Chemical components of plastics as endocrine disruptors: overview and commentary

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BRIEF REPORT

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Chemical components of plastics as endocrine disruptors: Overview and commentary

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Abstract

Bisphenol A and phthalate esters are used as additives in the manufacture of plastic materials, but their ability to leach out with age and heat has resulted in their becoming ubiquitous contaminants of the ecosystem including within human body tissues. Over recent years, these compounds have been shown to possess endocrine disrupting properties with an ability to interfere in the actions of many hormones and to contribute to human health problems. Much of the reported disruptive activity has been in relation to the action of estrogens, androgens, and thyroid hormones, and concerns have been raised for adverse consequences on female and male reproductive health, thyroid function, metabolic alterations, brain development/function, immune responses, and development of cancers in hormone-sensitive tissues. A recurring theme throughout seems to be that there are windows of susceptibility to exposure in utero and in early postnatal life, which may then result in disease in later life without any need for further exposure. This commentary highlights key issues in a historical context and raises questions regarding the many data gaps.

KEYWORDS

bisphenols, breast cancer, developmental disorders, endocrine disruptors, estrogen, obesity, phthalates, plastic, reproduction, susceptibility windows

1 | INTRODUCTION

An endocrine disruptor is defined as "an exogenous substance that causes adverse health effects in an intact organism, and/or its progeny, consequent to changes in endocrine function". **(Weybridge report, *1996*)**

Normal growth, development, and maintenance of multicellular organisms are dependent on a functional endocrine system. However, over recent years, many environmental chemicals, including bisphenol A (BPA) and phthalate esters used as additives in the manufacture of plastic materials, have been shown to possess the ability to interfere in hormone action. Such endocrine-disrupting chemicals (EDCs) may act by altering hormone synthesis in the endocrine gland, by altering transport/metabolism/excretion of the hormone, or by competing with physiological hormone for binding to receptors in target cells and in so doing to mimic inappropriately or antagonize hormone actions (Figure 1) (Darbre, 2015). Much of the reported disruptive activity of BPA and the phthalate esters have been in relation to the action of estrogens, androgens, and thyroid hormones, and concerns have been raised for adverse consequences on human health ranging from female and male

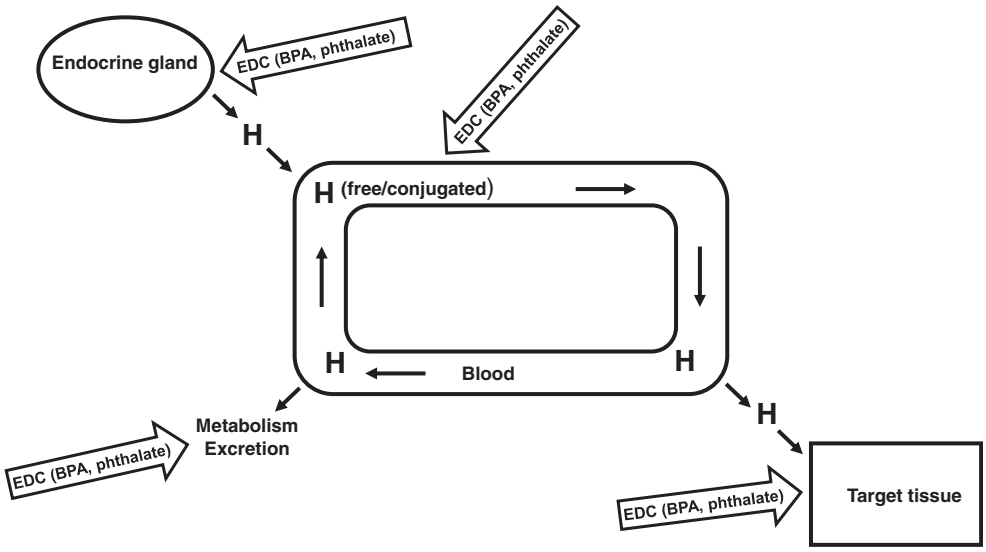

FIGURE 1 Mechanisms by which endocrine-disrupting chemicals (EDCs) may interfere in hormone action. EDCs, such as bisphenol A (BPA) and phthalates, may interfere in hormone (H) synthesis in the endocrine gland, in the transport of the hormone around the bloodstream and in the hormone actions at target tissues. They may also alter the metabolism and excretion of the hormones (Darbre, 2015)

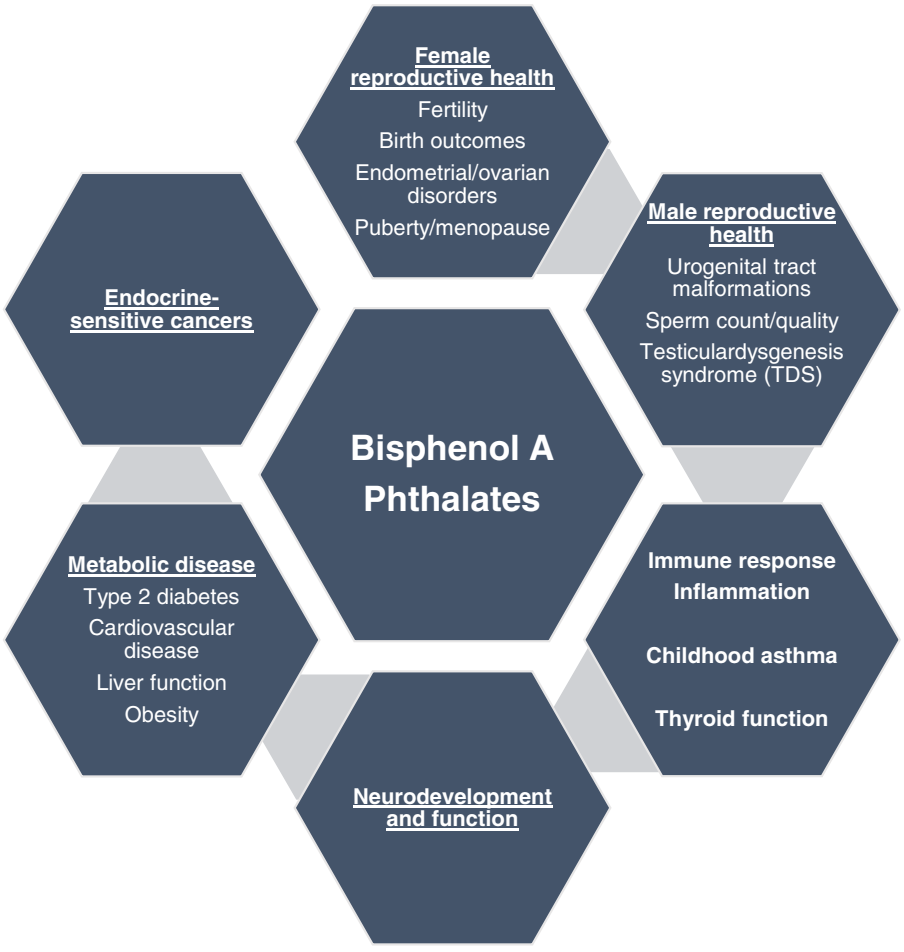

FIGURE 2 Overview of concerns for human health following exposure to endocrine-disrupting chemicals (EDCs) such as bisphenol A (Rochester, 2013) and phthalates (Hauser & Calafat, 2005)

reproductive health, to thyroid function, to metabolic alterations underlying diabetes, cardiovascular disease, and obesity, to impaired brain development/function and compromised immune responses, and to cancers in hormone-sensitive tissues (Figure 2) (Darbre, 2015). Windows of susceptibility for EDC exposure appear to be most notably in utero and in early postnatal life, with consequences of such exposures often not visible until later in adult life and sometimes even carried into future generations (Darbre, 2015).

Plastics are made as organic polymers mixed with a blend of additives to provide targeted properties such as

toughness, flexibility, and color. Their versatility, durability, and light weight have resulted in widespread use as construction materials, in packaging applications, and in household and medical products. BPA is used for its cross-linking properties as an additive in polycarbonate plastics and epoxy resins to harden the product for use as food storage containers and water bottles. Phthalates are esters of phthalic acid, which are used as plasticizers to reduce brittleness and increase flexibility especially in polyvinyl chloride (PVC) plastics but are also added to many other consumer goods, including adhesives, paints, air-freshener products, and personal care products. Early experiments, reporting that BPA could leach out of plastic materials when heated (Krishnan, Stathis, Permuth, Tokes, & Feldman, 1993), have led to a more general understanding of the ability of these widely used additives to leach out of plastic materials with heat and age to become ubiquitous contaminants of the ecosystem including human body tissues.

2 | EVIDENCE FOR ENDOCRINE DISRUPTING PROPERTIES OF BPA

Synthesis of BPA was first described in 1891 (Dianin, 1891) and its estrogenic properties reported in the 1930s (Dodds & Lawson, 1936). During the 1930s, chemicals with estrogenic properties were being sought for their medicinal properties, but more potent estrogens such as diethylstilboestrol (DES) were adopted in preference to the weaker compounds such as BPA. Prescription of DES to prevent miscarriage (Smith, 1948) was used until 1971 and use was ceased following the report of rare vaginal cancers in daughters of mothers who had taken the drug during pregnancy (Herbst, Ulfelder, & Poskanzer, 1971). Further studies over the following decades have revealed the numerous reproductive abnormalities and cancers in sons (Palmer et al., 2009) as well as daughters (Hoover et al., 2011) following exposure in utero to this potent estrogen and have served as a warning of the legacy of developmental consequences from in utero exposures to endocrine-disrupting agents (Harris & Mainwaring, 2012).

BPA was never used as a drug but instead found its way into the manufacture of epoxy resin and polycarbonate plastics, turning it into a high volume production chemical (OECD, 2004), which has become widely distributed including in human tissues and urine (Calafat, Ye, Wong, Reidy, & Needham, 2008). Its ability to mimic physiological estrogens derives from its phenolic groupings (Figure 3), which are now known to determine binding to estrogen receptors (Brzozowski et al., 1997). In vitro, it has been shown to bind to estrogen receptors ERα and ERβ, to stimulate estrogen-dependent gene expression and to increase proliferation of estrogen-responsive cells (Wetherill et al., 2007), but it can also act via membrane estrogen receptors including the G-protein-coupled receptor GPR30 and via non-genomic mechanisms (Rubin, 2011). It has also been shown able to

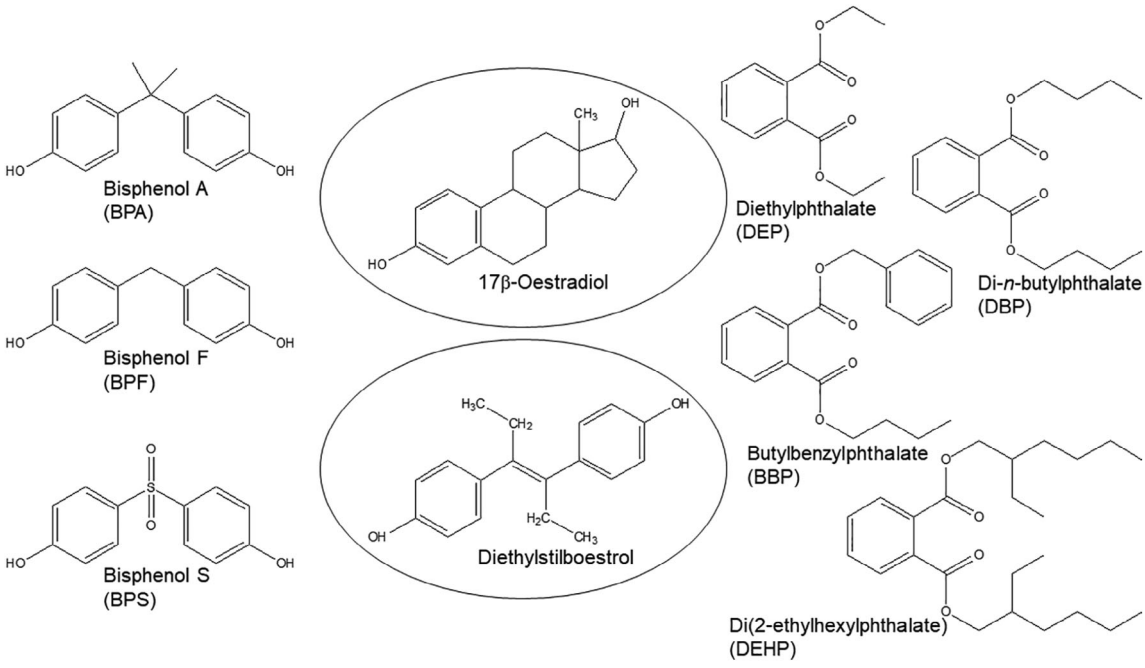

FIGURE 3 Chemical structures of bisphenols and phthalate esters in relation to that of the physiological estrogen 17β-oestradiol and the synthetic estrogen diethylstilboestrol

increase the expression of aromatase, the key enzyme necessary for the conversion of androgens into estrogens (Williams & Darbre, 2019). In addition to its estrogenic activity, it can also bind to the androgen receptor and give antiandrogenic responses (Sohoni & Sumpter, 1998). BPA can also bind to thyroid hormone receptors and interfere in thyroid function (Wetherill et al., 2007). Furthermore, BPA can also bind to and interfere in the actions of peroxisome proliferator-activated receptors (PPARs) (Gao et al., 2020). Animal models have demonstrated adverse effects on male and female reproductive function (Rochester, 2013; Rubin, 2011). Epidemiological studies suggest a link between BPA exposure in humans and multiple adverse endocrine consequences, including not only male and female reproductive functions but also alterations to thyroid hormones, immune function, disruption of glucose homeostasis (diabetes), cardiovascular disease, and obesity (Rochester, 2013). Exposure to BPA has also been linked to the development of hormone-sensitive cancers, most notably breast cancer (Hafezi & Abdel-Rahman, 2019). Animal models have shown that exposure to BPA during critical windows of development of the mammary gland in utero can alter mammary gland biology and increase the risk of subsequent breast cancer in later life (Soto, Brisken, Schaeberie, & Sonnenschein, 2013).

Due to the endocrine-disrupting properties of BPA, much effort has been devoted to the development of analogs such as bisphenol F (BPF) and bisphenol S (BPS) (Figure 3) in the hope that substitutes might be found without adverse activity. However, models both in vivo (Mu et al., 2018) and in vitro (Kojima et al., 2019) have shown that these analogs can still bind to estrogen receptors and give estrogenic responses on gene expression albeit with some differences in detailed mechanisms of action at a molecular level, (Li et al., 2018).

3 | EVIDENCE FOR ENDOCRINE DISRUPTING PROPERTIES OF PHTHALATES

Phthalates are esters of phthalic acid, which comprise a large family of compounds derived from the many combinations of alkyl and aryl ester groupings and producing compounds from low to high molecular weight (Figure 3). Therefore, unlike BPA, which is a single compound, the endocrine-disrupting properties of phthalates are more complex with different compounds having different potencies and effects. Di(2-ethylhexyl) phthalate (DEHP) is the main plasticizer used in PVC due to its low cost. Butylbenzylphthalate (BBP) is used in the manufacture of foamed PVC for flooring materials. Diethylphthalate (DEP) is added to many personal care products to stabilize fragrance. Many of the phthalates are so widely used that they are now individually listed as high production volume chemicals by the OECD (2004). Early studies in vitro showed that several phthalate esters could bind to estrogen receptors, stimulate estrogen-dependent gene expression and increase the growth of estrogen-responsive cells (Harris, Henttu, Parker, & Sumpter, 1997; Jobling, Reynolds, White, Parker, & Sumpter, 1995). However, some phthalate esters can also interfere in the action of PPARs, which act as lipid sensors in the regulation of lipid homeostasis. Several EDCs have been shown to alter adipogenesis through interfering in PPARγ actions (Janesick & Blumberg, 2011). Although many phthalates show greater responses through PPARα than on PPARγ (Hurst & Waxman, 2003), the phthalate metabolite mono (2-ethylhexyl) phthalate is a potent activator of PPARγ (Maloney & Waxman, 1999) and BBP has been shown to promote adipogenesis in 3T3-L1 preadipocytes (Yin, Yu, Lu, & Yu, 2016). Many in vivo models have demonstrated that in utero exposure to phthalates impacts negatively on reproductive development in male rodents with a striking similarity to the testicular dysgenesis syndrome in humans (Howdeshell, Hotchkiss, & Gray, 2017), suggesting that phthalate exposure may adversely impact on male reproductive health.

4 | SOURCES OF HUMAN EXPOSURE TO BPA AND PHTHALATES

Since BPA and phthalates are ubiquitous environmental pollutants, human exposure may result from inhalation, ingestion, and dermal absorption. In the air, BPA is now a ubiquitous pollutant albeit with considerable variation across different parts of the world, from the highest levels in urban India (200–17,400 pg/m^3), but even detectable in polar regions (1–17 pg/m^3) (Fu & Kawamura, 2010). Correlations have been reported in the air between levels of BPA and 1,3,5-triphenylbenzene, which is a tracer for plastic burning, suggesting a source of the atmospheric BPA could be burning of plastic materials (Fu & Kawamura, 2010). BPA is also widely present in food, following leaching out from the plastic packaging (Andujar et al., 2019) and is present at low levels in drinking water (Arnold et al., 2013).

Phthalates are ubiquitous in air, especially in the indoor environment, and in one study in the Richmond area of the USA were measured as present in 100% of homes (Rudel et al., 2010). The more volatile phthalates dimethylphthtalate (DMP), DEP, and dibutylphthalate (DBP) are present at higher concentrations in the air than the heavier, less volatile phthalates such as DEHP and BBP, which are more prevalent in house dust (Heudorf, Mersch-Sundermann, & Angerer, 2007; Rudel, Camann,

Spengler, Korn, & Brody, 2003). Higher ambient temperatures are associated with higher air concentrations of phthalates (Uhde, Bednarek, Fuhrmann, & Salthammer, 2001) and the presence of PVC flooring has been associated with higher levels of DEHP and BBP in house dust (Bornehag et al., 2004, 2005). Diet is generally considered as the main route of exposure (Serrano, Braun, Trasande, Dills, & Sathyanarayana, 2014). However, the dermal absorption of phthalates from the topical application of personal care products has also been demonstrated (Janjua, Frederiksen, Skakkebaek, Wulf, & Andersson, 2008). Phthalate metabolites have been detected in almost all human urine samples indicating widespread exposure of the population (Silva et al., 2004). Urinary concentrations of the main metabolite of DEP have been positively associated with the use of personal care products, reflecting the use of DEP as a fixative for fragrance (Philippat, Bennett, Calafat, & Picciotto, 2015).

5 | CONCERNS FOR HUMAN HEALTH AND THE CONSEQUENCES OF EARLY LIFE EXPOSURES

Exposure to EDCs, which includes BPA and phthalates, has long been a matter of concern in relation to human health (Darbre, 2015) (Figure 2). The reported lack of fertility in farm animals in the 1920–1940s following consumption of plant-based phytoestrogens provided a warning of the potential for consequences of exposure to potent estrogenic compounds on human reproductive health, as did also the many reports of reproductive failures in wildlife following exposure to pollutant chemicals with endocrine-disrupting properties (Darbre, 2015). However, it was the many long-term side-effects of prescription of DES to women during pregnancy, which brought evidence of the consequences specifically for humans as well as animals (Harris & Mainwaring, 2012). The link between fetal development and adult disease, as uncovered in the mid-1990s (Barker, 1995), brought a new concept of the possibility of fetal origins of adult disease (Barker, 1995), and this unfolding legacy of DES showed that exposure to untoward endocrine agents in utero could have long-term effects into adult life (Harris & Mainwaring, 2012). Although endocrine-disrupting agents have been implicated in a wide range of human health problems, a recurring theme throughout seems to be that there are windows of susceptibility in utero and in early postnatal life, which may then herald in disease in later life without any need for further chemical exposure.

Effects of in utero exposure to certain phthalate esters and consequences for male reproductive health have been a matter of long-standing research both using animal models and human epidemiological approaches (Hauser & Calafat, 2005). Although animal models reveal a clear link, human epidemiological studies are more mixed. Such variations from epidemiological research probably reflect the environmental reality of the complexity of studying mixture effects, not only mixtures of different esters themselves but also mixtures involving other EDCs (Howdeshell et al., 2017).

Mouse models have shown that exposure to BPA during critical windows of susceptibility during either fetal (Vandenberg et al., 2007) or early postnatal (Munoz de Toro et al., 2005) life can lead to altered mammary gland biology and increased risk of mammary cancers (Soto et al., 2013). Dose-response studies of mammary budding showed that the increase in duct and bud growth, which were stimulated at low concentrations, was inhibited at higher concentrations (Vandenberg et al., 2006). This is reflective of the non-monotonic actions of many EDCs (Vandenberg et al., 2012) and highlighted the ability of BPA to act in early life at low doses in a different manner from higher doses and to act adversely at low doses rather than higher doses. In human epidemiological studies of breast biology, a positive association has been reported in postmenopausal women between serum BPA levels and mammographic breast density (Sprague et al., 2013), which is a predictive marker of breast cancer risk (Boyd et al., 2010).

Some EDCs, now termed obesogens, can interfere in the endocrine regulation of energy metabolism and development of adipose tissue architecture, most notably in early life, leading then to weight gain and obesity in adulthood (Darbre, 2017). Animal models have shown that early exposure to BPA (vom Saal, Nagel, Coe, Angle, & Taylor, 2012) or BPS (Ivry Del Moral et al., 2016) can predispose animals to weight gain, and transgenerational studies in rodents have further reported the passing of heritable traits towards obesity following exposure to BPA and some phthalates (DEHP and DBP) (Manikkam, Tracey, Guerrero-Bosagna, & Skinner, 2013). in vitro models have shown that BPA (Masuno et al., 2002), BBP (Yin et al., 2016), and a phthalate metabolite (Feige et al., 2007) can promote adipogenesis in 3T3-L1 preadipocytes. Epidemiological studies have reported that early-life exposure to BPA is associated with increased weight gain in children (Vafeiadi et al., 2016) and have noted an association between urinary concentrations of phthalate metabolites and increased waist circumference (Hatch et al., 2008; Stahlhut, vanWijngaarden, Dye, Cook, & Swan, 2007). BPA levels have also been found to correlate in adult humans with circulating levels of leptin and ghrelin (Rönn et al., 2014), hormones secreted by the adipose tissue to regulate hunger. This suggests that BPA may also

be able to interfere with hormonal control of hunger and satiety (Rönn et al., 2014), and this has been supported by a report of increased production of leptin mRNA in the 3T3L1 adipocyte model after 3 weeks of exposure to 1 nM BPA (Ariemma et al., 2016).

Other studies are also implicating early life exposure to EDCs, including these plastics additives, to altered development of the brain and immune system. Prenatal exposures to BPA (Mustieles, Perez-Lobato, Olea, & Fernandez, 2015) and phthalates (Ejaredar, Nyanza, Eycke, & Dewey, 2015) are being associated with adverse cognitive and behavioral outcomes in children. Early life exposures to EDCs are also being reported to suppress inflammatory processes leading to insufficient immune responses against bacteria, viruses, fungi, and cancer cells (Bansal, Henao-Meja, & Simmons, 2018; Nowak, Jablonska, & Ratajczak-Wrona, 2019). In one rodent model, exposure of pregnant animals to BPA modulated the innate immunity of their offspring against the influenza virus type A (Roy, Bauer, & Lawrence, 2012). Therefore in writing during the global COVID-19 pandemic, it may also be pertinent to raise the question as to whether compromise of the immune system by exposure to EDCs, such as BPA and phthalates, could have impacted also on susceptibility to infection by SARS-CoV-2 (COVID-19) coronavirus, and whether differing previous EDC exposures could have contributed to the variation in severity of symptoms and outcomes for individual people.

6 | FINAL COMMENTS AND DATA GAPS

Plastics are now ubiquitous in both our indoor and outdoor environments, and the ability of chemical additives to leach out with age and heat is a particular problem when these chemicals can interfere with hormonal systems, which are fundamental to the regulation of the human body. Of course, like all things, our bodies can tolerate small levels of such pollutants, but the problems arise as use increases and exposures rise. And furthermore, this is compounded by the ability of multiple pollutant chemicals to act by similar mechanisms, thus enabling the BPA and phthalates to feed into an even bigger picture of endocrine disruption resulting from exposures to mixtures of low doses of many EDCs over the long-term (Darbre, 2015). One solution would certainly be to replace the BPA and phthalate esters with other compounds lacking the endocrine-disrupting properties, but so far efforts at finding substitutes have not proved easy as illustrated by the adverse properties being uncovered for other bisphenol substitutes. With our increasing dependence on plastic materials, much needs to be done in educating consumers in ways of avoiding or reducing their exposures on a daily basis.

Although much has been learned over the past few decades concerning potential consequences of exposure to EDCs such as BPA and phthalate esters, more definitive research is needed to give greater clarity of specific associations and particularly in the assessment of mixtures. Adverse effects seem now unlikely to result from single sources or even single chemicals but rather from long-term low-dose mixtures of chemicals with additive, overlapping, or complementary mechanisms of action. With this in mind, it is all the more imperative to continue the assessment of the contribution of BPA and phthalate exposures to human health problems and to determine the underlying mechanisms of individual susceptibility.

CONFLICT OF INTEREST

The author declares no conflicts of interest.

DATA AVAILABILITY STATEMENT

This is a review/commentary and contains no original data.

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