia-Lopez et al⁸⁶⁻⁸⁸ who also studied the effect of heating on BPA migration in canned jalapeño peppers and tuna fish. As jalapeño peppers have a lower pH than tuna fish, the heat processing conditions required for product sterilization were milder (9 minutes at 100°C vs 90 minutes at 121°C). The authors found that the migration of BPA in tuna fish was high immediately after the sterilization process and remained constant during 40 and 70 days of storage, while the concentrations of BPA found in jalapeño peppers were very low after the sterilization process and increased with storage time. Finally, Kang et al⁸⁹ reported that temperature influences BPA migration from cans more than heating time in water samples. Moreover, the can content also affects BPA migration. In fact, the presence of glucose, NaCl, or oil determines a higher release of BPA from heated cans.^{89,90}

Many worldwide studies have determined BPA concentration in canned food,^{82,83,90-98} and BPA has been detected in 59% to 100% of the analyzed samples.⁸¹ Table 1 shows the mean values of BPA concentrations in canned food and beverages from studies reported in the literature. Large between-study differences in BPA concentration in the same foods are reported. For example, BPA concentration in tuna fish ranges between 9.8 ng g⁻¹ in Japan⁹² and 288 ng g⁻¹ in Turkey.⁹⁰ Similarly, BPA in corn was found to be 22-fold more concentrated (7.2-175.7 ng g⁻¹) in cans purchased in Turkey⁹⁰ than in Korea.⁹³ Beans were found to be contaminated by BPA in concentrations ranging from not detectable amounts to 650.1 ng g⁻¹.^{90,91} At the same time, a large variation in BPA concentration was found in different samples of the same food within the same study. Indeed, the study of Sungur et al⁹⁰ reports beans with a BPA concentration ranging from 85.1 to 1858.7 ng g⁻¹ and Thomson and Grounds⁹¹ reports a

concentration in tuna fish of BPA between <20 and 109 ng g⁻¹. Such variations are probably due to the different analytical methods and sensitivities used for BPA determination, different canned food manufacturer processing conditions, and the different kinds of can and coating used. Given its low water solubility, it has been suggested that BPA tends to favor partitioning in the solid fraction rather than in the liquid when both are present in the same can, especially for food items of high fat content.⁹⁴ This would explain the high BPA levels found in tuna fish and other food items rich in fat, and also the level found in beans, corn, and peas where no, or little, fat is present.

Bisphenol A was also found, though in lower concentrations, in canned beverages.^{93,94,99-101} However, differently from the canned food data, the data of the beverages were more homogeneous in the different studies reported. Moreover, the range of values of the individual BPA concentration studies of the different samples of the same beverage was smaller than that reported for canned foods. These lower values could be explained by the milder sterilization conditions, the different can types, and coatings used.⁸¹ However, it should be kept in the mind that total BPA intake is the result of the amount ingested and the consumption frequency of BPA contaminated foods. Therefore, large amounts and/or frequently consumed foods (like canned beverages) could contribute significant quantities of BPA despite low BPA concentrations.

Epoxy resins are not only used as the internal coating of cans but are also on the metal lids of glass jars. However, as the contact between food and the lid is lower than that between food and the internal surface of the can, the concentration of BPA in these foods is lower. Studies have found a BPA concentration <1 ng g⁻¹ in the majority of analyzed samples (70%), with an overall average concentration of 1.1 ng g⁻¹.⁸¹ Bisphenol A is also used in the production of polycarbonate bottles and containers. Polycarbonates may release residual BPA into the food by diffusion after the manufacturing process and by hydrolysis of BPA polymers catalyzed by bases.¹⁰² The principal factors influencing the release of BPA from polycarbonates are temperature, contact time, and pH of the liquid food,¹⁰³ but few studies are available on BPA release from polycarbonate products.¹⁰⁴ Hoekstra and Simoneau¹⁰⁴ reported BPA concentrations beneath the limit of detection in food or food simulant. In fact, BPA was not detected in fruit juice, milk formula,¹⁰⁵ soup, steamed hot rice, or cooked hot pork.¹⁰⁶ Polycarbonates are also used in the production of baby bottles. Many studies focused their attention on the release of BPA from these containers, revealing a BPA migration level ranging between 0.3 and 521 µg L⁻¹.⁸¹ However, the highest releases of BPA were found in bottles exposed to elevated temperature and/or to long contact time conditions (eg, heating water at 70°C for 6 days), unlikely conditions in real life.⁸¹ In fact, De Coensel et al¹⁰⁷ reported low BPA concentrations in these food items (6-13 ng L⁻¹) under normal conditions.

Furthermore also fresh, daily consumed food has been revealed to contain BPA; indeed, Cao et al⁸² found low BPA levels (0.4-1.73 ng g⁻¹) in bread and cereal, vegetables, cheese (0.68-2.24 ng g⁻¹), and in fast food composite samples

Table 1. BPA Mean Concentrations in Canned Food and Beverages.^a

Food Item	Mean (ng/g)	Range	Ref	Food Item	Mean (ng/g)	Range	Ref
Fish				Pasta			
Tuna fish	88.9	9.8-288	83,90-96	Ravioli	51.5	29.9-73.1	82,94,95
Salmon	10.6	3.4-13.7	83,92-94	Pasta	18.9	ND-32	83,91,95
Anchovy	0.9		94				
Mackerel	25.7	ND-77.8	83,92,93,95	Soups and sauces			
Saury	58.5		93	Vegetable soup	27.9	5-63	83,92,94,95
Mussel	11.0		93	Chicken soup	31.2	9.2-49.3	82,83,92,94,95
Crab	11.7		93	Fish soup	16.0		92
Smoked oyster	44.7		93	Cream	114.6	73.1-156	90,92
Sardines	20.0		83	Meat sauce	8.0		92
				Brown sauce	605.7		92
Meat				Beverages			
Ham and Sausages	47.9	ND-117	83,93,94	Cola	0.32	0.15-0.79	94,99-101
Chili	77.4		95	Energy drink	1.31	0.55-2.3	94,99,101
Canned meat	29.4	10.6-65.7	83,91-93	Beer	0.70	0.29-1.46	94,99,101
				Sport drink	1.53		94
Fruit				Iced tea	0.52	0.34-0.69	94,99
Fruit mix	12.1	ND-31.3	83,91,93,94	Apple juice	2.55	0.36-4.73	94,99
Peaches	10.8	ND-29.4	91-95	Orange juice	3.96		94
Pears	10.1		94	Vegetable juice	0.88		94
Pineapple	0.9	ND-3.2	82,91-93,95	Tropical juice	1.93		94
Grape	4.2	ND-8.48	92,93	Soda drink	0.51	0.12-0.98	94,99,100
Apricots	ND		91	Tonic water	0.03	ND-0.06	94,99
				Sparkling water	0.00		94
Vegetables				Coffee	45.5		93
Olives	13.6	8-21.4	91,92,94	Ginger ale	0.25	ND-0.49	99,100
Carrots	26.0	25.9-26	83,94				
Corn	46.0	7.2-175.7	83,90-95	Infant formula			
Beans	113.4	ND-650.1	83,90-96	Liquid milk	4.42	2.75-5.53	82,97,98
Peas	71.6	4.25-166.4	83,90,91,95	Liquid soy	5.89	5.75-6.03	97,98
Tomatoes	21.2	2.6-70	82,83,90-95	Concentrate milk	6.16		97
Bamboo	14.0	ND-28	93,94	Concentrate soy	4.84		97
Mushrooms	45.4	ND-116.3	92-94	Powder milk	ND		97
Beetroot	20.5		91	Powder soy	ND		97
Asparagus	78.0		92				

Abbreviations: BPA, bisphenol A; ND, not detectable amounts.

^aBPA mean concentration range was reported when more than one value was available for the same food item.

(1.1-10.9 ng g⁻¹). The bread contamination may be explained by the presence of BPA in the baking powder (0.64 ng g⁻¹) and yeast (8.52 ng g⁻¹), which may have been contaminated by the packaging used, such as packaging film in Polyvinyl chloride (PVC) where BPA is used as an additive, or by contamination during the production process.⁸¹ Furthermore, PVC film also could be the origin of the cheese and fast food products contamination. Finally, contamination of the vegetables could have occurred during the packaging, transport, and manufacturing phases. Although the fresh food presented BPA concentrations lower than the canned food, its frequency of consumption is much higher, so its contribution to BPA human exposure may not be as negligible as previously thought.

Conclusion

Many of today's cross-sectional studies support, sometimes contradictorily, an adverse effect of BPA exposure on obesity,

type 2 diabetes mellitus, and CVD. However, few prospective observational studies support an adverse effect of BPA exposure on type 2 diabetes mellitus and CVDs.

No intervention studies have been conducted to evaluate the causality of these associations to date. Indeed, this striking lack of evidence is not casual, it is the result of the lack of knowledge of food BPA content and, consequently, on the impossibility of quantifying the daily dietary BPA intake. At best, individual urinary or plasma samples could reflect a single day's BPA intake, but certainly not the customary and cumulative BPA exposure over time. To provide an example: it would be like trying to assess the effect of sodium intake on the risk of hypertension by measuring a single-sample urinary sodium concentration. For this reason, in our review, data available on BPA food content has been provided. An inspection of such data strongly urges that further effort be made to investigate the determinants of dietary BPA intake, in order to provide databases that are detailed enough to quantify BPA

exposure in humans at both the individual and population level. Such databases, which are currently lacking, would be instrumental to definitively clarifying the relationship between BPA, obesity, and cardiometabolic risk.

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