A not so circular healthcare economy

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A not so circular healthcare economy: A review of challenges with plastic associated chemicals

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ABSTRACT

The versatility of plastic products results from additives, plasticizers, and chemicals that are included to obtain desired qualities. Research shows that these chemicals can leach from the plastic product throughout the lifecycle and cause negative effects to consumers and the environment. Health effects of these chemicals range from endocrine disrupters to carcinogens, yet the fate of these chemicals is still not well understood. When considering the healthcare sector's reliance on single-use plastics, the concern of leaching chemicals to vulnerable groups of patients becomes high. Furthermore, it's paramount to consider the substitution of these chemicals to ensure nonhazardous circularity and or recyclability of materials. Findings from this review suggest that while health effects of plastic associated chemicals addressed in this review are well studied, the implications of these chemicals on the circularity of materials are novel and must be considered in product design, within comprehensive regulations, and by healthcare facilities.

1. Introduction

The harmful effects of plastic-associated chemicals on human health are well studied [1–4]. Plastic-associated chemicals pose a threat to human health and the planetary boundaries including physical threats (the persistence of plastic in the environment), chemical threats (contributing to greenhouse gas emissions) and biological threats (toxicity affecting reproduction, early development, and cancer) [5]. While certain regulations within the European Union target some plastic-associated chemicals, comprehensive and global regulations that consider the entire value chain of plastic products are lacking. With a growing population and increased global demand for resources, the current linear economy or produce-use-dispose model is being challenged. The circular economy is regarded by researchers and global political bodies as a remedy to reduce global greenhouse gas emissions and keep resources within value chains [6].

When considering current efforts to increase the circularity of plastic products, most efforts focus on waste management and the recycling of plastic polymers. These efforts negate other substances in the product, including additives, which hinder recyclability and can result in the total loss of the polymer matrix and all additives therein [7]. In addition, current product design favor functionality and performance thus outweighing aspects such as collectability, separability, and recyclability [7].

Stabilizers, colorants, and flame retardants are included in the plastic production process, depending on desired product function, to increase flexibility, rigidity, color, and texture among other functions [8]. While highly coveted for their functions, these chemicals and additives are often not chemically or covalently bound to the plastic polymer, aside from certain flame retardants, and therefore have the potential to leach from the product throughout the products' life cycle and at the end-of-life [9–12]. Currently there are no methods available that analyze the combination of product-substance across the value chain, which could allow for localization of specific exposure routes [13]. Furthermore, the lack of publicly available data hampers the ability to produce global production estimates of these potential hazards [8].

Plastic has become ubiquitous among all sectors but especially within the healthcare sector where the convenience, flexibility, and light

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Table 1
An overview of the current chemical regulations in the EU that are addressed in this review as they relate to PFAS, phthalates, and BPA. Current gaps within these regulations pertaining to these specific chemical groups are illustrated by the lack of an "X" in the respective box.

Regulation:	Per- and polyfluoroalkyl substances (PFAS)	Phthalates	Bisphenols A (BPA)
Regulation (EC) No 1907/2006 of the European Parliament and of the Council of 18 December 2006 concerning the Registration, Evaluation, Authorization and Restriction of Chemicals (REACH) ***(Article 59(10) of the REACH Regulation: Substances of Very High Concern)***	x	x	x
Regulation (EU) No 2019/1021 on Persistent Organic Pollutants (POP)	x		
Council Directives 90/385/EEC and 93/42/EEC on Medical Device Regulation		x	

weight nature of plastic products have revolutionized the sector [14]. However, healthcare facilities should consider the risk of further exposing vulnerable groups of patients to these harmful chemicals and increase efforts to mitigate these exposures.

In this review, current chemical regulations and policies within the EU are used as a reference as the EU can be considered a frontrunner in the production of chemicals, chemical regulation, and implementation of circularity. We aim to highlight current EU regulations on chemicals, as well as documented health effects of these chemicals, to assess the remaining gaps of knowledge that should be considered by the UN within the upcoming Plastic Treaty. While environmental impacts from these chemicals are nonnegligible, this review focuses on the continued use of these medical plastic-associated chemicals for human health (patients) and the implications these chemicals have on the circularity of these materials.

2. Chemical regulations in the European Union

In the European Union (EU), chemicals present in medical plastics are regulated by different legislations that cover chemicals in general (*e.g. Regulation (EC) No 1907/2006 of the European Parliament and of the Council of 18 December 2006 concerning the Registration, Evaluation, Authorization and Restriction of Chemicals (REACH)* and the Regulation (EU) No 2019/1021 of the European Parliament and of the Council on Persistent Organic Pollutants [POP]) or are more specific to the medical field, as the Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017 on medical devices, amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 and repealing Council Directives 90/385/EEC and 93/42/EEC (Medical Devices Regulation) [15] (Table 1).

REACH and the POP regulation ban the production and use of certain PFAS substances, such as PFOS (perfluorooctane sulfonate) and PFOA (perfluorooctanoic acid) [16,17]. The recent European Chemicals Strategy for Sustainability [18] presents EU's vision for future chemical policy and intends to minimize the use of substances of concern for a safer use of chemicals, setting goals to 2050. It addresses issues and classes of chemicals relevant to medical plastics, such as chemical mixtures, endocrine disruptors, and persistent, mobile, and toxic substances.

More specifically to the medical field, the Medical Devices Regulation [15] addresses, among others, the "risk posed by contaminants and residues to patients", including substances, degradation products and processing residues that may be released by medical devices. Under this regulation, devices and materials that come into direct contact with the human body, transport, store or administer substances, must not contain CMR (Carcinogenic, Mutagenic, Reprotoxic substances) or endocrine disruptors above 0.1% (w/w), to limit their potential release and patient exposure. However, these thresholds are often enacted for a single compound and do not account for mixtures of chemicals [19].

The Medical Devices Regulation also specifically recognizes and addresses the risk of phthalates and refers to guidelines provided by the Scientific Committee on Health, Environmental and Emerging Risks [20]. This document intends to provide guidance on the benefit-risk assessment of the presence of phthalates with CMR or endocrine disrupting properties. Some phthalates (14 in total) are also present in Article 59(10) of the REACH Regulation: Substances of Very High Concern (SVHC) candidate list and will be banned if further placed on the Authorization list, unless specific exceptions are allowed by the European Commission.

Bisphenols A (BPA) is also present on the SVHC candidate list and is restricted under REACH since 2018. Although not completely prohibited yet, its use in some products like toys and food contact materials is already restricted. Even if BPA is further added to the Authorization list and completely banned, other bisphenols present in medical plastics can be problematic. For this reason, the European Chemical Agency assessed groups of bisphenols based on their properties and found that 34 of them may require further restriction under REACH.

As mentioned above, some PFAS are regulated under REACH. However, this group comprises thousands of substances that are currently not regulated. The large quantities of PFAS produced for the same uses makes it possible to produce each substance at rather low tonnage, which does not entail registration under REACH [21]. Additionally, many PFAS are polymers, which are not subject to registration either. However, due to the serious concerns posed by this class of chemicals, PFAS are specifically addressed in the Chemicals Strategy for Sustainability [18]. It aims to ban all PFAS for certain uses by 2050 and to regulate PFAS with a group approach to circumvent the issue of their presence in very high amounts. However, their use would be allowed when essential for society, highlighting the need to clearly define the essential-use concept [22]. Finally, some countries (Germany, Denmark, Netherlands, Norway, and Sweden) submitted a restriction proposal in January 2023 to ban all PFAS for production and use within EU.

3. Groups of chemicals

Below, three main groups of plastic-associated chemicals are analyzed through literature with a focus on their application in the medical sector. Phthalates, per- and polyfluoroalkyl substances, and Bisphenols A are specifically addressed as chemicals that have known negative effects on human health yet are currently still in use.

3.1. Phthalates

Phthalates, a common industrial compound that has been referred to as the most abundant man-made pollutant, contains the common chemical structure of dialkyl or alkyl/aryl esters of 1,2-benzenedicarboxylic acid [23]. Their physical properties, and therefore application, depends on the length and branching of the alcohol portion of the ester and are often added to products to hold color or fragrance, to provide a film or gloss, also in the case of some pharmaceuticals to provide timed releasing [23]. Phthalates, often referred to as plasticizers, in the form of polyvinyl chloride (PVC) are added to plastic medical products including tubing (used to administer oxygen to patients), to act as a lubricant between polymer chains and to maintain the PVC from becoming brittle at room temperature [24,25]. Excessive use (such as

flexing and handling) of the products (for examples tubes) can volatilize these chemicals into the tubing airspace [25].

Additionally, these plasticizers often contain smaller molecules compared to the larger polymer chains indicating that they are more prone to dissolving in aqueous environments, potentially increasing the risk of exposure to human, animals, and microbes [12]. The most commonly used plasticizers were phthalates, specifically di (2-ethylhexyl)phthalate (DEHP), which in many cases has been reported to be toxic and disrupt normal endocrine function in humans [26–28]. DEHP is one of the most widely used plasticizers in PVC medical devices (including blood bags, hemodialysis tubes, catheters, and gloves among other products) and includes properties such as suitability for steam sterilization, resistance to kinking, and surface finish, making PVC rather favorable in the healthcare sector [29]. In a study by Tickner et al., 2001 it was reported that in some instances, humans are exposed to clinically important levels of DEHP through exposure from PVC medical devices which may lead to adverse health effects in certain groups of patients [29]. DEHP is not bound to the PVC polymer and can leach from medical products when heated up or in contact with blood, drugs or IV fluids [29]. DEHP and other phthalates have been associated with a range of adverse effects on the liver, reproduction tract, obesity, and DNA stress or damage [30–32]. Previous studies have tested the negative effects of DEHP on animals and have further proven negative health effects such as acute toxicity of the liver and kidney, disruption of the endocrine system, and carcinogenic effects in rats and mice [33–35].

Altogether 14 phthalates (including DEHP) are on the authorization list which prohibits their use unless the European Commission specifically authorizes continued use, due to their endocrine disrupting potential [36]. Phthalates are further regulated in REACH, toy safety regulations, plastic in food packaging, hazardous substances in electrical and electronic equipment, and the Waste Framework Directive [36].

3.2. Bisphenols A (BPA)

Bisphenols constitutes a large group of synthetic chemicals with similar chemical structures, which are synthesized by the condensation of phenol with acetone [37] to produce plastics and resins [38–40]. Bisphenols A (BPA) is an organic compound with the chemical formula $C_{15}H_{16}O_2$ and has been added to many consumer products, including plastic products, since the 1950s. Its extensive production and application have resulted in PBAs global contamination of both the environment and humans. Due to the known impact of BPA, its use is being limited in the EU to protect human health and the environment [41].

BPA is primarily used in the production of polycarbonate plastics, epoxy resins, and as an additive in polyvinyl chloride (PVC) plastics. Polycarbonate is clear, lightweight, heat resistant, and strong which makes it suitable for a variety of applications such as baby bottles, reuseable water bottles, food containers, tableware, medical devises, dental sealants, protective and corrective eyewear, optical discs, bicycle helmets, transparent and heat resistant food containers, and electronic equipment (e.g., cell phones, laptops) [42–44]. Epoxy resins with BPA are used as protective coatings in, for example, hulls of ships, offshore oil drilling platforms, water ballast tanks, in electronic parts, on steel furniture, metal roofing, tools etc. BPA application in medical devices is extensive and includes products and devices such as medical tubing (as mentioned), hemodialysis devices, newborn incubators, respiratory masks (PVC) and dental composites [45,46].

BPA can leach from plastic products to food, air, soil, wildlife, and humans. Cimmino et al. (2020) reported that BPA is released to the environment during its full life cycles from production, over consumption to disposal, and that the routes of BPA exposure include ingestion, maternofetal transmission, inhalation, skin, and eye contact. Leaching from medical devices is considered an important source of BPA exposure in humans, where BPA has been found in human samples and tissues such as blood, urine, placental tissue, and breast milk [47,48]. BPA is an endocrine disrupter (EDC) acting as an agonist on estrogen receptors and as antagonist on androgen receptors and have several negative health impacts such as cancers, cardiovascular diseases, obesity, diabetes, reproduction, and neurological and behavioral disorders [45].

BPA is on the EUs list of very problematic compounds (SVHC list). It has been restricted as a substance on its own and in mixtures for consumer use in EU since March 2018, its use in thermal paper has been restricted since January 2020, it is banned from use in polycarbonate used in baby bottles since June 2011, and in drinking cups and flasks used for children below 3 years of age since September 2018 [41].

3.3. Per- and polyfluoroalkyl substances (PFAS)

Per- and polyfluoroalkyl substances (PFAS), also known as “forever chemicals”, are used in products or as precursors during production and manufacturing, due to their water-resistant properties, and consist of polymers and nonpolymers. They are class of chemicals that contains thousands of different substances which differ in the length of the carbon backbone (e.g., long-chain perfluorinated carbons versus short-chain molecules) [49]. PFAS are used in production of fluoropolymers, thermoplastics, polypropylene, epoxy resins and polyurethane elastomers as mold-release agents [50,51]. Their extensive production and use, since the 1940s, has led to widespread contamination and they have been identified as potentially hazardous in society [52].

In a review documenting the uses and functions of PFAS substances [53], identified more than 200 uses in 64 categories, including medical utensils. These were further grouped into 14 subcategories, including coatings for devices, apparel (surgical drapes and gowns) and equipment, electronic devices (e.g., defibrillators, pacemakers, video endoscopes, X-ray imaging), eye drops and contact lenses, utensils for retinal detachment surgery, filters, tubing, O-rings, seals, and gaskets used in dialysis machines, sutures, and X-ray films. The authors report that more than 100 PFAS were identified as used in medical utensils [53]. Beyond these uses, PFAS can also be found in medical facilities via incorporation into the built environment including electronic cable insulation, piping and linings of pipes, vessels, and valves, as well as in cleaning chemical containers [50]. Fluoropolymers, fluorocarbon-based polymers, including chemical-resistant, hydrophobic and lipophobic surface treatments, are used in various biomedical applications and pharmaceutical delivery systems [54]. Fluoropolymers are known to leach low molecular weight PFAS during processing and use [51].

Currently, 437 PFAS are identified in REACH [55]. However, in Nordic countries (Denmark, Finland, Norway, Sweden), substances do not need to be registered under the Substances in preparations in Nordic Countries (SPIN) if they are used in medicinal products [53], and they are exempted from mandatory registration. Furthermore, the use of PFAS in the plastics value chain is often not communicated to downstream actors resulting in knowledge gaps concerning exact uses, PFAS types and chemical structures, and concentrations or formulations, so little is publicly known about these substances in different products [56].

While the exposure routes for PFAS are many [57], the use of PFAS in medical equipment and utensils can be an additional exposure route for patients and staff, though this specific pathway is understudied. There are several negative health outcomes and disease clusters associated with PFAS exposure including certain cancers, hyperthyroidism, diabetes and obesity, fatty liver disease and immunosuppression [58–62]. For these reasons, there are calls for banning use of PFAS [63,64].

4. Human health impacts of these chemicals

Human homeostasis is tightly controlled by a series of different systems and mechanisms. A particular important part of this control is performed by the endocrine system that is composed of glands that secrete messenger molecules (hormones) that interact with specific targets (receptors), leading to the regulation of functions throughout the

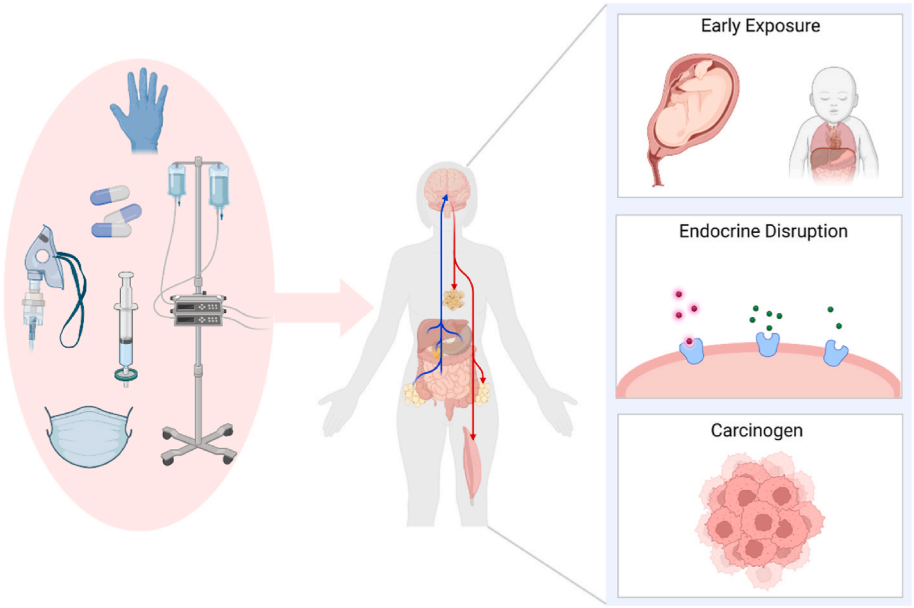

Fig. 1. Visual representation of sources, fate, and human health effects that plastic-associated additives have been linked to. While undergoing treatment, patients are exposed to cocktails of plastic-associated chemicals that leach from the product to the patient and cause a myriad of health implications such as early exposure to vulnerable children and neonates, endocrine disruption, and cancer. Created with BioRender.com.

body [65]. Multiple studies from the last decades have shown that chemicals from plastic (such as BPAs, phthalates and PFAs) can inadvertently interfere with this critical cellular system and cause adverse health effects on reproduction, energy balance, metabolism, immune defense, body weight regulation and during growth, resulting in what have been termed endocrine disruption [65,66] (Fig. 1).

A particular chemical class that is known to cause widespread effects is phthalates. Phthalates have been shown to increase the risk of reproductive impairment [67–69], cognitive deficits [70,71] and metabolic diseases [72], among others. The mechanisms behind such diverse actions are complex and dependent on disruption on the cellular level in a particular tissue as well as on circadian rhythms, seasonal changes, and sex [73]. The specific way that a given chemical is exerting its effects can vary considerably and can include antagonizing or activating receptors, changing key gene expression, changing signal transduction in hormone responsive cells, decreasing hormone synthesis or distribution [65]. This becomes even more complicated as effects can also include changing epigenetic programming or the fate of differentiating hormone-producing and hormone responsive cells, emphasizing that risk of lifelong adverse health effects is enhanced when exposure occurs during early development and associated differentiation and organ system formation [65].

In the adult, functional hormonal feedback regulation can ensure appropriate homeostasis is maintained even in the face of severe endocrine disruption [74]. However, during development such mechanisms are not yet in place. Thus, even short-term exposure during sensitive time windows have been shown to have adverse effects and result in permanent changes of morphology [75]. Due to the widespread use of plastics in health care, patients are exposed to a wide range of these exogenous chemicals which becomes problematic for vulnerable patients (such as neonates) that might unintentionally be exposed to a cocktail of different chemicals (Fig. 1).

5. Implications on circularity

The effects of leaching chemicals covered in the review range from endocrine disrupters to carcinogens. Most of the risks are well-documented in the literature, but some uncertainties still exist primarily related to the end of life and the fate of these leaching chemicals.

The European Green Deal [16] The EU Strategy for Plastic in the Circular Economy [76], and the Circular Economy Action Plan [77] aims to create a climate neutral and circular economy [78]. To meet the objectives of these policies, the healthcare sector, as a vital part of the economy, must contribute to the transformation towards a circular economy. In the circular economy, products and materials will be reused and recycled multiple times over the material lifecycle [79,80]. Waste products and packaging materials will be looped back into production of new products and services and the complexity of exposure scenarios will increase significantly [81,82].

The knowledge of risks associated with healthcare plastics, identified in this review, has several implications. First and foremost, related to the use of chemicals in healthcare plastic products, and secondly to the extensive consumption of single-use plastic in the health care sector [83]. Our review indicates that the design of future products and packaging must take into consideration the existing knowledge of chemical-associated risks to protect vulnerable groups from negative health effects. We suggest, first, to strategically target the phase-out of hazardous chemicals used in healthcare plastics. The literature suggests multiple strategies and principles that can be deployed by decision-makers in the healthcare sector to reduce exposure to hazardous chemicals. These principles and strategies cover the use of principles for circular chemistry [84], regulatory measures [85,86] and using green chemical principles in management [87]. Secondly, to reduce, reuse and recycle healthcare plastics [88,89]. [90] The healthcare sector is characterized by widespread use of SUPs [90,91] and extensive use of plastic packaging, generating huge amounts of plastic waste [92–94]. SUPs were originally introduced in medical product design to improve infection control, reduce costs and for practical reasons [91]. Kane et al. [95] argue that changes to product design in the healthcare sector comes at a higher risk than in other sectors of society, risks such as reduced functionality or increased infection risks caused by altered product design potentially could endanger already vulnerable patients' safety. However, despite such concerns, the literature indicates that potentials for reducing plastic consumption in hospitals exist, for example in operation theatres [94], medical product design [90,95,96] and in hospital cafeterias [92]. The studies suggest that such potential can be achieved without compromising patients' safety. In fact, the review of the health effects of chemical additives, ranging from endocrine

disrupters to carcinogens, presented above further indicates that reduced exposure to medical plastic products containing hazardous chemical additives could have positive health effects for vulnerable patients. Finally, we emphasize, that while the knowledge about negative health effects from plastic-associated chemicals may not be entirely new, the fact that plastic products will be recycled multiple times in the future circular economy will create complex and uncertain exposure scenarios [8] and does raise concern about the sustainability of the plastic consumption in healthcare sector.

6. Conclusion

While regulation in the EU has included considerations towards plastic-associated chemicals, more comprehensive and global regulations are lacking. The impact of plastic associated chemicals leaching from a products lifecycle are vast, and the current value chain of these chemicals and products are not sustainable. Our review of select groups of chemicals (phthalates, BPA, and PFAs) documents existing risks associated with these chemicals in healthcare plastics, products, and packaging and highlights current gaps within existing regulations pertaining to these chemicals. These gaps should be considered by upcoming legislations, including the UN Plastics Treaty, to increase the usability of these materials at the end of life and to further aid in the circularity of these materials. As legislations and regulations are beginning to favor reduced emissions, more circularity, and less waste generation, the healthcare sector should consider their role by reducing excessive use of single use plastics. Furthermore, legislation should also favor the phasing out of these hazardous chemical cocktails, only then will producers and manufacturers of plastic (medical) products be forced to reconsider current product designs.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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