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Abstract

With over 95% of BPA used in the production of polycarbonate (PC) and epoxy resins, termed herein 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 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. BPA restrictions 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. And 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.

Keywords: bisphenol-A (BPA); plastics; plastic waste; endocrine-disrupting chemicals; bioaccumulation; health effects

Introduction

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

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 and 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 and Nerín, 2020).

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). BPA 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 U.S. and Southeast Asian countries (Almeida et al., 2018). The worldwide production of BPA surpassed 6.5 million tonnes (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 produce epoxy resins (Hermabessiere et al., 2017), 65% is used in the manufacturing 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. PC 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 and Jwad, 2018)), safety equipment, automobiles, and a range of consumers items such as contact lenses and glasses, baby feeding bottles, CDs, DVDs, cosmetics, toys, and food containers including reusable drink 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) and wood-based products, and as a composite in paints (Hahladakis et al., 2018; Konieczna et al., 2015; Rochester, 2013; Shelby, 2008; Włodarczyk, 2015); offering

high thermal and fungicidal activity (antifungal agent) (ANSES, 2011); and as a sealant in dentistry due to their anti-inflammatory properties (Kitamura et al., 2002).

Present 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, 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 the 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 life cycle system (i.e. production-consumption-management).

In the 'Methodology' section, the study provides a short methodological description of the work that has been carried out, and in the section of 'Properties, occurrence and regulations regarding the use of BPA', there is 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 unpacks the potential human exposure to BPA via the lifecycle of BPA-based plastic MCPs. This part focuses on prevalent sources, mechanisms of release, and exposure pathways (via airways, or through ingestion of contaminated food and drink) 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' Section, 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 the 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, i.e., "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

BPA 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 Fig. 1) (Kang et al., 2006; Michałowicz, 2014; Proshad et al., 2018).

Figure 1. Chemical structure of BPA

BPA has fairly low solubility in water and volatility, with a relatively high melting point (at c.a. 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). BPA has, also, a high reactivity owing to the hydroxyl groups, which enables it to convert into ethers, esters and salts (Almeida et al., 2018). The majority of BPA's physicochemical properties can be found in Table 1.

Table 1. Physicochemical properties of BPA

Historically, the bioaccumulation potential of BPA is considered to be moderate, albeit the limited evidence on the degree to which BPA accumulates in the human body (Corrales et al., 2015). There has been little concern about bioaccumulation assuming that BPA is rapidly metabolised 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 and 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 photo-transformation of BPA occurs rapidly and, due to its chemical nature, hydrolysis may take place under irregular ambient/environmental conditions (Ajong et al., 2020). In soil, BPA is almost immobile due to its high soil–water partitioning coefficient of 314-1,524 and can formulate non-extractable residues in a short time (approx. 3 days) (Fent et al., 2003). BPA ionization could 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 and Kookana, 2005).

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 (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 (QA) and quality control (QC) issues, poor maintenance and pathology practices which could have produced ambiguous research results. Despite GAO's inspection, NCI and NTP did not re-evaluate the carcinogenicity of BPA with the latter reporting that

there is “no convincing evidence” for BPA’s carcinogenicity was found (see details in (Vogel, 2009)) (Huang et al., 2018; Huang et al., 2012).

In 2012, a collaborative research program was launched by FDA, NTP and the US National Institute of Environmental Health and Sciences (NIEHS) – 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 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 behavioural change (Patisaul, 2020).

In 2012 the FDA amended their food additive regulations, and particularly, removed those related to the use of PC in baby bottles, sippy cups and infant intended packaging, 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, BPA’s use 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 re-evaluation 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 re-assessment 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 µg/kg body weight per day to 0.04 ng/kg body weight per day (EFSA, 2021). This recent EFSA opinion stresses the adverse effects of BPA on the immune systems, especially in animals (EFSA, 2021), and highlights the importance of continuous re-assessment 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 surprise, and the future may bring further advancements and reforms.

Table 2 EU legislation regarding the use of BPA in plastic MCPs, and current permitted SMLs.

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 mg/kg to 0.05 mg/kg for BPA present in varnishes and coating and expanded its ban in the PC infant feeding bottles and cups (EU 2018/213, 2018). The EU Regulation 2018/213 specifies, also, that a written declaration of compliance (DoC) 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 analogues 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 in several end-users is mainly driven by the automotive industry (e.g. manufacturing of car headlights, bumpers, and dashboards) and manufacturing 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 and Flaws, 2018), has promoted the use of BPA by the BPA-based plastics 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 and Vandenberg, 2020). Historically, these traditional methods were carried out under high-dose testing taking the assumption of a linear dose-response curve (Warner and Flaws, 2018). However, scientific evidence suggests that these dose-response curves can be non-monotonic 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 non-monotonicity 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 and therefore setting safe limits for BPA is complex and currently deficient (Kumar et al., 2020).

Although European Commission 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 recognized the importance of implementing the ALARA principle to increase efforts for limiting human exposure to BPA (Legeay and Faure, 2017). CLARITY-BPA project highlighted that 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 plastics MCPs (Warner and 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 ageing (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/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/ beverage depends on: a) contact time between packaging and food; b) temperature (higher temperatures are associated with higher migration rates); c) food/ beverage composition (fatty foods are associated with increased migration of lipophilic molecules); d) type of contact between food/ beverage and packaging (Almeida et al., 2018; Hoekstra and Simoneau, 2013).

A few biomonitoring studies suggest that there might be several non-dietary exposure routes for BPA; supported by observations of BPA levels in humans that reached a plateau during an 8.5–24 hrs.' fasting interval (Stahlhut et al., 2009; Vandenberg et al., 2010). Non-dietary (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, etc. 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 and 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 and 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, i.e., 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.

Table 3 List of typical and most prevalent sources of BPA in BPA-based plastic MCPs and possible exposure pathways categorized based on the applications outlined by PlasticsEurope; Adapted by (Geens et al., 2011). 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.

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 non-oral exposure routes. By themselves, these exposure routes may lead to negligible effects, yet the cumulative behaviour 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. BPA has been detected in all environmental media, e.g. air, soil, water, landfill leachate, at concentrations ranging at levels between 5 and 1,950 ng/L (Li et al., 2020; Schug and Birnbaum, 2014; Zhao et al., 2019). Detailed description and exploration of the environmental impacts arising from these potential pathways fall outside the scope of this study.

The following sub-sections 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 get occupationally exposed to the compound. Employees that spend most of their time in the indoor environment, where BPA is produced and used, could be severely affected by it. Although data is 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 plastic industries) must be closely monitored to ensure the safety of workers in the plastics production industry (Berkner et al., 2004; Fu and 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). BPA concentration levels in the production facilities of BPA and plastics, need to be closely monitored and make sure 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/Use stage

Amongst 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

paediatric 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 drink). Glass and PET drink bottles which are 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 drink); higher than in cans and PET bottles (0.37-21.83 µg/L drink) (Khan et al., 2020). In addition, (González et al., 2020) estimated that dietary intake of BPA through the consumption of canned and non-canned 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 non-canned food is considerably lower (36% (González et al., 2020)). Several researchers have observed a 1,200% 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/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; Pivnenko et al., 2016b). For example, Nam et al. (2010) reported that alkaline pH and high temperatures (>80ºC) during sterilization of PC products can cause hydrolysis of carbonate linkage and increase d-spacing of PC 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 section 'Properties, occurrence and regulations regarding the use of BPA'. Baby bottles had been found to exponentially release BPA at approximately a rate of $4.9x10^{-2}$ 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 µg/kg water 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 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 to 14.3 µg/kg for all samples, filled with boiled water and left for 45 min at ambient temperature.

Cling film that is widely used to store 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 USA, found BPA concentration levels at 3.93, 3.82, 3.30, 17.67 and 57.75 µg/L, respectively. The intake (per day) were 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. BPA content varied among samples (3.3-7.57 µg/L) and the -per day- intake was found between 0.165-20.11 µg/kg body weight per day. Regarding food grade cling film samples, German was found to be the most appropriate and American the less suitable, respectively. In addition, the average BPA concentration level and per day intake, with all samples taken into consideration, were found at 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 0.013-30 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 USA (Bagley et al., 2021).

Other sources of exposure to BPA (e.g., transdermal, inhalation of air and dust, hand-to-mouth behaviour), such as medical devices, children's toys, electrical and electronic products (Geens et al., 2012a; Vandenberg et al., 2013), are considered to be contributing 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), and sport (e.g. sports equipment and clothing), and textile particularly in Asian countries (e.g. coated fabrics) (BPF, 2021b). While the focus of the study is on BPA-based plastic MCPs, we cannot ignore mentioning the occurrence of BPA in PVC MCPs. It is worth mentioning that in the study of (Geens et al., 2012a), BPA was detected in PVC film and ranged from 43-483 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 of 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

and 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 non-toxic 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 sector 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 push-through-blisters for pharmaceutical products (Du and 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 and 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. BPA may be deposited in the slag and fly ash produced, which are further treated (Arp et al., 2017; Im and Löffler, 2016). Currently, there is a lack of insight on the fate of BPA in waste-related outputs, and by-products, produced/used in the industrial sector.

In recycling facilities, the emission/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 isn't much evidence on the recycling of PC MCPs, limited information on BPA release from other plastics, such as PET, where BPA is found as a 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 (394-10120 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 post-consumer 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 on the quality of recycled PET, widely known as rPET (Gerassimidou et al., 2022; Schyns and 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 towards a more circular economy.

The inappropriate disposal of plastic waste due to the lack of regulations and proper infrastructure in developing countries (Vasiljevic and 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, etc., can be important sources of BPA release to the environment and subsequently to humans (Flint et al., 2012; Fu and 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 barrel 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 and Kawamura, 2010; Owens et al., 2007). However, owing to its low volatility and short photo-oxidation half-life (< 7 hours) 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). PC exhibits low solvent resistance (Pascault et al., 2012) due to carbonate groups being easily hydrolysed (Ortmann et al., 2014), which in turn, indicates that PC disposed of in the marine environment can be slowly degraded into microplastics (Artham and Doble, 2009). The percentage contribution of PC on the plastic soup 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 and 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 oxidised products in the supernatant (Artham and 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 and 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), wood (floor tiles, furniture). Exposure routes can be sub-categorised concerning occupational hazards

(prolonged or short-term exposure), intentional hazards (deliberate, frequent but controlled exposure that occurs mostly at the production and/or use stage), unintentional hazards (accidental release via improper waste management practices, inappropriate effluent discharges), etc. (Abraham and Chakraborty, 2020; Hahladakis 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 hormones' actions such as estradiol and this affects the organism's development in the early stages, bypassing the blood-brain and placental barrier (Abraham and Chakraborty, 2020).

BPA's impact on children's health

BPA can cause obesity in children and different other conditions, which makes it essential for BPA and its derivatives to be tracked in adipose tissue of children. The permissible dose of BPA, which can be absorbed within 24 hours, is 0.05 mg/kg body weight (Włodarczyk, 2015). (Trasande, 2014) investigated the potential health and economic benefits by removing BPA from food uses in the US estimating that BPA exposure was associated with 12,404 cases of childhood obesity and 33,863 cases of adult coronary heart disease resulting in a social cost of 2.98 USD billion in 2008. While sensitivity analysis showed that eliminating BPA from food uses could lead to the prevention of 6,236 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 at early life below the reference dose (specified at 50 μg/kg weight per day) may lead to mammary and prostate cancer due to its tumour-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, if pregnant women get exposed to BPA it can influence the proper development of their children. According to (Chou et al., 2011), the level of BPA detected in the placental blood evidence that the compound can be transported through the placental barrier to a fetus. Increased prenatal exposure to BPA has, also, been found to increase the risk of low birth weight and reduced gestational age and to cause adverse effects on adipokines in newborns, particularly in male babies (Bloom et al., 2011a; Bloom et al., 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, that 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). BPA 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 the placental (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 behaviour 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).

BPA impact on adults' health

BPA present in the human body has been associated with cardiovascular diseases, chronic respiratory failure, breast cancer, endometriosis, developmental disorders or autoimmune diseases (Vogel, 2009). This is also confirmed by literature findings that analysed 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, impacting negatively an embryo development; something that 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 had 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 easier and any hemodialysis filters can add a BPA burden in patients that undergo hemodialysis (HD). The serum levels of BPA and its analogues bisphenol-B (BPB), BPF and bisphenol-S BPS were monitored on patients with CKD, treated with 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. BPA 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 BPs 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 analogues (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 non-authentic 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 sulphate 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 non-pregnant 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 multi-laboratory 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; 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 additional monitoring of BPA bioaccumulation in humans.

Future clinical-epidemiological research on human exposure time to BPA (including prolonged exposure (Abraham and Chakraborty, 2020), population-specific BPA consumption patterns and a better understanding of action mechanisms mostly related to foetal 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 health care decision-makers for the minimisation 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, and wood beams and furniture), are worrisome. BPA-based plastic MCPs are crucial sources of BPA leading to a multitude of exposure pathways; reinstating the fact that BPA-based plastic MCPs 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 large. 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 are currently 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 prioritises the design of BPA substitutes (i.e. BPF and BPS) whose impacts on the environment and human health are critically underexplored. This raises the question of whether replacing BPA is better than reducing it; with the latter implying the prevention of BPA-based plastics production altogether. In between, researchers are trying to prove the cumulative effects of BPA on human health over short windows of research programmes, and instigate a paradigm shift from evaluating BPA effects based on the 'dose'. To this end, the CLARITY-BPA is strongly positioned to re-establishing 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 involved in the BPA-based plastic MCPs value chain need to collaborate to co-design and co-create 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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