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Critical Review

An overview of the occurrence, fate, and human risks of the bisphenol-A present in plastic materials, components, and products

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Abstract

With over 95% of bisphenol-A (BPA) used in the production of polycarbonate (PC) and epoxy resins, termed here as BPA-based plastic materials, components, and products (MCPs), an investigation of human exposure to BPA over the whole lifecycle of BPA-based plastic MCPs is necessary. This mini-review unpacks the implications arising from the long-term human exposure to BPA and its potential accumulation across the lifecycle of BPA-based plastics (production, use, and management). This investigation is timely and necessary in promoting a sustainable circular economy model. Restrictions of BPA in the form of bans and safety standards are often specific to products, while safety limits rely on traditional toxicological and biomonitoring methods that may underestimate human health implications and therefore the "safety" of BPA exposure. Controversies in regards to the: (a) dose–response curves; (b) the complexity of sources, release mechanisms, and pathways of exposure; and/or (c) the quality and reliability of toxicological studies, appear to currently stifle progress toward the regulation of BPA-based plastic MCPs. Due to the abundance of BPA in our MCPs production, consumption, and management systems, there is partial and inadequate evidence on the contribution of BPA-based plastic MCPs to human exposure to BPA. Yet, the production, use, and end-of-life management of plastic MCPs constitute the most critical BPA source and potential exposure pathways that require further investigation. Active collaboration among risk assessors, government, policy-makers, and researchers is needed to explore the impacts of BPA in the long term and introduce restrictions to BPA-based MCPs. *Integr Environ Assess Manag* 2022;00:1–18. © SETAC

KEYWORDS: Bisphenol-A (BPA), Endocrine-disrupting chemicals, Health effects, Plastic waste, Plastics

INTRODUCTION

Plastic is an indispensable material in the modern world, providing several benefits to the society global economy and environment in specific stages of the value chain, for example, lightweight vehicles in the automotive sector at the stage of use, or lightweight food packaging in the food sector at the stage of distribution (British Plastics Federation [BPF], 2021a). The combination of versatility, durability, and cost-effectiveness has made plastics ubiquitous in many applications of everyday life, which include food and beverage containers, adhesives, synthetic fibers, medical devices, coatings, packaging, construction, clothing, and numerous other goods (Hahladakis, 2020; PlasticsEurope, 2016).

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During the manufacturing process of myriads of plastic materials, components, and products (MCPs) produced worldwide, chemical substances are intentionally added (i.e., catalysts, additives, and monomers), to initiate the polymerization process and enhance the properties and functionalities of plastic MCPs. These are known as *intentionally added substances* (IAS). In addition to IAS, *non-intentionally added substances* (NIAS) may be present in plastic MCPs in the form of impurities and degradation products. The list of both IAS and NIAS present in the manufacturing process is long, and many of these are known to be chemicals of concern (Groh et al., 2019; Leslie et al., 2016; Thompson et al., 2009; Wagner & Schlummer, 2020). These chemicals can migrate from plastics to a surrounding medium during their lifecycle, presenting many short- and long-term human and environmental hazards (Hahladakis et al., 2018). The release, migration, and fate of some prevalent IAS and NIAS from several plastic MCPs have been comprehensively reviewed at all stages of their lifecycle (Bhunia et al., 2013; Hahladakis et al., 2018; Wrona & Nerín, 2020).

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A particularly challenging chemical substance of concern often found in plastics is 2,2-bis (4-hydroxyphenyl) propane, widely known by its commercial name, bisphenol-A (BPA) (Almeida et al., 2018; Hahladakis et al., 2018; Vogel, 2009). Bisphenol-A is an industrial, synthetic compound used in the production of polymers since the 1950s (Vogel, 2009), and a proven endocrine-disrupting chemical (EDC), with a regulatory safety standard (tolerable daily intake [TDI]: 4 μg/kg body weight per day as referred to EU 2018/282 [EU 2018/213, 2018], which is currently under revision [European Commission, 2021]). Exposure to BPA at levels higher than the TDI may lead to adverse health impacts (Vogel, 2009). Notwithstanding the implicated risks, the use of BPA is allowed in many countries around the globe, including the European Union (EU), the United States, and Southeast Asian countries (Almeida et al., 2018). The worldwide production of BPA surpassed 6.5 million tons (Mt) in 2012 (Wang et al., 2016) and reached 7.7 Mt in 2015 (Almeida et al., 2018). In 2019, the global production of BPA reached >8 Mt (Galloway et al., 2019).

Around 30% of BPA's volume produced globally is used to make epoxy resins (Hermabessiere et al., 2017), 65% is used in the manufacture of polycarbonate (PC) via the polymerization process (Hahladakis et al., 2018; Hermabessiere et al., 2017; Konieczna et al., 2015; Rochester, 2013), and the remaining 5% is used in other applications. Polycarbonate is a thermoplastic polymer that, due to its strength and scratch resistance, can be used in engineering applications as a steel replacement, or as a glass replacement used in electronics (e.g., mobile phone screen protectors [Saad & Jwad, 2018]), safety equipment, automobiles, and a range of consumers items, such as contact lenses and glasses, infant feeding bottles, compact discs, digital video discs, cosmetics, toys, and food containers including reusable beverage bottles (Almeida et al., 2018; Chang et al., 2012; Vogel, 2009). Epoxy resins are used as protective coatings for metal equipment, casings and pipes, food can linings, floor coverings (plastic- and wood-based tiles), wood-based products, and as a composite in paints (Hahladakis et al., 2018; Konieczna et al., 2015; Rochester, 2013; Shelby, 2008; Włodarczyk, 2015); they offer high-thermal and fungicidal activity (antifungal agent) (ANSES, 2011) and are also used as a sealant in dentistry due to their anti-inflammatory properties (Kitamura et al., 2002).

Current studies have looked at the presence of BPA in plastic MCPs other than PC and epoxy resins, focusing particularly on polyvinyl chloride (PVC), where BPA is an IAS (Wang et al., 2021), and in polyethylene terephthalate (PET), where BPA is found as a NIAS (Dreolin et al., 2019). Furthermore, BPA in protective glasses, infant incubators, and thermal paper has also been investigated (Ćwiek-Ludwicka, 2015; Huang et al., 2012; Shelby, 2008; Žalmanová et al., 2016). Nevertheless, insights on human exposure to BPA via interaction with the plastic MCPs and the synergistic relationship of BPA with other chemical substances in MCPs are limited. This is an important blind spot in the plastics system (i.e., all stages of plastic MCPs value chain—from feedstock extraction to end-of-life management—including materials, structures, processes, activities, and interactions [Iacovidou et al., 2020a]) that needs to be explored.

To contribute to this knowledge gap, this study retraces the theoretical and experimental evidence on the health risks and implications of long-term human exposure to BPA via the use of polymer-based MCPs, with emphasis on PC and epoxy resins (mainly used in the manufacture of sealers and coatings), which are termed here as BPA-based plastic MCPs. Specifically, the study aims to unpack the implications arising from the long-term human exposure to BPA and potential (bio)accumulation across the lifecycle of BPA-based MCPs, looking at their production, use, and management, including also limited insights on PVC and PET where BPA is used or detected, and which are intertwined with the BPA-based MCPs lifecycle system (i.e., production–consumption–management).

The "Methodology" section provides a short methodological description of the work that has been carried out, and the section "Properties, occurrence, and regulations regarding the use of BPA" provd an overview of BPA's properties, occurrence in our system, and measures that regulate its manufacture and use in plastic MCPs. Then, the "Sources and pathways: Human exposure to BPA via the lifecycle production–use–management of BPA-based plastic MCPs" section explains the potential human exposure to BPA via the lifecycle of BPA-based plastic MCPs. This section focuses on prevalent sources, mechanisms of release, and exposure pathways (via airways, or through ingestion of contaminated food and beverage) and generates insights on human health implications arising from long-term exposure to BPA. The section "Human risks and implications from exposure to BPA" provides insights on the risks of exposure to BPA to children and adults. Finally, the "Conclusions" provides the main insights generated in this study and recommendations for future research.

METHODOLOGY

A narrative review of the occurrence and human hazards of BPA-based plastic MCPs across all stages of lifecycle was carried out. Despite the lack of acknowledged guidelines for narrative reviews, this section provides a general approach for conducting the literature search. The literature strategy of this work is based on three key research questions related to (i) the main sources of BPA in plastic MCPs, (ii) exposure routes that could lead to BPA uptake across each stage of plastic MCPs lifecycle, and (iii) related adverse health effects associated with human exposure to BPA.

Several combinations of key terms were searched in the scientific databases of Scopus, Web of Science, and Google Scholar, such as "Bisphenol A," "BPA," "bioaccumulation," "health impact," "exposure," "biomonitoring," "epoxy resins," "polycarbonate," "plastics," "lifecycle" and its stages, that is, "production," "use," "consumption," "plastic management."

We set two main eligibility criteria to include only studies that focused on: (i) BPA contained in plastic MCPs, and (ii)

health implications arising from the continuous exposure to BPA-based plastic MCPs.

PROPERTIES, OCCURRENCE, AND REGULATIONS REGARDING THE USE OF BPA

Physicochemical properties and occurrence

Bisphenol-A is a synthetic, organic compound of the wider "family" group of diphenylmethane derivatives and bisphenols (BPs) (Cimmino et al., 2020). It consists of two phenolic groups and an acetone molecule that is condensed under acidic or basic conditions, at room temperature, to formulate a white crystalline solid (Almeida et al., 2018). The compound produced consists of two phenolic rings that are linked by a methyl bridge, attached to two functional methyl groups (see Figure 1) (Kang et al., 2006; Michałowicz, 2014; Proshad et al., 2018).

Bisphenol-A has fairly low solubility in water and volatility, with a relatively high melting point (at ca 156 °C), a high boiling point (at 360.5 °C atmospheric pressure), and an octanol–water partition coefficient (K_{ow}) of 3.6 ± 0.3 (Borrirukwisitsak et al., 2012). K_{ow} is often used as an indicator of bioaccumulation in marine organisms; a high log K_{ow} implies lipophilicity and this raises the chance that this molecule will accrue in organisms (Hermabessiere et al., 2017). Bisphenol-A also has a high reactivity due to its hydroxyl groups, which enables BPA to convert into ethers, esters, and salts (Almeida et al., 2018). The majority of BPA's physicochemical properties can be found in Table 1.

Historically, the bioaccumulation potential of BPA is considered to be moderate, although the evidence on the degree to which BPA accumulates in the human body is limited (Corrales et al., 2015). There has been little concern about bioaccumulation assuming that BPA is rapidly metabolized and excreted from the body, but research evidence supports that BPA likely bioaccumulates to some degree in human body compartments with long elimination times (Genuis et al., 2012; Stahlhut et al., 2009). Despite its low half-life and moderate bioaccumulation potential, BPA has been detected in almost all environmental media (e.g., soil, water, and air), as well as in humans. This has raised concerns regarding its short- and long-term human health implications (Im & Löffler, 2016). Indicative concentrations of BPA detected in different types of effluents and natural ecosystems can be found in Im and Löffler (2016).

In the air, the phototransformation of BPA occurs rapidly and, due to its chemical nature, hydrolysis may take place under irregular ambient conditions (Ajong et al., 2020). In soil, BPA is almost immobile due to its high soil–water partitioning coefficient of 314–1524 and can formulate nonextractable residues in a short time (approximately three days) (Fent et al., 2003). Ionization of BPA can occur under extreme pH soil conditions, a fact that could potentially cause high leaching or percolation to groundwater (Zeng et al., 2006). In addition, it is not strongly bound to soil's organic carbon (Höllrigl-Rosta et al., 2003). In water, BPA was found to biodegrade, and at a fast rate (Ying & Kookana, 2005).

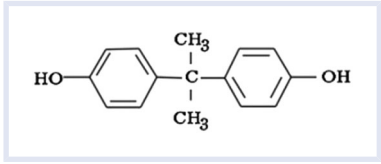

FIGURE 1 Chemical structure of bisphenol-A (BPA)

Regulations

According to the US Food and Drug Administration (FDA), the 1958 Federal Food, Drug and Cosmetics Act has prohibited chemicals that could contaminate food at all stages (e.g., production, processing, packaging, and distribution). Early research considered that BPA does not raise any significant concern over toxicity risk and food migration (Vogel, 2009). As with most chemicals introduced in our system (i.e., production, consumption, and management), BPA's safety had been perceived as specified based on the presumption that its toxicity effect at low concentrations is considered to be marginal (Vogel, 2009). As a result, the FDA considered that current levels of exposure to BPA from uses of food contact materials have an adequate margin of safety (U.S. FDA, 2008). It is only recently that toxicological studies have provided insights on the adverse health effects of BPA at low concentrations, which call for further BPA restrictions.

According to the Delaney Clause in the Federal Food, Drug and Cosmetics Act enacted in 1958 as a response to concerns about the safety of food additives, carcinogens were rendered as "hazards substance per se," regardless of their dose and toxicity level, and would need to be banned. However, BPA's carcinogenicity was examined many years later. Specifically, a study on the carcinogenicity of BPA began in 1977 and was carried out by the National Cancer Institute (NCI). The study was performed according to the standard protocol for assessing cancer risk; however, during the study, the "carcinogenesis" assessment responsibility was transferred from the NCI to the National Toxicology Program (NTP). During this transfer, the General Accounting Office (GAO) was asked to perform an investigation on the quality of the private laboratories involved in research regarding the Carcinogenesis Bioassay Program; GAO's investigation found extensive fraudulent practices, quality assurance and quality control (QC) issues, and poor maintenance and pathology practices, which could have produced ambiguous research results. Despite GAO's inspection, NCI and NTP did not reevaluate the carcinogenicity of BPA with the latter reporting that there is "no convincing evidence" for BPA's carcinogenicity (see details in Vogel, 2009; Huang et al., 2012, 2018).

In 2012, a collaborative research program was launched by FDA, NTP, and the US National Institute of Environmental Health and Sciences—called the Consortium Linking Academic and Regulatory Insights on BPA Toxicity (CLARITY-BPA). The scope of CLARITY-BPA was to address knowledge gaps on the safety of BPA by informing risk

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TABLE 1 Physicochemical properties of bisphenol-A (BPA)

Property	Value
Molecular type	$C_{15}H_{16}O_2$
m	228.29
ρ	1.17 g/ml (average value), at 20 °C–25 °C
Boiling point	360 °C at 760 mm Hg
Octanol-water partition coefficient (log K_{ow})	3.64 ± 0.32
Heat of combustion	−7.46 J/kmol
Color and form	White or creamy crystal flakes; forms prisms and needles, in acetic acid and water, respectively
Dissociation constant (pK_a)	10.29 ± 0.69
Henry constant	4.0×10^{-11} atm-cu m/mol, at 25 °C
Critical *T* and *P*	849 K and 2.93×10^6 Pa, respectively
Melting point	153 °C
Bioconcentration factor (BCF)	220–344[a], 5.1–73.4[b]
Solubility	210 mg/(average value in water), at 25 °C. Solubility increases in alcohol and acetone
Odor	Mild phenolic odor
Hydroxyl radical reaction rate constant	8.1×10^{-11} cm^3/molecule/s, at 25 °C
Vapor pressure	4.0×10^{-8} mm Hg, at 25 °C
Half-life (day)	38 (in water), 75 (in soil), 340 (in sediment), and 0.2 (on air)

[a]Values reported in the USEPA's EPI Suite program.
[b]Values reported in the US NIHHS Data Bank TOXNET, and represent findings for aquatic organisms reported in scientific articles.

assessment; setting QC processes; and shedding light on doses, endpoints, and methods (Schug et al., 2013). Specifically, CLARITY-BPA performed a regulatory-style study carried out by academic laboratories using identical animal strains and experimental conditions indicating that developmental exposure to BPA at low doses that do not exceed regulatory limits considered "safe" can contribute to brain and behavioral change (Patisaul, 2020).

In 2012, the FDA amended its food additive regulations, and, particularly, removed those related to the use of PC in baby bottles, sippy cups, and infant food packaging products, following a petition by the American Chemistry Council that claimed the permanent and complete abandonment of PC use in making these products. It is worth noting that this amendment was not made based on safety but on the abandonment clause, with the American Chemistry Council, which represents chemicals manufacturers, insisting there was no longer a need for a revision on the FDA's safety assessment regarding the presence of BPA in food packaging (Arnich et al., 2011). These actions highlight the need to revise the risk assessment for vulnerable populations (e.g., children, pregnant women).

In Europe, there is an ongoing debate on the use of BPA. Initially, use of BPA was regulated by the European Commission (EC) Directive 72/2002 on the manufacture of plastic materials oriented for food contact, which set its specific migration limit (SML) at 3 mg/kg of food. This SML was revised and amended to 0.6 mg/kg in the EC Regulation No. 10/2011 (January 2011) on plastics oriented for food contact (Arnich et al., 2011; European Commission, 2011a). In EU Regulation No. 10/2011, BPA was banned from plastic baby bottles made from PC, based on the precautionary principle (EU Regulation No. 321/2011) (Almeida et al., 2018). In 2015, the European Food Safety Authority (EFSA) published a reevaluation of BPA exposure and toxicity reducing the TDI for BPA from 50 to 4 μg/kg body weight per day (EFSA, 2015), and in 2017 developed a hazard assessment protocol to ensure the continuous reassessment of BPA's safety. Four years later (in 2021) EFSA published a scientific opinion based on recent evidence on BPA toxicity, asserting that the TDI of BPA in foodstuffs should be lowered 100 000 times more, from 4 to 0.04 ng/kg body weight per day (EFSA, 2021). This recent EFSA opinion stresses the adverse effects of BPA on the immune system, especially in animals (EFSA, 2021), and highlights the importance of continuous reassessment of toxicity and safety limits. The rapid evolution of the European legislation on the use and regulation of BPA presented in Table 2 comes as no

TABLE 2 European Union (EU) legislation regarding the use of bisphenol-A (BPA) in plastic materials, components, and products (MCPs), and current permitted specific migration limits (SMLs)

Legislation	Scope	BPA SML	Date in effect	References
Directive 2002/72/EC	Authorized the use of BPA as a monomer for manufacturing plastics that were oriented for food contact materials. This was by the Scientific Committee on Food (SCF) and the European Food Safety Authority (EFSA).	3 mg/kg	August 2002	European Commission (2002)
Regulation (EC) No. 1935/2004	Mandated that any type of food contact material should not contain any substances that could be transferred to food, in quantities that could potentially harm human health or induce any change in the food composition. NOTE: While not directly related to BPA, this Regulation was used by the Danish and French Governments to introduce a ban on BPA used in plastic materials containing food and/or those oriented for children aged 0–3.	n/a	November 2004	European Commission (2004)
Regulation (EC) No. 1272/2008	Mandated that substances and mixtures used in products must be classified and labeled according to their human and environmental hazardousness. BPA was classified as toxic, with regards to reproduction (Category 2), with concentrations that should be smaller than the ones set for classifying mixtures that contain it as carcinogenic, mutagenic, or toxic for reproduction (CMR), namely, 5% as from 2013 and 3% as from 2015, respectively.	n/a	December 2008	European Commission (2008)
Directive 2009/48/EC	Introduced to ensure the safety of toys designed or intended for use by children under 14 years old. It set generic requirements for substances classified as CMR under the EC Regulation No. 1272/2008. Note: No specific reference to BPA.	n/a	June 2009	European Commission (2009)
Directive 2011/8/EU	**Amended Directive 2002/72/EC** introduced a prohibition on the import, manufacture, and market placing of baby bottles containing BPA (March 1 and June 1, respectively).	n/a	March/June 2011	European Commission (2011b)
Regulation (EU) No. 10/2011	Limited the use of BPA on plastic materials oriented for food contact; however, it did not contain any BPA restrictions that were included in the 2002/72/EC Directive by the 2011/8/EU Directive.	0.6 mg/kg	May 2011	European Commission (2011c)
Regulation (EU) No. 321/2011	**Amended Regulation (EU) No. 10/2011** included the BPA restrictions introduced in the 2002/72/EC Directive by Directive 2011/8/EU in Annex I of EU No 10/2011, column 10, that is "not to be used in manufacturing PC infant feeding bottles."	0.6 mg/kg	May 2011	European Commission (2011d)
Regulation (EU) No. 609/2013	Laid down the rules on the use of chemical substances on food for infants and youngsters, for medical purposes, and as a diet, replacement to control weight.	n/a		European Commission (2013)
Directive 2014/81/EU	**Amended Directive 2009/48/EC**, Appendix C of Annex II incorporated an SML of BPA found in toys oriented for children up to 3 years old, and in any toys to be placed in the mouth irrespective of age.	0.1 mg/l	December 2015	European Commission (2014)

(*Continued*)

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Table 2 (*Continued*)

Legislation	Scope	BPA SML	Date in effect	References
Directive (EU) 2017/898	**Amended Directive 2009/48/EC**, Appendix C of Annex II again referred to the SML set on the BPA found in toys for children up to 3 years old, and in any toys intended to be placed in the mouth irrespective of age.	≤0.04 mg/l	January 2020	European Commission (2017)
Regulation (EU) 2018/213	**Amended Regulation (EC) No. 10/2011** referred to the SML of BPA found in plastic materials intended for food contact.	≤0.05 mg/kg	November 2018	European Commission (2018)
	It introduced a BPA SML for food used in varnished or coated products.[a]	≤0.05 mg/kg		
	It banned BPA use in PC beverage bottles, cups, and bottles (intended for babies and youngsters), as set in the EU No. 609/2013, and other varnished or coated food contact materials for youngsters under the EU 609/2013.	Prohibited		

[a]"Varnishes" or "coatings" refers to materials consisting of one or multiple nonself-supporting layer(s) manufactured via the use of BPA, applied on the material to provide specific properties on it or to enhance its technical characteristics and performance.

surprise, and the future may bring further advancements and reforms.

In 2018, the EC amended the BPA SML in varnishes and coatings, mentioned in Regulation (EU) 2018/213, and further restricted the presence of BPA in certain food-contact materials. They reduced the SML from 0.6 to 0.05 mg/kg for BPA present in varnishes and coatings and expanded its ban in the PC infant feeding bottles and cups (EU 2018/213, 2018). The EU Regulation 2018/213 also specifies that a written declaration of compliance should cover all stages (manufacture, processing, and distribution), ensuring that coated or varnished materials do not contain BPA above the permitted limit (see Table 2). These regulations have led to the use of BPA substitutes, with bisphenol-F (BPF) and bisphenol-S (BPS) being the most prevalent. The structure of BPF and BPS is similar to BPA, which infers that their application might induce similar hazards to BPA (Moon, 2019). Moreover, there is a wide misinterpretation in the use of BPF and BPS that they are safe because they are BPA-free, while biomonitoring data on these bisphenol analogs is sparse (Moon, 2019).

Despite the regulatory bans, the global market of BPA is expected to witness an upward trend within the period 2021–2026 attaining a value of about USD 10.92 billion in 2020 and reaching a value of 30.62 USD billion by 2026 (Research and Markets, 2021b). This evidence suggests that the BPA market is expected to grow at a Compound Annual Growth Rate (CAGR) of 7.8% within this forecast period, although concerns over the adverse effect of the use of BPA by the regulatory and scientific community may lead to a lower growth rate (ca. 4.5% CAGR) (Research and Markets, 2021a). The increasing demand for BPA by several end-users is mainly driven by the automotive industry (e.g., manufacture of automobile headlights, bumpers, and dashboards) and manufacture of machinery and electronic components (Research and Markets, 2021b). The main reason BPA is still widely used is due to the misalignment between policies, technological innovation, and economic interests of the BPA and plastics production industries (Mandel et al., 2020), and scientific evidence on the implications of BPA, mainly controlled by the interests of powerful stakeholders (i.e., BPA producers and brand owners of plastic MCPs) (Gerassimidou et al., 2021).

The lack of robust evidence that incriminates BPA's harmful nature, due to increased reliance on traditional endpoints of toxicity formulated based on traditional toxicological methods employed over 50 years ago (Warner & Flaws, 2018), has promoted the use of BPA by the BPA-based plastic MCPs production industry. Additionally, regulatory agencies continue to claim that the regulatory limits for BPA exposure are safe relying on four misguided assumptions: (i) dose–response curves are monotonic; (ii) below a threshold limit no effects are induced; (iii) both sexes (female, male) respond similarly to BPA exposure; and (iv) only toxicological guideline studies—that may borrow control data from prior studies—are valid (vom Saal & Vandenberg, 2020). Historically, these traditional methods

were carried out under high-dose testing taking the assumption of a linear dose–response curve (Warner & Flaws, 2018). However, scientific evidence suggests that these dose–response curves can be nonmonotonic and therefore adverse health effects from high-dose testing cannot be extrapolated to low doses (Kumar et al., 2020). A recent study as part of CLARITY-BPA investigated the effects of BPA on the developing rat mammary gland under low and high doses revealing the nonmonotonicity of the BPA dose–response curve (Montévil et al., 2020). This means that low-dose exposure to EDCs (i.e., BPA) can cause adverse effects on humans, hence setting safe limits for BPA is complex and currently deficient (Kumar et al., 2020).

Although EC has set maximum regulatory levels for several food contaminants following good practices at all stages of the food chain based on as low as reasonably achievable (ALARA) principle (European Commission, 2006), the implementation of the ALARA principle has not yet been implemented for well-established contaminants such as BPA. So far, only the Canadian government has recognized the importance of implementing the ALARA principle to increase efforts for limiting human exposure to BPA (Legeay & Faure, 2017). The CLARITY-BPA project highlighted that the no observed effect concentration (NOEC) for BPA needs to be revised by regulators (Vandenberg et al., 2019). This statement has emerged from the fact that BPA exposure was found to induce statistically significant adverse effects (i.e., endocrine, reproductive, neurobiological, and immune system impairments) at low doses (2.5 μg/kg body weight per day) far below the reference dose (50 μg/kg body weight per day) (Vandenberg et al., 2019). An active collaboration among risk assessors, government, policy-makers, and researchers could reinforce efforts to further explore the impacts of BPA and introduce restrictions to other plastic MCPs (Warner & Flaws, 2018).

SOURCES AND PATHWAYS: HUMAN EXPOSURE TO BPA VIA THE LIFECYCLE PRODUCTION–USE–MANAGEMENT OF BPA-BASED PLASTIC MCPS

Understanding the mechanisms by which the migration and release of BPA occur is a complex task. It depends on many factors, including the form in which the polymer is used (rigid, flexible, coating), the application in which it is used, polymer aging (Benhamada et al., 2016), levels of BPA in the final components and products, as well as the environmental conditions and the wear and tear processes.

The dietary intake of BPA (e.g., via BPA leaching from can surfaces, plastic containers) (Geens et al., 2011; Vandenberg et al., 2007) is regarded as the main exposure route for BPA, also known as *dietary exposure*. For example, Hoekstra and Simoneau (2013) suggested that BPA could leach from PC used in food packaging applications via two mechanisms: (1) diffusion of any residual BPA that exists in PC (after the manufacturing stage), and (2) hydrolysis of the PC component and/or product catalyzed by hydroxide in contact with aqueous food and simulants. The first mechanism (diffusion) applies to both dry and liquid foods, whereas the second mechanism (hydrolysis) applies only to liquid foods. In both cases, any BPA release from the PC container into food and/or beverage depends on: (a) contact time between packaging and food, (b) temperature (higher temperatures are associated with higher migration rates), (c) food and/or beverage composition (fatty foods are associated with increased migration of lipophilic molecules), and (d) type of contact between food and beverage and packaging (Almeida et al., 2018; Hoekstra & Simoneau, 2013).

A few biomonitoring studies suggest that there might be several nondietary exposure routes for BPA, supported by observations of BPA levels in humans that reached a plateau during an 8.524-h fasting interval (Stahlhut et al., 2009; Vandenberg et al., 2010). Nondietary (ingestion) exposure could be attributed to BPA absorption through the skin via *transdermal exposure* (Zalko et al., 2011), which refers to the frequent and continuous contact with PC products that may release BPA, or via the BPA *inhalation* of air and dust. Experiments of transdermal exposure to BPA were shown to result in the biotransformation of BPA, indicating that skin contact could be an additional factor in human exposure to BPA, particularly when contact occurs with the free monomer (Zalko et al., 2011). Inhalation of BPA via air and dust, especially in indoor environments or inside a room or vehicle, greenhouse, and so forth, is considered a possible exposure route, though its contribution to the overall BPA exposure is not clear yet. In the indoor air environment, considerable levels of BPA are reported due to its tendency to bind to dust particles (Vasiljevic & Harner, 2021). A recent review study found that the levels of BPA in the indoor air environment are considerably high and comparable to the levels of BPA observed in the outdoor ambient air, which may be linked to reduced ventilation and reliance on air conditioning systems (Vasiljevic & Harner, 2021). Another plausible exposure route was suggested by Geens et al. (2011), who observed that the distribution of BPA to fat tissues or tissues with increased fat content may lead to a gradual release of BPA (Geens et al., 2011).

Table 3 outlines the main sources of BPA categorized according to the classification of the most prevalent uses of PC and epoxy resins in plastic applications outlined by PlasticsEurope, and their potential exposure routes. It must be emphasized that besides ingestion, that is, dietary exposure to BPA, which has been well documented in the global literature, the rest of the exposure pathways (e.g., transdermal and inhalation) outlined in Table 3 are mainly hypothetical.

The information presented in Table 3 is indicative of the potential exposure pathways to BPA and highlights the importance of gaining a better understanding of the impact of nonoral exposure routes. By themselves, these exposure routes may lead to negligible effects, yet the cumulative behavior of all exposure routes could contribute to important health implications.

In addition to the exposure pathways outlined in Table 3, there are also less-discussed exposure pathways in the outdoor environment that may require consideration.

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Bisphenol-A has been detected in all environmental media, for example, air, soil, water, and landfill leachate, at concentrations ranging at levels between 5 and 1950 ng/l (Li et al., 2020; Schug & Birnbaum, 2014; Zhao et al., 2019). A detailed description and exploration of the environmental impacts arising from these potential pathways fall outside the scope of this study.

The following subsections outline the occurrence of BPA in different environmental media at the production, use/consumption, and management stages of the plastic MCPs, some of which are listed in Table 3.

Production stage

At its production stage, BPA can be released in the indoor atmosphere of the plastic resins and plastic manufacturing plants, and variable amounts of BPA may be transported from the indoor to the outdoor environment. When released into the atmosphere, BPA—due to its low volatility—is expected to enter the other environmental compartments (i.e., water, air, soil) via a range of mechanisms, thereby posing several risks to humans and ecological health (Kang et al., 2006). The transport of indoor BPA to the outdoor environment and the resulting concentrations in the nearby environmental compartments must be determined to gain a better insight into the potential environmental exposures.

As the production and demand for BPA have increased over the years, so has the number of people who are occupationally exposed to the compound. Employees who spend most of their time in the indoor environment, where BPA is produced and used, could be severely affected by BPA. Although data are not readily available to extract robust conclusions, a few studies reported that BPA levels in air (outdoor, indoor, workplace offices, and occupational exposure during work in plastics industries) must be closely monitored to ensure the safety of workers in the plastics production industry (Berkner et al., 2004; Fu & Kawamura, 2010; He et al., 2009; Rudel et al., 2011; Wilson et al., 2007). The maximum reported BPA indoor air concentrations, measured at resin factories in China, were >50 000 ng/m^3, whereas the lowest (<100 ng/m^3) were found in commercial buildings and residencies (Rudel et al., 2011; Wilson et al., 2007). Concentration levels in the production facilities of BPA and plastics need to be closely monitored to ensure the ventilation rate and the rate of removal in the building function properly. This is necessary to create the right preventive measures when needed (Ribeiro et al., 2017).

Consumption and use stage

Among the various applications presented in Table 3, the use of plastic food packaging as a source of human exposure to BPA (via ingestion) has gained increased research attention. Interestingly, a recent study determined the levels of BPA in urine in an Italian pediatric cohort under a diet regimen based on reduced consumption of food contained in plastic packaging over six months (at three time points) and assessed the relationship of BPA concentrations in urine with food plastic packaging consumption (Sessa et al., 2021). Results showed a statistically significant difference ($p < 0.05$) assessing both inter- (reduced consumption of food in plastic-packaging versus unmodified meal habits) and intra- (among three testing times) groups, indicating that a plastic-free lifestyle may lead to reduced levels of BPA in urine (Sessa et al., 2021).

However, the level at which a plastic-free lifestyle can reduce human exposure to BPA compared to other sources remains underexplored. Recent literature findings indicate that BPA ubiquity in the food production chain goes beyond the use of packaging materials (González et al., 2020). Nonetheless, the consumption of canned foods is widely accepted as one of the primary routes (dietary) of exposure to BPA (Cao et al., 2021; Geens et al., 2012b). For example, Khan et al. (2020) determined the occurrence of BPA in carbonated beverage cans from the Saudi Arabian market and found that these may be a significant source of dietary exposure to BPA (measured at 0.64–11.41 μg/l beverage). Glass and PET beverage bottles considered to be BPA-free packaging materials were also analyzed in the same study and found that BPA concentrations in glass-bottled beverages were surprisingly high (1.92–29.56 μg/l beverage); higher than in cans and PET bottles (0.37–21.83 μg/l beverage) (Khan et al., 2020). In addition, González et al. (2020) estimated that dietary intake of BPA through the consumption of canned and noncanned foodstuffs was 24.9 and 3.11 μg/day, respectively, demonstrating that epoxy resins used as a coating in canned foodstuffs can contribute substantially to the BPA-related human exposure. Recent scientific evidence showed that the detection rate of BPA in canned food exceeds 90% (Cao et al., 2021; González et al., 2020), while in noncanned food is considerably lower (36%; González et al., 2020). Several researchers have observed a 1200% increase in BPA concentrations in urine after the consumption of a canned soup over five days (Carwile et al., 2011; Ye et al., 2015), and any diet modification that excluded canned or packaged foods exhibited reduced urinary BPA concentrations (Rudel et al., 2011). The sterilization temperature of the food can and the acidity of the food contained seem to be the most crucial factors that determine the overall BPA migration rate (Goodson et al., 2004).

Laboratory studies have concluded that active BPA in PC plastic components and products can undergo incomplete degradation and depolymerization over time and continuous use can cause the BPA monomers to leach out and/or migrate (e.g., reusable containers, PC water bottles, drink dispensers, and children's plastic toys) (Hermabessiere et al., 2017; Viñas et al., 2010). This may also be caused by cleaning processes employed to make reusable plastic products hygienic again including pH changes or high temperatures, such as sterilizing, boiling, autoclaving, and microwaving procedures (Lim et al., 2009; Nam et al., 2010; Pivnenko et al., 2016a, 2016b). For example, Nam et al. (2010) reported that alkaline pH and high temperatures (>80 °C) during sterilization of PC products can cause hydrolysis of carbonate linkage and increase d-spacing of PC,

TABLE 3 List of typical and most prevalent sources of bisphenol-A (BPA) in BPA-based plastic materials, components, and products (MCPs) and possible exposure pathway categorized based on the applications outlined by PlasticsEurope[a]

Form	Application	Production of	Potential exposure route at use stage
PC	Packaging	Infant bottles, plastic food and beverage containers, reusable plastic bottles, containers for microwave heating, reusable dishes and bowls, reusable cups, plastic reusable utensils	Ingestion; transdermal
	Building and construction	Drinking water pipes, roofing, glazing, roof lights, facades, security windows, shelters	Ingestion (water pipes); inhalation via air and dust
	Electrical and electronic equipment (EEE)	Refrigerators, food mixers, coffee machines, washing machines, electric kettles, electrical razors, cell phones and/or smartphones, hairdryers, distributor boxes, plugs and plug connectors, fax machines, screen protectors	Ingestion (e.g., kettles, food mixers); transdermal; inhalation (e.g., hairdryers)
	Automotive and transport	Rear and fixed side windows, bumpers, dashboards, road signs, protective paneling	Transdermal (car interior); inhalation (car interior)
	Agriculture	Plastic sheets for greenhouses	Inhalation (occupational only); ingestion (via food chain)
	Healthcare	Contact lenses, eyeglass lenses, tube connections, blood oxygenators, dialysis equipment, inhalers, humidifiers, newborn incubators	Transdermal; inhalation
	Sports, leisure, and other applications	Children's toys, sports equipment (e.g., helmets), safety goggles, musical instrument mouthpieces, sunglasses, compact discs, digital video discs, humidifiers, large volume water bottles and dispensers, face shields	Ingestion (e.g., chew toys, mouthpieces for musical instruments); transdermal; inhalation (via wear and tear)
Epoxy resins	Packaging	The inner lining of metal food cans and beverage containers	Ingestion
	Building and construction	Protective coating on drinking water distribution pipes, metal water tanks, powder and coil coating of construction panels, and steel furniture	Ingestion; transdermal
	Automotive and transport	Powder coating on automotive parts	Inhalation; transdermal
	EEE	Encapsulation of electronic parts, printed circuit boards, and coil coating on electronic appliances	Inhalation; transdermal
	Agriculture	–	–
	Healthcare	Dental sealants and composites	Ingestion; transdermal
	Sports, leisure, and other applications	Coatings on digital video discs, compact discs (and their plastic cases) and sports equipment, and coil coating of furniture	Transdermal; inhalation

Adapted by Geens et al. (2011).
[a]Besides the ingestion exposure route for which evidence exists, the rest of the exposure pathways are mainly hypothetical as evidence is inadequate to make any assertions.

resulting in increased levels of BPA migration. A strong example that showcases the relevance of the above points about the BPA pathway to exposure is the use of baby bottles.

The migration of BPA from baby bottles has gained traction over the last decades as it can be an important pathway of exposure to BPA, also noted in the section "Properties, occurrence, and regulations regarding the use of BPA." Baby bottles had been found to exponentially release BPA at approximately a rate of 4.9×10^{-2} μg/kg water per time used and at a temperature range from 40 °C to 100 °C (Nam et al., 2010). Specifically, the BPA concentration detected in brand new baby bottles ranged from 0.03 μg/kg at 40 °C to 0.13 μg/kg water at 95 °C, which increased to 0.18 and 18.47 μg/kg water at 40 °C and 95 °C after a six-month use period (Nam et al., 2010). Maragou et al. (2008) investigated the BPA migration from 31 unused PC baby bottles under different in-use and washing conditions, including the continuous

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washing of bottles using a dishwasher or a scrubbing brush. It was found that BPA was released from baby bottles into the water at a concentration range of 2.4–14.3 μg/kg for all samples, filled with boiled water, and left for 45 min at ambient temperature.

Cling film, or plastic wrap that is widely used to cover and protect food has also been found to result in high BPA exposure in the household. A study that examined the concentration of BPA in the cling films used in Iran, Poland, Germany, Korea, Canada, and the United States found BPA concentration levels at 3.93, 3.82, 3.30, 17.67, and 57.75 μg/l, respectively. The intake (per day) was, respectively, 0.196 for Iranian, 0.165 for German, 0.883 for Canadian, 0.191 for Polish, and 2.887 μg/kg body weight per day for American samples. The BPA content varied among samples (3.3–7.57 μg/l) and the intake was found to be between 0.165 and 20.11 μg/kg body weight per day. Regarding food grade cling film samples, the German sample was found to be the most appropriate and the American sample less suitable. In addition, the average BPA concentration level and per day intake, with all samples taken into consideration, were found to be 81.46 and 4.072 μg/kg body weight per day, respectively (Pourzamani et al., 2016).

Dental fillings consisting of epoxy resins usually contain BPA, and this can be another pathway of exposure (Bagley et al., 2021; Geens et al., 2012a; Rubin, 2011). Van Landuyt et al. (2011) concluded that an amount of BPA ranging from 0.013 to 30 mg may potentially be released within one day of implantation, although there is always the 30 mg release scenario of the short duration (Geens et al., 2012a). A more recent study evaluated the human oral exposure to BPA from dental sealants, adhesives, and restorative products reporting that the predicted exposure is relatively low in the general population (median 0.010 mg per treatment) compared to daily BPA exposure in the United States (Bagley et al., 2021).

Other sources of exposure to BPA (e.g., transdermal, inhalation of air and dust, hand-to-mouth behavior), such as medical devices, children's toys, and electrical and electronic products (Geens et al., 2012a; Vandenberg et al., 2013) are considered to contribute less to BPA exposure. The cumulative effect of exposure to BPA from these sources needs to be investigated (Healy et al., 2015). A review study reported that nearly 9.5%–33% of applied BPA dose is transferred to the human body through transdermal exposure (Healy et al., 2015).

Despite epoxy resins and PC MCPs that are made of BPA, BPA is used as an additive in PVC-containing MCPs (Wang et al., 2021). Effectively, this means that humans can also be exposed to BPA via the various applications of PVC MCPs, such as in construction (e.g., wallcoverings, flooring, and roofing membranes), healthcare (e.g., drug and medical packaging), electronics (e.g., cable insulators), automotive (covering and coatings), sports (e.g., sports equipment and clothing), and textiles, particularly in Asian countries (e.g., coated fabrics) (British Plastics Federation [BPF], 2021b). While the focus of this study is on BPA-based plastic MCPs, we cannot ignore mentioning the occurrence of BPA in PVC MCPs. In the study of Geens et al. (2012a), BPA was detected in PVC film and ranged from 43 to 483 μg/g, whereas in the work of Testai et al. (2016) BPA in PVC products was found at 68 ± 3.5, 60.5 ± 2.8, and 290.1 μg/g for wrap film, gloves, and hose, respectively. In addition, Wang et al. (2021) determined the migration of BPA from PVC films to packaged food samples in China indicating a migration range of 0.079–0.403 mg/kg in food, which was considerably higher than the European permitted SML (0.05 mg/kg), in most of the samples. Specifically, the authors highlighted that the migration of BPA was prompted by fatty foods, followed by pickled products, alcoholic beverages, and acidic foods (Wang et al., 2021).

Human exposure to BPA through the use of PVC packaging MCPs can spatially vary since PVC packaging applications are more intensely used in Asian countries (e.g., China; Du & Stern, 2021), while in Europe there has been a steady decline in PVC packaging use. This can be confirmed by a recent study (as part of the CLARITY-BPA program) in which the estimated daily BPA intake was in the range of 0.01–5 μg/kg body weight per day for adults and 0.01–13 μg/kg body weight per day for children in Western countries, while exposures in Asian countries were found to be higher (Vandenberg et al., 2019). The EU Zero-Pollution Plan and nontoxic environment initiatives have stated that the elimination of PVC MCPs to the highest possible extent is necessary for both the environment and human health; hence PVC is mainly used in the construction and agriculture sectors in Europe (Zero Waste Europe, 2021). However, significant amounts of PVC packaging MCPs are imported to Europe from China in the form of textiles and pharmaceutical blister packaging (Du & Stern, 2021). For that reason, the trading of PVC-containing plastic MCPs has to be explored in a holistic appraisal of BPA exposure.

End-of-life stage: Plastic waste management

Plastic waste management processes such as sorting, thermal treatment (i.e., incineration, gasification, and pyrolysis), and landfilling can potentially release varying amounts of BPA into the indoor and outdoor environment depending on the waste treatment option used (Morin et al., 2015). For example, the landfilling of plastic waste has been suggested to be the greatest source of BPA emissions from waste (particularly plastic and e-waste; Martínez-Ibarra et al., 2021) with a study suggesting that concentration levels of BPA were up to 17.2 mg/l in landfills leachate samples from Japan (Arp et al., 2017). Waste that is disposed of in landfills and dumpsites can degrade slowly, leading to a continuous release and/or leaching of BPA into the environment (Hahladakis et al., 2018; M'Rabet et al., 2018). Concerning this, a recent study evaluated the latest information on the ambient levels of BPA in the air at several geographical locations around the world reporting the highest concentration of BPA outdoors in a low-tech e-waste recycling site in China (1.1×10^6 pg/m^3) (Vasiljevic & Harner, 2021).

The controlled incineration of plastic waste was found to be an efficient way of reducing BPA emissions, given that the best available techniques are used in the facilities to prevent emissions. Bisphenol-A may be deposited in the slag and fly ash produced, which are further treated (Arp et al., 2017; Im & Löffler, 2016). Currently, there is a lack of insight on the fate of BPA in waste-related outputs and by-products produced and/or used in the industrial sector.

In recycling facilities, the emissions and/or release of BPA is pertinent to the type of waste and recycling process used. For example, at an e-waste recycling plant in China, the BPA levels released into the soil were greater than 100 μg/kg (Huang et al., 2014). While there is not much evidence on the recycling of PC MCPs, limited information on BPA release from other plastics, such as PET, where BPA is found as an NIAS (Dreolin et al., 2019) raises concerns. In this study, it was found that the concentration of BPA in virgin PET was significantly lower (25–432 μg/kg) than in recycled PET (394–10 120 μg/kg) insinuating that high concentrations of BPA in plastics could be related to the recycling process (Dreolin et al., 2019). Cross-contamination at the stage of production at a lower extent (e.g., by raw materials and processing equipment), and more so at the collection and reprocessing (e.g., by other postconsumer BPA-containing MCPs such as PVC and labels) stages may lead to considerable levels of BPA in PET (Dreolin et al., 2019) and can impact the quality of recycled PET, widely known as rPET (Gerassimidou et al., 2022; Schyns & Shaver, 2021). Recent review work on the identification of food contact chemicals that could be migrating from PET bottles to food samples across all stages of PET bottles' lifecycle reported that considerably higher levels of BPA may be found in the water contained in rPET bottles compared to virgin PET bottles (Gerassimidou et al., 2022). The study also concluded that the efficiency of the sorting processes (i.e., presence of impurities) and the substances (intentionally) added during the reprocessing (i.e., antioxidants, chain extenders, fillers, and plasticizers) of plastic waste can tamper with the levels of contaminants and/or side products that may be unintentionally added. Consequently, reprocessing when not properly done, may concentrate NIAS, such as BPA, which, in turn, may or may not be present in recycled plastics, hence constituting another potential source of NIAS, such as BPA (Brosché et al., 2021; Gerassimidou et al., 2022). For that reason, recycled plastic (secondary material that is entering the production stage) must be further examined on its safety credential as we are increasingly moving toward a more circular economy.

The inappropriate disposal of plastic waste due to the lack of regulations and proper infrastructure in developing countries (Vasiljevic & Harner, 2021), as well as the mismanagement and/or illegal activities (e.g., fly-tipping and open burning), including uncontrolled leachate production on landfills, disposal to dumpsites, open burning, and so forth, can be important sources of BPA release to the environment and subsequently to humans (Flint et al., 2012; Fu & Kawamura, 2010; Hahladakis, 2020; Healy et al., 2015; Teuten et al., 2009).

For example, the open burning of domestic waste and e-waste in dumpsites and other open areas (e.g., backyard open barrels of domestic waste; Sidhu et al., 2005) is considered a common practice to eliminate space and volume of waste, especially in developing countries where waste infrastructure is lacking. This constitutes an important source of BPA release in the outdoor air environment, representing an important pathway of BPA exposure via inhalation (Fu & Kawamura, 2010; Owens et al., 2007). However, due to its low volatility and short photo-oxidation half-life (<7 h) based on hydroxyl radical attack, BPA is considered to have a time-limited and almost negligible atmospheric presence (Cousins et al., 2002).

Plastic littering caused by accidental, deliberate, illegal, or uncontrolled disposal of plastics in the environment has led to widespread marine plastic pollution with questionable implications for human health (Iacovidou et al., 2020b). Polycarbonate exhibits low solvent resistance (Pascault et al., 2012) due to carbonate groups being easily hydrolyzed (Ortmann et al., 2014), which, in turn, indicates that PC disposed of in the marine environment can be slowly degraded into microplastics (Artham & Doble, 2009). The percentage contribution of PC on the plastic accumulation might be lower compared to other plastic MCPs, but it can be potentially more harmful due to the release of BPA in the marine environment (Artham & Doble, 2009). A study that examined the biofouling and microbial degradation of PC in seawater through immersion of the sample in the sea for three months and under in vitro laboratory conditions for one year reported a 9% weight loss of PC after one year of incubation and 9 μg/ml release of BPA and its oxidized products in the supernatant (Artham & Doble, 2009). The degradation of PC in the sea was mainly attributed to photo-oxidation, whereas hydrolysis was the major degradation type in the laboratory (Artham & Doble, 2009).

Marine plastic pollution is responsible for considerable levels of bioaccumulation in fresh fish tissues and seafood, hence affecting humans via the food chain (Russo et al., 2019). The continuous and ever-increasing accumulation of BPA-based plastic MCPs in the environment may in turn result in a steadily growing concentration of BPA in the aquatic environment and consequently in the food chain that may exceed the NOEC in the human body.

HUMAN RISKS AND IMPLICATIONS FROM EXPOSURE TO BPA

Humans can be affected by the production, use, and end-of-life management of BPA-based plastic MCPs, and those containing BPA intentionally (i.e., PVC) and unintentionally (i.e., PET) via a diverse set of pathways across the plastic MCPs value chain. It must be emphasized that BPA-based plastic material value chains may include components and products other than plastic-based, such as metals (food cans, pipes, water tanks) and wood (floor tiles, furniture). Exposure routes can be subcategorized into occupational hazards (prolonged or short-term exposure), intentional hazards (deliberate, frequent but controlled exposure that

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occurs mostly at the production and/or use stage), unintentional hazards (accidental release via improper waste management practices, inappropriate effluent discharges), and so forth (Abraham & Chakraborty, 2020; Hahladakis, Iacovidou, et al., 2020).

The effects of BPA on human health arising from BPA interfere with hormone synthesis, bioavailability, and molecular mechanisms of action leading to the alteration of cellular proliferation and differentiation, tissue development, and regulation of several physiological processes (Martínez-Ibarra et al., 2021). Specifically, BPA has a lipophilic nature that enables it to cross the cell membrane and accumulate in the adipose tissue (Fernandez et al., 2007). It can also mimic the actions of hormones such as estradiol, which may affect the organism's development in the early stages, bypassing the blood–brain and placental barriers (Abraham & Chakraborty, 2020).

Impact of BPA impact on children's health

Bisphenol-A can cause obesity and other conditions in children, which makes it essential to track BPA and its derivatives in the adipose tissue of children. The permissible dose of BPA that can be absorbed within 24 h is 0.05 mg/kg body weight (Włodarczyk, 2015). Trasande (2014) investigated the potential health and economic benefits of removing BPA from food uses in the United States, estimating that BPA exposure was associated with 12 404 cases of childhood obesity and 33 863 cases of adult coronary heart disease, which resulted in a social cost of 2.98 USD billion in 2008. Sensitivity analysis showed that eliminating BPA from food uses could lead to the prevention of 6236 cases of childhood obesity and 22 350 cases of newly incident coronary heart disease per year, with potential annual economic benefits (i.e., avoided medical costs and lost productivity related to the onset of these chronic conditions) of 1.74 USD billion (Trasande, 2014).

Another work reviewed the carcinogenic potential of BPA highlighting that there is substantial evidence from rodent studies that BPA exposure in early life below the reference dose (specified at 50 μg/kg weight per day) may lead to mammary and prostate cancer due to its tumor-promoting properties (Seachrist et al., 2016). In another study, it was reported that BPA contributes to the impairment of the pathway that insulin stimulates glucose uptake and therefore to the development of type 2 diabetes (Wade et al., 2020).

Furthermore, BPA can impact fetal development if women are exposed to BPA during pregnancy. According to Chou et al. (2011), the level of BPA detected in placental blood shows that the compound can be transported through the placental barrier to the fetus. Increased prenatal exposure to BPA has also been found to increase the risk of low birth weight, reduce gestational age, and cause adverse effects on adipokines in newborns, particularly in male babies (Bloom et al., 2011a, 2011b). This is in line with Martínez-Ibarra et al. (2021), who reported that prenatal exposure to BPA can alter fetal programming of the liver through an epigenetic mechanism, which may lead to the development of various chronic pathologies later in adulthood, such as metabolic, reproductive, and degenerative diseases, as well as certain types of cancer (Martínez-Ibarra et al., 2021).

Since young children and infants often cannot metabolize xenobiotics, they possess a greater risk of being exposed to and accumulating BPA (Nahar et al., 2013). The compound has been found in fetal cord blood (Aris, 2014; Unal et al., 2012), fetal liver (Cao et al., 2012; Nahar et al., 2013; Zhang et al., 2011), and amniotic fluids (Chen et al., 2011; Edlow et al., 2012) at concentrations within the range of 0.14–9.2, 1.3–50.5, and 0.36–5.62 ng/g, respectively. This indicates that the embryo is possibly exposed to BPA via maternal uptake. Additionally, BPA has been detected in up to 273.9 ng/g in placental blood (Troisi et al., 2014) and up to 66.48 ng/ml in the mother's blood (Lee et al., 2008). Nonetheless, since there is the release possibility of BPA from medical devices, any exposure indicated in the aforementioned studies could have taken place by routes other than maternal uptake (Hengstler et al., 2011).

Furthermore, any exposure to BPA during the gestational period can cause anxiety, depression, and hyperexcitability in the behavior of children up to 3 years old. Such effects are more pronounced in girls than in boys, which can result from their higher susceptibility to BPA during the prenatal period (Włodarczyk, 2015).

Impact of BPA on adults' health

Bisphenol-A present in the human body has been associated with cardiovascular diseases, chronic respiratory failure, breast cancer, endometriosis, developmental disorders, and autoimmune diseases (Vogel, 2009). This is also confirmed by literature findings that analyzed BPA concentrations in urine reporting a correlation of BPA levels in urine with increased incidence of cardiovascular diseases, diabetes, and disorders of hepatic enzymes (Lang et al., 2008; Martínez-Ibarra et al., 2021; Melzer et al., 2010).

Men exposed to BPA are likely to have the quality of their sperm affected, hence negatively impacting embryo development, which was observed during in vitro fertilization (Cariati et al., 2019). Moreover, hormonal changes in men can also be associated with high exposure to BPA; a correlation has been found between daily excretion of high amounts of BPA and an increase in the total concentration of testosterone in serum (Galloway et al., 2010).

According to Shen et al. (2019), patients with chronic kidney disease (CKD) may accumulate BPA more easily and any hemodialysis (HD) filters can add a BPA burden in patients that undergo HD. The serum levels of BPA and its analogs bisphenol-B (BPB), BPF, and BPS were monitored in patients with CKD undergoing dialysis, while other healthy people were used as "control samples." The serum levels of BPA had an *r*-value of −0.746, while BPS had a value of −0.433 in the 58 CKD patients, and 30 healthy controls were related with a dropdown in the calculated glomerular filtration rate. Bisphenol-A was the main form of the BPs

present in the polyamide (18.70 ± 2.88 ng/mg) and polysulfone membrane (20.86 ± 1.18 ng/mg). The results of this experiment agreed with the ones produced by BP concentrations in the dialysis filters. In conclusion, insufficient renal functions can lead to accumulations of BPs in patients with CKD (Shen et al., 2019).

A study was performed to determine the association of BPA and its analogs (BPF, BPS) with blood pressure and hypertension. When compared to the BPA reference group, individuals in the high and middle exposure groups exhibited an odds ratio value of 1.30 and 1.40 for hypertension, and 3.08 and 2.82 mm Hg higher systolic blood pressure (SBP) levels, respectively. This elevated risk of hypertension and SBP levels, with different dose–response relations, was attributed to exposure to BPA and BPS (Jiang et al., 2020).

Limitation of biomonitoring methods and data

Biomonitoring data are mainly obtained by conducting indirect analytical methods through enzymatic deconjugation with nonauthentic reference standards (i.e., crude enzyme solution from the snail *Helix pomatia*) instead of authentic standards used in direct methods (i.e., synthesized BPA glucuronide and BPA sulfate standard) (Gerona et al., 2020). Hence, while the above scientific evidence is undoubtedly useful, biomonitoring testing might underestimate human exposure to BPA. Recently, it was found that BPA levels in 29 urine samples from pregnant and nonpregnant women were measured almost 19 times lower through indirect methods (geometric mean: 2.77 μg/l) than those through direct methods (geometric mean: 51.99 μg/l) (Gerona et al., 2020). This was also confirmed by Vandenberg et al. (2014), who performed a multilaboratory round robin assay that measured BPA concentration in human serum through direct and indirect methods identifying that direct quantification of BPA metabolites in serum is more sensitive and accurate than indirect analysis (Vandenberg et al., 2014).

Additionally, stand-alone biomonitoring testing might not be adequate to estimate the real levels of BPA in the human body. For example, Genuis et al. (2012) and Gerona et al. (2020) carried out BPA biomonitoring through blood, urine, serum, and sweat testing in 20 participants reporting that BPA was identified in the sweat of many participants in whom no BPA was detected in their serum or urine, highlighting that sweat testing can be used as an additional monitor tool for BPA bioaccumulation in humans.

Future clinical–epidemiological research on human exposure time to BPA (including prolonged exposure; Abraham & Chakraborty, 2020), population-specific BPA consumption patterns, and a better understanding of action mechanisms mostly related to fetal programming and early growth could offer valuable scientific evidence on the implications of BPA in human health contributing to the adoption of necessary measures by healthcare decision-makers for the minimization of human exposure to BPA at the stage of its production and consumption (Martínez-Ibarra et al., 2021).

CONCLUSIONS

There is mounting evidence that shows that BPA is a significant contributor to long-term human exposure to EDCs, and yet, the demand for BPA presents an upward trend. The widespread use of BPA-based plastic MCPs, their mismanagement and presence in the environment as litter, coupled with the fact that there is a plethora of components and products that are not plastic-based but contain plastic material coatings and sealants in the form of epoxy resins (e.g., metal cans and casing, wood beams, and furniture) are worrisome. Being crucial sources of BPA, BPA-based plastic MCPs lead to a multitude of exposure pathways, further supporting the fact that they are responsible for BPA's ubiquitous presence in the environment. Existing evidence hints also at a potential BPA accumulation in humans, but a detailed assessment of the related bioaccumulation mechanisms in the human body is yet to be carried out.

Presently, the criteria and/or methods for BPA testing and restrictions in the production of plastic MCPs, as well as the quality and reliability of toxicological studies, are quite controversial. This is not surprising given that evidence is rather limited and inconclusive and the stakes are too high. Hence, politicians and BPA-based plastic MCPs manufacturing industries are reluctant to set lower exposure limits, impose bans, or seek alternatives. Nonetheless, in the long term, the economic and political implications due to the rising human health incidents and associated increases in healthcare spending worldwide could outweigh the economic and political implications of replacing or even banning BPA.

Substantial knowledge gaps on BPA exposure and its impact on human health act as barriers to promoting a collaborative (i.e., regulators, industry, and researchers) response to BPA production and use. On the one hand, regulators appear to rely almost exclusively on “guideline” studies on hazard evaluation, overlooking independent hypothesis-driven studies in risk assessment (e.g., monotonic versus non-monotonic dose–response curves), which leads to scientifically invalid decision-making (Vandenberg et al., 2020). On the other hand, the industry prioritizes the design of BPA substitutes (i.e., BPF and BPS) whose impacts on the environment and human health are critically underexplored. This then raises the question of whether replacing BPA could be a better solution than reducing it, with the latter implying a phase-out of BPA-based plastics. Meanwhile, researchers are trying to prove the cumulative effects of BPA on human health over short windows of research programs, and instigate a paradigm shift from evaluating BPA effects based on the “dose.” To this end, the CLARITY-BPA is strongly positioned to reestablish what is considered to be “safe,” and thus, trigger change.

The production and use of BPA is a complex and persistent problem created and supported by systemic failures deeply engrained in the present social, economic, and political systems. To address this problem, all stakeholders

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involved in the BPA-based plastic MCPs value chain need to collaborate to codesign and cocreate widely accepted solutions. Future research is vital in creating this level playing field and promoting transparency and progress in understanding the long-term effects of BPA on human health, a process that needs to be instigated and fostered by policy and decision-makers. A better understanding of the longevity of BPA and the mechanisms of its release in the indoor and outdoor environment via the use of BPA-based plastic MCPs is needed to illuminate further potential pathways and long-term implications on human health.

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DATA AVAILABILITY STATEMENT

Data, associated metadata, and calculation tools are available from the corresponding author John N. Hahladakis (john_chach@yahoo.gr, ichachladakis@qu.edu.qa).

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REFERENCES

Abraham, A., & Chakraborty, P. (2020). A review on sources and health impacts of bisphenol A. *Reviews on Environmental Health*, *35*, 201–210.

Ajong, A. B., Kenfack, B., Ali, I. M., Yakum, M. N., Aljerf, L., & Telefo, P. B. (2020). Hypocalcaemia and calcium intake in pregnancy: A research protocol for critical analysis of risk factors, maternofoetal outcomes and evaluation of diagnostic methods in a third-category health facility, Cameroon. *PLoS One*, *15*, e0241812.

Almeida, S., Raposo, A., Almeida-González, M., & Carrascosa, C. (2018). Bisphenol A: Food exposure and impact on human health. *Comprehensive Reviews in Food Science and Food Safety*, *17*, 1503–1517.

ANSES. (2011). *Health effects of bisphenol A—Collective expert report*.

Aris, A. (2014). Estimation of bisphenol A (BPA) concentrations in pregnant women, fetuses and nonpregnant women in Eastern Townships of Canada. *Reproductive Toxicology*, *45*, 8–13.

Arnich, N., Canivenc-Lavier, M.-C., Kolf-Clauw, M., Coffigny, H., Cravedi, J.-P., Grob, K., Macherey, A.-C., Masset, D., Maximilien, R., Narbonne, J.-F., Nesslany, F., Stadler, J., & Tulliez, J. (2011). Conclusions of the French Food Safety Agency on the toxicity of bisphenol-A. *International Journal of Hygiene and Environmental Health*, *214*, 271–275.

Arp, H. P. H., Morin, N. A. O., Hale, S. E., Okkenhaug, G., Breivik, K., & Sparrevik, M. (2017). The mass flow and proposed management of bisphenol A in selected Norwegian waste streams. *Waste Management*, *60*, 775–785.

Artham, T., & Doble, M. (2009). Fouling and degradation of polycarbonate in seawater: Field and lab studies. *Journal of Polymers and the Environment*, *17*, 170–180.

Bagley, B. D., Smith, J. N., & Teeguarden, J. G. (2021). Risk assessment of predicted serum concentrations of bisphenol A in children and adults following treatment with dental composite restoratives, dental sealants, or orthodontic adhesives using physiologically based pharmacokinetic modelling. *Regulatory Toxicology and Pharmacology*, *120*, 104839.

Benhamada, M., Bouzid, D., Boyron, O., & Taam, M. (2016). The relationship between the ageing of polycarbonate characterized by SEC and the release of bisphenol A quantified by HPLC–UV. *European Food Research and Technology*, *242*, 227–232.

Berkner, S., Streck, G., & Herrmann, R. (2004). Development and validation of a method for determination of trace levels of alkylphenols and bisphenol A in atmospheric samples. *Chemosphere*, *54*, 575–584.

Bhunia, K., Sablani, S. S., Tang, J., & Rasco, B. (2013). Migration of chemical compounds from packaging polymers during microwave, conventional heat treatment, and storage. *Comprehensive Reviews in Food Science and Food Safety*, *12*, 523–545.

Bloom, M. S., Kim, D., vom Saal, F. S., Taylor, J. A., Cheng, G., Lamb, J. D., & Fujimoto, V. Y. (2011a). Bisphenol A exposure reduces the estradiol response to gonadotropin stimulation during in vitro fertilization. *Fertility and Sterility*, *96*, 672–677.

Bloom, M. S., vom Saal, F. S., Kim, D., Taylor, J. A., Lamb, J. D., & Fujimoto, V. Y. (2011b). Serum unconjugated bisphenol A concentrations in men may influence embryo quality indicators during in vitro fertilization. *Environmental Toxicology and Pharmacology*, *32*, 319–323.

Borrirukwisitsak, S., Keenan, H. E., & Gauchotte-Lindsay, C. (2012). Effects of salinity, pH and temperature on the octanol–water partition coefficient of bisphenol A. *International Journal of Environmental Science and Development*, *3*, 460–464.

British Plastics Federation (BPF). (2021a). *Is plastic packaging bad for the environment?*

British Plastics Federation (BPF). (2021b). *Polyvinyl chloride PVC*.

Brosché, S., Strakova, J., Bell, L., & Karlsson, T. (2021). *Widespread chemical contamination of recycled plastic pellets globally*. International Pollutants Elimination Network (IPEN).

Cao, P., Zhong, H.-N, Qiu, K., Li, D., Wu, G., Sui, H.-X., & Song, Y. (2021). Exposure to bisphenol A and its substitutes, bisphenol F and bisphenol S from canned foods and beverages on the Chinese market. *Food Control*, *120*, 107502.

Cao, X. L., Zhang, J., Goodyer, C. G., Hayward, S., Cooke, G. M., & Curran, I. H. (2012). Bisphenol A in human placental and fetal liver tissues was collected from the Greater Montreal area (Quebec) during 1998–2008. *Chemosphere*, *89*, 505–511.

Cariati, F., D'Uonno, N., Borrillo, F., Iervolino, S., Galdiero, G., & Tomaiuolo, R. (2019). Bisphenol A: An emerging threat to male fertility. *Reproductive Biology and Endocrinology*, *17*, 6.

Carwile, J. L., Ye, X., Zhou, X., Calafat, A. M., & Michels, K. B. (2011). Canned soup consumption and urinary bisphenol A: A randomized crossover trial. *Journal of the American Medical Association*, *306*, 2218–2220.

Chang, S. W., Chen, C. M., & He, J. L. (2012). Power modulated plasma-polymerized gradient anti-fingerprint transparent protective coating with a gradient composition. *Advanced Materials Research*, *509*, 135–137.

Chen, F., Ying, G.-G., Kong, L.-X., Wang, L., Zhao, J.-L., Zhou, L.-J., & Zhang, L.-J. (2011). Distribution and accumulation of endocrine-disrupting chemicals and pharmaceuticals in wastewater irrigated soils in Hebei, China. *Environmental Pollution*, *159*, 1490–1498.

Chou, W. C., Chen, J. L., Lin, C. F., Chen, Y. C., Shih, F. C., & Chuang, C. Y. (2011). Biomonitoring of bisphenol A concentrations in maternal and umbilical cord blood in regard to birth outcomes and adipokine expression: A birth cohort study in Taiwan. *Environmental Health*, *10*, 94.

Cimmino, I., Fiory, F., Perruolo, G., Miele, C., Beguinot, F., Formisano, P., & Oriente, F. (2020). Potential mechanisms of bisphenol A (BPA) contributing to human disease. *Internationa Journal of Molecular Sciences*, *21*, 5761.

Corrales, J., Kristofco, L. A., Steele, W. B., Yates, B. S., Breed, C. S., Williams, E. S., & Brooks, B. W. (2015). Global assessment of bisphenol A in the environment: Review and analysis of its occurrence and bioaccumulation. *Dose-Response: An International Journal*, *13*, 1559325815598308.

Cousins, I. T., Staples, C. A., Klečka, G. M., & Mackay, D. (2002). A Multimedia assessment of the environmental fate of bisphenol A. *Human and Ecological Risk Assessment: An International Journal*, *8*, 1107–1135.

ĆĆwiek-Ludwicka, K. (2015). Bisphenol A (BPA) in food contact materials—New scientific opinion from EFSA regarding public health risk. *Roczniki Państwowego Zakładu Higieny*, *66*, 299–307.

Dreolin, N., Aznar, M., Moret, S., & Nerin, C. (2019). Development and validation of a LC–MS/MS method for the analysis of bisphenol a in polyethylene terephthalate. *Food Chemistry*, *274*, 246–253.

Du, D., & Stern, N. D. (2021). *Analysis of the Chinese PVC industry*, CHINADIRECT.BIZ. https://mst.dk/media/220519/analysis-of-the-chinese-pvc-industry.pdf

Edlow, A. G., Chen, M., Smith, N. A., Lu, C., & McElrath, T. F. (2012). Fetal bisphenol A exposure: Concentration of conjugated and unconjugated bisphenol A in amniotic fluid in the second and third trimesters. *Reproductive Toxicology*, *34*, 1–7.

EFSA. (2015). *Bisphenol A*. Retrieved April 22, 2021, from: https://www.efsa.europa.eu/en/topics/topic/bisphenol

EFSA. (2021). *Bisphenol A: EFSA draft opinion proposes lowering the tolerable daily intake*.

EU 2018/213. (2018). Commission Regulation (EU) 2018/213 of 12 February 2018 on the use of bisphenol A in varnishes and coatings intended to come into contact with food and amending Regulation (EU) No. 10/2011 as regards the use of that substance in plastic food contact materials. *Official Journal of the European Union*, L 41, 6–12.

European Commission. (2002). *Directive 2002/72/EC*. https://eur-lex.europa.eu/legal-content/EN/ALL/?uri=CELEX%3A32002L0072

European Commission. (2004). Regulation (EC) No. 1935/2004. https://eur-lex.europa.eu/legal-content/EN/ALL/?uri=CELEX%3A32004R1935

European Commission. (2006). Commission Regulation (EC) 1881/2006 of 19 December 2006 setting maximum levels for certain contaminants in foodstuffs. *Official Journal of the European Union, L 364*, 5–24.

European Commission. (2008). *Regulation (EC) No. 1272/2008*. https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=celex%3A32008R1272

European Commission. (2009). *Directive 2009/48/EC*. https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A32009L0048

European Commission. (2011a). Commission Regulation (EU) No. 10/2011 of 14 January 2011 on plastic materials and articles intended to come into contact with food. *Official Journal of the European Union, IO L 12*, 1-89.

European Commission. (2011b). *Directive 2011/8/EU*. https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A32011L0008

European Commission. (2011c). *Regulation (EU) No 10/2011*. https://eur-lex.europa.eu/eli/reg/2011/10/oj

European Commission. (2011d). *Regulation (EU) No 321/2011*. https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A32011R0321

European Commission. (2013). *Regulation (EU) No 609/2013*. https://eur-lex.europa.eu/legal-content/EN/ALL/?uri=CELEX%3A32013R0609

European Commission. (2014). *Directive 2014/81/EU*. https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=celex%3A32014L0081

European Commission. (2017). *Directive (EU) 2017/898*. https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A32017L0898

European Commission. (2018). *Regulation (EU) 2018/213*. https://eur-lex.europa.eu/eli/reg/2018/213/oj

European Commission. (2021). *Revision of EU rules on food contact materials*.

U.S. FDA. (2008). *Draft assessment of bisphenol A for use in food contact applications (14th August 2008)*. Retrieved June 22, 2020, from: http://wayback.archive-it.org/7993/20180126150108/. https://www.fda.gov/ohrms/dockets/ac/08/briefing/2008-0038b1_01_02_FDA%20BPA%20Draft%20Assessment.pdf

Fent, G., Hein, W. J., Moendel, M. J., & Kubiak, R. (2003). Fate of 14C-bisphenol A in soils. *Chemosphere*, *51*, 735–746.

Fernandez, M. F., Arrebola, J. P., Taoufiki, J., Navalón, A., Ballesteros, O., Pulgar, R., Vilchez, J. L., & Olea, N. (2007). Bisphenol-A and chlorinated derivatives in adipose tissue of women. *Reproductive Toxicology*, *24*, 259–264.

Flint, S., Markle, T., Thompson, S., & Wallace, E. (2012). Bisphenol A exposure, effects, and policy: A wildlife perspective. *Journal of Environmental Management*, *104*, 19–34.

Fu, P., & Kawamura, K. (2010). Ubiquity of bisphenol A in the atmosphere. *Environmental Pollution*, *158*, 3138–3143.

Galloway, T., Cipelli, R., Guralnik, J., Ferrucci, L., Bandinelli, S., Corsi, A. M., Money, C., McCormack, P., & Melzer, D. (2010). Daily bisphenol A excretion and associations with sex hormone concentrations: Results from the InCHIANTI adult population study. *Environmental Health Perspectives*, *118*, 1603–1608.

Galloway, T. S., Lee, B. P., Burić, I., Steele, A. M., Kocur, A. L., George Pandeth, A., & Harries, L. W. (2019). Plastics additives and human health: A case study of bisphenol A (BPA). In R. E. Hester, & R. M. Harrison (Eds.), *Issues in environmental science and technology No. 47. Plastics and the environment* (131-155). Royal Society of Chemistry.

Geens, T., Aerts, D., Berthot, C., Bourguignon, J.-P., Goeyens, L., Lecomte, P., Maghuin-Rogister, G., Pironnet, A.-M., Pussemier, L., Scippo, M.-L., Van Loco, J., & Covaci, A. (2012a). A review of dietary and non-dietary exposure to bisphenol-A. *Food and Chemical Toxicology*, *50*, 3725–3740.

Geens, T., Goeyens, L., & Covaci, A. (2011). Are potential sources for human exposure to bisphenol-A overlooked? *International Journal of Hygiene and Environmental Health*, *214*, 339–347.

Geens, T., Goeyens, L., Kannan, K., Neels, H., & Covaci, A. (2012b). Levels of bisphenol-A in thermal paper receipts from Belgium and estimation of human exposure. *Science of the Total Environment*, *435–436*, 30–33.

Genuis, S. J., Beesoon, S., Birkholz, D., & Lobo, R. A. (2012). Human excretion of bisphenol A: Blood, urine, and sweat (BUS) study. *Journal of Environmental and Public Health*, *2012*, 185731.

Gerassimidou, S., Lanska, P., Hahladakis, J. N., Lovat, E., Vanzetto, S., Geueke, B., Groh, K. J., Muncke, J., Maffini, M., Martin, O. V., & Iacovidou, E. (2022). Unpacking the complexity of the PET drink bottles value chain: A chemicals perspective. *Journal of Hazardous Materials*, *430*, 128410.

Gerassimidou, S., Lovat, E., Ebner, N., You, W., Martin, T. G. O. V., & Iacovidou, E. (2021). Unpacking the complexity of the UK plastic packaging value chain: A stakeholder perspective. *Sustainable Production and Consumption*, *30*, 657–673.

Gerona, R., Saal, V., & Hunt, P.A., F. S. (2020). BPA: Have flawed analytical techniques compromised risk assessments? *The Lancet Diabetes Endocrinology*, *8*, 11–13.

González, N., Cunha, S. C., Ferreira, R., Fernandes, J. O., Marquès, M., Nadal, M., & Domingo, J. L. (2020). Concentrations of nine bisphenol analogues in food purchased from Catalonia (Spain): Comparison of canned and non-canned foodstuffs. *Food and Chemical Toxicology*, *136*, 110992.

Goodson, A., Robin, H., Summerfield, W., & Cooper, I. (2004). Migration of bisphenol A from can coatings—effects of damage, storage conditions and heating. *Food Additives & Contaminants*, *21*, 1015–1026.

Groh, K. J., Backhaus, T., Carney-Almroth, B., Geueke, B., Inostroza, P. A., Lennquist, A., Leslie, H. A., Maffini, M., Slunge, D., Trasande, L., Warhurst, A. M., & Muncke, J. (2019). Overview of known plastic packaging-associated chemicals and their hazards. *Science of the Total Environment*, *651*, 3253–3268.

Hahladakis, J. N. (2020). Delineating and preventing plastic waste leakage in the marine and terrestrial environment. *Environmental Science and Pollution Research*, *27*, 12830–12837.

Hahladakis, J. N., Iacovidou, E., & Gerassimidou, S. (2020). Chapter 19—Plastic waste in a circular economy. In T. M. Letcher (Ed.), *Plastic waste and recycling* (pp. 481–512). Academic Press.

Hahladakis, J. N., Velis, C. A., Weber, R., Iacovidou, E., & Purnell, P. (2018). An overview of chemical additives present in plastics: Migration, release, fate and environmental impact during their use, disposal and recycling. *Journal of Hazardous Materials*, *344*, 179–199.

He, Y., Miao, M., Wu, C., Yuan, W., Gao, E., Zhou, Z., & Li, D. K. (2009). Occupational exposure levels of bisphenol A among Chinese workers. *Journal of Occupational Health*, *51*, 432–436.

Healy, B. F., English, K. R., Jagals, P., & Sly, P. D. (2015). Bisphenol A exposure pathways in early childhood: Reviewing the need for improved risk assessment models. *Journal of Exposure Science and Environmental Epidemiology*, *25*, 544–556.

Hengstler, J. G., Foth, H., Gebel, T., Kramer, P. J., Lilienblum, W., Schweinfurth, H., Völkel, W., Wollin, K. M., & Gundert-Remy, U. (2011). Critical evaluation of key evidence on the human health hazards of exposure to bisphenol A. *Critical Reviews in Toxicology*, *41*, 263–291.

Hermabessiere, L., Dehaut, A., Paul-Pont, I., Lacroix, C., Jezequel, R., Soudant, P., & Duflos, G. (2017). Occurrence and effects of plastic additives on marine environments and organisms: A review. *Chemosphere*, *182*, 781–793.

Hoekstra, E. J., & Simoneau, C. (2013). Release of bisphenol A from polycarbonate—A review. *Critical Reviews in Food Science and Nutrition*, *53*, 386–402.

Höllrigl-Rosta, A., Vinken, R., Lenz, M., & Schäffer, A. (2003). Sorption and dialysis experiments to assess the binding of phenolic xenobiotics to dissolved organic matter in soil. *Environmental Toxicology and Chemistry*, *22*, 746–752.

Huang, D. Y., Zhao, H. Q., Liu, C. P., & Sun, C. X. (2014). Characteristics, sources, and transport of tetrabromobisphenol A and bisphenol A in soils from a typical e-waste recycling area in South China. *Environmental Science and Pollution Research*, *21*, 5818–5826.

Huang, R.-P., Liu, Z.-H., Yin, H., Dang, Z., Wu, P.-X., Zhu, N.-W., & Lin, Z. (2018). Bisphenol A concentrations in human urine, human intakes across six continents, and annual trends of average intakes in adult and child populations worldwide: A thorough literature review. *Science of the Total Environment*, *626*, 971–981.

Huang, Y. Q., Wong, C. K. C., Zheng, J. S., Bouwman, H., Barra, R., Wahlström, B., Neretin, L., & Wong, M. H. (2012). Bisphenol A (BPA) in China: A review of sources, environmental levels, and potential human health impacts. *Environment International*, *42*, 91–99.

Iacovidou, E., Ebner, N., & Orsi, B. (2020a). Plastic-packaging: How do we get to where we want to be? Brunel University London, University of Leeds in collaboration with the Department for Environment, DEFRA.

Iacovidou, E., Martin, V., & Jobling, S. (2020b). Chapter 4—Review of sources and pathways of marine plastic pollution. In *Marine plastic pollution—Evidence review*. Department for Environment, Food and Rural Affairs (DEFRA). http://randd.defra.gov.uk/Document.aspx?Document=14689_02MarinePlasticPollutionEvidenceReview.pdf

Im, J., & Löffler, F. E. (2016). Fate of bisphenol A in terrestrial and aquatic environments. *Environmental Science & Technology*, *50*, 8403–8416.

Jiang, S., Liu, H., Zhou, S., Zhang, X., Peng, C., Zhou, H., Tong, Y., & Lu, Q. (2020). Association of bisphenol A and its alternatives bisphenol S and F exposure with hypertension and blood pressure: A cross-sectional study in China. *Environmental Pollution*, *257*, 113639.

Kang, J.-H., Kondo, F., & Katayama, Y. (2006). Human exposure to bisphenol A. *Toxicology*, *226*, 79–89.

Khan, M. R., Alammari, A. M., Aqel, A., & Azam, M. (2020). Trace analysis of environmental endocrine-disrupting contaminant bisphenol A in canned, glass and polyethylene terephthalate plastic carbonated beverages of diverse flavors and origin. *Food Science and Technology*, *41*, 210–217.

Kitamura, S., Jinno, N., Ohta, S., Kuroki, H., & Fujimoto, N. (2002). Thyroid hormonal activity of the flame retardants tetrabromobisphenol A and tetrachlorobisphenol A. *Biochemical and Biophysical Research Communications*, *293*, 554–559.

Konieczna, A., Rutkowska, A., & Rachoń, D. (2015). Health risk of exposure to bisphenol A (BPA). *Roczniki Państwowego Zakładu Higieny*, *66*, 5–11.

Kumar, M., Sarma, D. K., Shubham, S., Kumawat, M., Verma, V., Prakash, A., & Tiwari, R. (2020). Environmental endocrine-disrupting chemical exposure: Role in non-communicable diseases. *Frontiers in Public Health*, *8*, 1–28.

Lang, I. A., Galloway, T. S., Scarlett, A., Henley, W. E., Depledge, M., Wallace, R. B., & Melzer, D. (2008). Association of urinary bisphenol A concentration with medical disorders and laboratory abnormalities in adults. *Journal of the American Medical Association*, *300*, 1303–1310.

Lee, Y. J., Ryu, H. Y., Kim, H. K., Min, C. S., Lee, J. H., Kim, E., Nam, B. H., Park, J. H., Jung, J. Y., Jang, D. D., Park, E. Y., Lee, K. H., Ma, J. Y., Won, H. S., Im, M. W., Leem, J. H., Hong, Y. C., & Yoon, H. S. (2008). Maternal and fetal exposure to bisphenol A in Korea. *Reproductive Toxicology*, *25*, 413–419.

Legeay, S., & Faure, S. (2017). Is bisphenol A an environmental obesogen? *Fundamental and Clinical Pharmacology*, *31*, 594–609.

Leslie, H. A., Leonards, P. E. G., Brandsma, S. H., de Boer, J., & Jonkers, N. (2016). Propelling plastics into the circular economy—Weeding out the toxics first. *Environment International*, *94*, 230–234.

Li, Y., Zhang, H., Rashid, A., Hu, A., Xin, K., Li, H., Adyari, B., Wang, Y., Yu, C.-P., & Sun, Q. (2020). Bisphenol A attenuation in natural microcosm: Contribution of ecological components and identification of transformation pathways through stable isotope tracing. *Journal of Hazardous Materials*, *385*, 121584.

Lim, D. S., Kwack, S. J., Kim, K. B., Kim, H. S., & Lee, B. M. (2009). Potential risk of bisphenol A migration from polycarbonate containers after heating, boiling, and microwaving. *Journal of Toxicology and Environmental Health: Part A*, *72*, 1285–1291.

M'Rabet, C., Pringault, O., Zmerli-Triki, H., Ben Gharbia, H., Couet, D., & Kéfi-Daly Yahia, O. (2018). Impact of two plastic-derived chemicals, the bisphenol A and the di-2-ethylhexyl phthalate, exposure on the marine toxic dinoflagellate *Alexandrium pacificum*. *Marine Pollution Bulletin*, *126*, 241–249.

Mandel, N. D., Gamboa-Loira, B., Cebrián, M. E., Mérida-Ortega, Á., & López-Carrillo, L. (2020). Challenges to regulate products containing bisphenol A: Implications for policy. *Salud pública de México*, *61*, 692–697.

Maragou, N. C., Makri, A., Lampi, E. N., Thomaidis, N. S., & Koupparis, M. A. (2008). Migration of bisphenol A from polycarbonate baby bottles under real use conditions. *Food Additives & Contaminants: Part A*, *25*, 373–383.

Martínez-Ibarra, A., Martínez-Razo, L. D., MacDonald-Ramos, K., Morales-Pacheco, M., Vázquez-Martínez, E. R., López-López, M., Rodríguez Dorantes, M., & Cerbón, M. (2021). Multisystemic alterations in humans induced by bisphenol A and phthalates: Experimental, epidemiological and clinical studies reveal the need to change health policies. *Environmental Pollution*, *271*, 116380.

Melzer, D., Rice, N. E., Lewis, C., Henley, W. E., & Galloway, T. S. (2010). Association of urinary bisphenol a concentration with heart disease: Evidence from NHANES 2003/06. *PLoS One*, *5*, e8673.

Michałowicz, J. (2014). Bisphenol A—Sources, toxicity and biotransformation. *Environmental Toxicology and Pharmacology*, *37*, 738–758.

Montévil, M., Acevedo, N., Schaeberle, C. M., Bharadwaj, M., Fenton, S. E., & Soto, A. M. (2020). A combined morphometric and statistical approach to assess nonmonotonicity in the developing mammary gland of rats in the CLARITY-BPA study. *Environmental Health Perspectives*, *128*, 057001.

Moon, M. K. (2019). Concern about the safety of bisphenol A substitutes. *Diabetes & Metabolism Journal*, *43*, 46–48.

Morin, N., Arp, H. P. H., & Hale, S. E. (2015). Bisphenol A in solid waste materials, leachate water, and air particles from norwegian waste-handling facilities: Presence and partitioning behavior. *Environmental Science & Technology*, *49*, 7675–7683.

Nahar, M. S., Liao, C., Kannan, K., & Dolinoy, D. C. (2013). Fetal liver bisphenol A concentrations and biotransformation gene expression reveal variable exposure and altered capacity for metabolism in humans. *Journal of Biochemical and Molecular Toxicology*, *27*, 116–123.

Nam, S.-H., Seo, Y.-M., & Kim, M.-G. (2010). Bisphenol A migration from polycarbonate baby bottle with repeated use. *Chemosphere*, *79*, 949–952.

Ortmann, P., Heckler, I., & Mecking, S. (2014). Physical properties and hydrolytic degradability of polyethylene-like polyacetals and polycarbonates. *Green Chemistry*, *16*, 1816–1827.

Owens, C. V., Jr., Lambright, C., Bobseine, K., Ryan, B., Gray, L. E., Jr., Gullett, B. K., & Wilson, V. S. (2007). Identification of estrogenic compounds emitted from the combustion of computer printed circuit boards in electronic waste. *Environmental Science & Technology*, *41*, 8506–8511.

Pascault, J. P., Höfer, R., & Fuertes, P. (2012). 10.04 - Mono-, di-, and oligosaccharides as precursors for polymer synthesis. In K. Matyjaszewski & M. Möller (Eds.), *Polymer science: A comprehensive reference* (pp. 59–82). Elsevier.

Patisaul, H. B. (2020). Achieving CLARITY on bisphenol A, brain and behaviour. *Journal of Neuroendocrinology*, *32*, e12730.

Pivnenko, K., Eriksen, M. K., Martín-Fernández, J. A., Eriksson, E., & Astrup, T. F. (2016a). Recycling of plastic waste: Presence of phthalates in plastics from households and industry. *Waste Management*, *54*, 44–52.

Pivnenko, K., Olsson, M. E., Götze, R., Eriksson, E., & Astrup, T. F. (2016b). Quantification of chemical contaminants in the paper and board fractions of municipal solid waste. *Waste Management*, *51*, 43–54.

PlasticsEurope. (2016). *Plastics—The facts 2016: An analysis of European plastics production, demand and waste data*. http://www.plasticseurope.org/documents/document/20161014113313-plastics_the_facts_2016_final_version.pdf

Pourzamani, H., Ebrahim, K., Mirlohi, M., Mirzaei, N., Bahrami, A. R., Rahimi, E., Saeidi, B., Falahati, M., Esfahani, B. N., & Safaei, H. (2016). Evaluation

of bisphenol A content in food contact PVC cling film. *Journal of Innovations in Pharmaceutical and Biological Sciences*, *3*, 12–16.

Proshad, R., Kormoker, T., Islam, M. S., Haque, M. A., Rahman, M. M., & Mithu, M. M. R. (2018). Toxic effects of plastic on human health and environment: A consequences of health risk assessment in Bangladesh. *International Journal of Health*, *6*, 1–5.

Research and Markets. (2021a). *Global bisphenol A (BPA) market report and forecast 2021–2026*.

Research and Markets. (2021b). *Global bisphenol—A market outlook to 2026*.

Ribeiro, E., Ladeira, C., & Viegas, S. (2017). Occupational exposure to bisphenol A (BPA): A reality that still needs to be unveiled. *Toxics*, *5*, 22.

Rochester, J. R. (2013). Bisphenol A and human health: A review of the literature. *Reproductive Toxicology*, *42*, 132–155.

Rubin, B. S. (2011). Bisphenol A: An endocrine disruptor with widespread exposure and multiple effects. *The Journal of Steroid Biochemistry and Molecular Biology*, *127*, 27–34.

Rudel, R. A., Gray, J. M., Engel, C. L., Rawsthorne, T. W., Dodson, R. E., Ackerman, J. M., Rizzo, J., Nudelman, J. L., & Brody, J. G. (2011). Food packaging and bisphenol A and bis(2-ethyhexyl) phthalate exposure: Findings from a dietary intervention. *Environmental Health Perspectives*, *119*, 914–920.

Russo, G., Barbato, F., Mita, D. G., & Grumetto, L. (2019). Occurrence of bisphenol A and its analogues in some foodstuff marketed in Europe. *Food and Chemical Toxicology*, *131*, 110575.

Saad, N. A., & Jwad, E. R. (2018). Investigation of addition titanium dioxide on general properties of polycarbonate. *Open Access Library Journal*, *5*, 1–11.

Schug, T. T., & Birnbaum, L. S. (2014). Human health effects of bisphenol A. In S. M. Snedeker (Ed.), *Toxicants in food packaging and household plastics: Exposure and health risks to consumers* (pp. 1–29). Springer.

Schug, T. T., Heindel, J. J., Camacho, L., Delclos, K. B., Howard, P., Johnson, A. F., Aungst, J., Keefe, D., Newbold, R., Walker, N. J., Thomas Zoeller, R., & Bucher, J. R. (2013). A new approach to synergize academic and guideline-compliant research: The CLARITY-BPA research program. *Reproductive Toxicology*, *40*, 35–40.

Schyns, Z. O., & Shaver, M. P. (2021). Mechanical recycling of packaging plastics: A review. *Macromolecular Rapid Communications*, *42*, 2000415.

Seachrist, D. D., Bonk, K. W., Ho, S.-M., Prins, G. S., Soto, A. M., & Keri, R. A. (2016). A review of the carcinogenic potential of bisphenol A. *Reproductive Toxicology*, *59*, 167–182.

Sessa, F., Polito, R., Monda, V., Scaranci, A., Salerno, M., Carotenuto, M., Cibelli, G., Valenzano, A. A., Campanozzi, A., & Mollica, M. P. (2021). Effects of a plastic-free lifestyle on urinary bisphenol A levels in school-aged children of Southern Italy: A pilot study. *Frontiers in Public Health*, *9*, 4.

Shelby, M. D. (2008). NTP-CERHR monograph on the potential human reproductive and developmental effects of bisphenol A. *NTP-CERHR MON*, *22*(22), v, vii–ix, 1–64 passim.

Shen, Y., Liu, T., Shi, Y., Zhuang, F., Lu, J., Zhu, Q., & Ding, F. (2019). Bisphenol A analogs in patients with chronic kidney disease and dialysis therapy. *Ecotoxicology and Environmental Safety*, *185*, 109684.

Sidhu, S., Gullett, B., Striebich, R., Klosterman, J., Contreras, J., & DeVito, M. (2005). Endocrine disrupting chemical emissions from combustion sources: Diesel particulate emissions and domestic waste open burn emissions. *Atmospheric Environment*, *39*, 801–811.

Stahlhut, R. W., Welshons, W. V., & Swan, S. H. (2009). Bisphenol a data in NHANES suggest longer than expected half-life, substantial nonfood exposure, or both. *Environmental Health Perspectives*, *117*, 784–789.

Testai, E., Hartemann, P., Rodríguez-Farre, E., Rastogi, S. C., Bustos, J., Gundert-Remy, U., Hensten, A., Kopperud, H. M., Olea, N., Piersma, A., & De Jong, W. (2016). The safety of the use of bisphenol A in medical devices. *Regulatory Toxicology and Pharmacology*, *79*, 106–107.

Teuten, E. L., Saquing, J. M., Knappe, D. R., Barlaz, M. A., Jonsson, S., Björn, A., Rowland, S. J., Thompson, R. C., Galloway, T. S., Yamashita, R., Ochi, D., Watanuki, Y., Moore, C., Viet, P. H., Tana, T. S., Prudente, M., Boonyatumanond, R., Zakaria, M. P., Akkhavong, K., … Takada, H. (2009). Transport and release of chemicals from plastics to the environment and to wildlife. *Philosophical Transactions of th Royal Society B. Biological Sciences*, *364*, 2027–2045.

Thompson, R. C., Moore, C. J., vom Saal, F. S., & Swan, S. H. (2009). Biological sciences plastics, the environment and human health: Current consensus and future trends. *Philosophical Transactions of th Royal Society B*, *364*, 2153–2166.

Trasande, L. (2014). Further limiting bisphenol a in food uses could provide health and economic benefits. *Health Affairs*, *33*, 316–323.

Troisi, J., Mikelson, C., Richards, S., Symes, S., Adair, D., Zullo, F., & Guida, M. (2014). Placental concentrations of bisphenol A and birth weight from births in the southeastern U.S. *Placenta*, *35*, 947–952.

Unal, E. R., Lynn, T., Neidich, J., Salazar, D., Goetzl, L., Baatz, J. E., Hulsey, T. C., Van Dolah, R., Guillette, L. J., Jr., & Newman, R. (2012). Racial disparity in maternal and fetal-cord bisphenol A concentrations. *Journal of Perinatology*, *32*, 844–850.

Van Landuyt, K. L., Nawrot, T., Geebelen, B., De Munck, J., Snauwaert, J., Yoshihara, K., Scheers, H., Godderis, L., Hoet, P., & Van Meerbeek, B. (2011). How much do resin-based dental materials release? A meta-analytical approach. *Dental Materials*, *27*, 723–747.

Vandenberg, L. N., Chahoud, I., Heindel, J. J., Padmanabhan, V., Paumgartten, F. J. R., & Schoenfelder, G. (2010). Urinary, circulating, and tissue biomonitoring studies indicate widespread exposure to bisphenol A. *Environmental Health Perspectives*, *118*, 1055–1070.

Vandenberg, L. N., Gerona, R. R., Kannan, K., Taylor, J. A., van Breemen, R. B., Dickenson, C. A., Liao, C., Yuan, Y., Newbold, R. R., & Padmanabhan, V. (2014). A round robin approach to the analysis of bisphenol A (BPA) in human blood samples. *Environmental Health*, *13*, 1–20.

Vandenberg, L. N., Hauser, R., Marcus, M., Olea, N., & Welshons, W. V. (2007). Human exposure to bisphenol A (BPA). *Reproductive Toxicology*, *24*, 139–177.

Vandenberg, L. N., Hunt, P. A., & Gore, A. C. (2019). Endocrine disruptors and the future of toxicology testing—Lessons from CLARITY–BPA. *Nature Reviews Endocrinology*, *15*, 366–374.

Vandenberg, L. N., Hunt, P. A., Myers, J. P., & Vom Saal, F. S. (2013). Human exposures to bisphenol A: Mismatches between data and assumptions. *Reviews on Environmental Health*, *28*, 37–58.

Vandenberg, L. N., Prins, G. S., Patisaul, H. B., & Zoeller, R. T. (2020). The use and misuse of historical controls in regulatory toxicology: Lessons from the CLARITY-BPA study. *Endocrinology*, *161*. https://doi.org/10.1210/endocr/bqz014

Vasiljevic, T., & Harner, T. (2021). Bisphenol A and its analogues in outdoor and indoor air: Properties, sources and global levels. *Science of the Total Environment*, *789*, 148013.

Viñas, P., Campillo, N., Martínez-Castillo, N., & Hernández-Córdoba, M. (2010). Comparison of two derivatization-based methods for solid-phase microextraction-gas chromatography-mass spectrometric determination of bisphenol A, bisphenol S and biphenol migrated from food cans. *Analytical and Bioanalytical Chemistry*, *397*, 115–125.

Vogel, S. A. (2009). The politics of plastics: The making and unmaking of bisphenol a "safety". *American Journal of Public Health*, *99*, S559–S566.

vom Saal, F. S., & Vandenberg, L. N. (2020). Update on the health effects of bisphenol A: Overwhelming evidence of harm. *Endocrinology*, 162.

Wade, M., Delawder, V., Reneau, P., & dos Santos, J. M. (2020). The effect of BPA exposure on insulin resistance and type 2 diabetes—The impact of muscle contraction. *Medical Hypotheses*, *140*, 109675.

Wagner, S., & Schlummer, M. (2020). Legacy additives in a circular economy of plastics: Current dilemma, policy analysis, and emerging countermeasures. *Resources, Conservation And Recycling*, *158*, 104800.

Wang, H., Jiang, L., Gu, S., & Wang, X. (2021). Migration of bisphenol A from polyvinyl chloride plastics to solvents of different polarities and packaged food in China. *Packaging Technology and Science*, *34*, 127–137.

Wang, Z., Liu, H., & Liu, S. (2016). Low-dose bisphenol A exposure: A seemingly instigating carcinogenic effect on breast cancer. *Advanced Science News*, *4*, 1600248.

Warner, G. R., & Flaws, J. A. (2018). Bisphenol A and phthalates: How environmental chemicals are reshaping toxicology. *Toxicological Sciences*, *166*, 246–249.

Wilson, N. K., Chuang, J. C., Morgan, M. K., Lordo, R. A., & Sheldon, L. S. (2007). An observational study of the potential exposures of preschool children to pentachlorophenol, bisphenol-A, and nonylphenol at home and daycare. *Environmental Research*, *103*, 9–20.

Wrona, M., & Nerín, C. (2020). Analytical approaches for analysis of safety of modern food packaging: A review. *Molecules*, *25*, 752.

Włodarczyk, E. (2015). Occurrence of bisphenol A and its effects on the human body. *Archives of Physiotherapy & Global Researches*, *19*, 13–26.

Ye, X., Wong, L. Y., Kramer, J., Zhou, X., Jia, T., & Calafat, A. M. (2015). Urinary concentrations of bisphenol A and three other bisphenols in convenience samples of U.S. adults during 2000–2014. *Environmental Science & Technology*, *49*, 11834–11839.

Ying, G. G., & Kookana, R. S. (2005). Sorption and degradation of estrogen-like-endocrine disrupting chemicals in soil. *Environmental Toxicology and Chemistry*, *24*, 2640–2645.

Zalko, D., Jacques, C., Duplan, H., Bruel, S., & Perdu, E. (2011). Viable skin efficiently absorbs and metabolizes bisphenol A. *Chemosphere*, *82*, 424–430.

Zeng, G., Zhang, C., Huang, G., Yu, J., Wang, Q., Li, J., Xi, B., & Liu, H. (2006). Adsorption behavior of bisphenol A on sediments in Xiangjiang River, Central-South China. *Chemosphere*, *65*, 1490–1499.

Zero Waste Europe. (2021). *The polyvinyl chloride debate: Why PVC remains a problematic material* (p. 33).

Zhang, J., Cooke, G. M., Curran, I. H., Goodyer, C. G., & Cao, X. L. (2011). GC-MS analysis of bisphenol A in human placental and fetal liver samples. *Journal of Chromatography B*, *879*, 209–214.

Zhao, X., Qiu, W., Zheng, Y., Xiong, J., Gao, C., & Hu, S. (2019). Occurrence, distribution, bioaccumulation, and ecological risk of bisphenol analogues, parabens and their metabolites in the Pearl River Estuary, South China. *Ecotoxicology and Environmental Safety*, *180*, 43–52.

Žalmanová, T., Hošková, K., Nevoral, J., Prokešová, S., Zámostná, K., Kott, T., & Petr, J. (2016). Bisphenol S instead of bisphenol A: A story of reproductive disruption by regretable substitution—A review. *Czech Journal of Animal Science*, *61*, 433–449.

