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Plastics and cardiovascular disease

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Abstract

Plastics are synonymous with modern life. Nevertheless, the ubiquity of plastics has resulted in their continuous exposure to humans, which can be harmful. The available literature suggests that this daily exposure might be contributing to cardiovascular disease.

Human exposure to plastics

From water bottles to jumbo jets, plastics are one of the most widely used materials in the world. Since the 1950s, global plastic production has increased rapidly from 2 million to 380 million metric tons annually[1], and a staggering 20,000 plastic bottles are produced globally every second. The term plastic refers to the plasticity of these materials, because synthetic polymers can be moulded or shaped under conditions of heat. Synthetic polymers are mixed with chemical additives (such as plasticizers and colouring agents) to manufacture plastic products with specific characteristics and mechanical properties. Given the versatility, durability and exceedingly low cost of production, plastics are used extensively to manufacture consumer goods and have become synonymous with modern life. Indeed, avoiding plastics is virtually impossible because their use has extended to food and beverage packaging, toys, clothing, electronics, safety equipment and more. Plastics are also found in clinical environments, where they are used for 'blue wrap' packaging in surgical suites to sterilize and protect equipment, to create single-use sterile products (such as blood storage bags, syringes, catheters and medical tubing), and to improve the durability and biocompatibility of implantable devices (such as ventricular assist devices, heart valves, stents, pacemakers and orthopaedic devices).

Plastics are indispensable materials; however, their ubiquity has raised concerns about the continuous exposure of humans to plastics. To date, these concerns are primarily directed towards plasticizer additives, such as di(2-ethylhexyl) phthalate (DEHP) and synthetic chemicals used to create polymers, such as bisphenol A (BPA). The use of DEHP in the health-care field began shortly after World War II. Carl Walter, a surgeon and inventor, used

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Competing Interests

The author declares no competing interests.

DEHP as a plasticizer to soften polyvinylchloride plastic to create plastic blood bags. These new, flexible storage bags could be transported more easily than glass and could withstand steam sterilization, which reduced bacterial contamination. As DEHP is not covalently bound to the polyvinylchloride matrix, DEHP is prone to leaching from the plastic material. This effect unexpectedly acts as a preservative to stabilize red blood cells in DEHP-containing bags. Unfortunately, chemical leaching or migration can also result in substantial exposure of humans to DEHP through contact with these flexible plastics.

BPA was initially investigated as a synthetic oestrogen, but diethylstilbestrol was preferred owing to superior oestrogenic properties (but the compound is now known to be a carcinogen). Renewed interest in BPA occurred in the 1950s, when it was discovered that BPA monomers could be used to manufacture durable and transparent polycarbonate plastics or epoxy resins for protective coatings (such as for canned foods). Subsequent studies showed that incomplete polymerization or degradation of BPA-containing products can also result in human exposure to BPA. This finding prompted consumer concerns, which led to the discontinuation of the use of BPA in baby bottles and infant food packaging (although BPA was often replaced with a different bisphenol chemical). Nevertheless, both BPA and DEHP are still manufactured in high volumes and are used to produce a variety of consumer and medical products.

Unsurprisingly given the ubiquity of phthalates and bisphenols, biomonitoring studies have reported detectable levels of DEHP and BPA in 75–90% of the general population (reviewed previously[2]. Furthermore, occupational or clinical environments can result in elevated exposures to these chemicals. For example, paediatric patients undergoing cardiac surgery had large postoperative increases in urinary BPA (42%) and DEHP metabolite (1,500–2,100%) levels[3]. Plastic chemical concentrations can remain elevated from hours to weeks after surgery, depending on the duration of treatment, the extent of chemical migration and the age or metabolic capacity of the patient. Accordingly, vulnerable patients can incur cumulative chemical exposures that are 4,000-fold higher than the levels that are considered to be safe[4].

These exposures are concerning because both DEHP and BPA have endocrine-disrupting properties and can alter both hormone homeostasis and signal transduction pathways (reviewed previously[5]). As a result, these environmental contaminants might be contributing to human health conditions. Indeed, a 10-year longitudinal study found that high exposure to BPA was associated with a 46–49% higher hazard ratio for cardiovascular mortality and all-cause mortality compared with low exposure to BPA[6]. Moreover, epidemiological studies have reported associations between elevated urinary phthalate or bisphenol levels and an increased risk of coronary and peripheral artery disease, chronic inflammation, myocardial infarction, angina, suppressed heart rate variability and hypertension (reviewed previously[2]). The association with hypertension was further supported by data from a randomized controlled trial, which found a direct link between drinking from BPA-lined cans, a sharp increase in urinary BPA levels and a ~4.5 mmHg increase in systolic blood pressure compared with participants drinking from glass containers[7].

Mechanisms of cardiovascular toxicity

The mechanisms underlying these effects are likely to be multifactorial, but both population-based and experimental studies point to inflammation, oxidative stress and hormone imbalance as potential mediators. For example, an observational study showed increased DEHP levels in premature infants requiring fluids via intravenous tubing[8]. Patients with high DEHP levels had an increased risk of developing idiopathic hypertension that was linked to dysregulation of cortisol, a glucocorticoid stress hormone[8]. Further studies are needed to provide additional insights into the effects of plastic chemical exposures on cardiovascular health and patient outcomes.

Determining disease causation can be difficult in population and epidemiological studies, but experimental work has clearly shown a direct link between plastic chemicals and cardiac dysfunction. For example, BPA exposure disrupts myocardial calcium signalling, which is an important regulator of electrical activity, contractile function and vasoactivity. Acute exposure to BPA inhibits voltage-gated calcium channels and impairs intracellular calcium dynamics in rodent cardiomyocytes and ex vivo rodent heart tissue. Furthermore, these perturbations impair mechanical function and precipitate triggered activities in cardiomyocytes after exposure to either BPA or bisphenol S (a newly developed alternative to BPA)[9]. Of note, the described effects are largely reversible, suggesting that bisphenol chemicals can interact directly with calcium channels or post-translationally modify calcium-cycling proteins. Furthermore, the effects of BPA might be sex-specific and mechanistically linked to oestrogenic activity, because these effects are largely negated in oestrogen-receptor loss-of-function mouse models.

By contrast, DEHP is broadly considered to be a cardiodepressive agent. Acute exposure to DEHP or its main metabolite, mono(2-ethylhexyl) phthalate, decreases coronary flow and systolic tension in rat intact heart preparations and decreases contractile function in atrial tissue preparations. Moreover, phthalate treatment slows heart rate, atrioventricular conduction and epicardial conduction velocity[10]. The negative inotropic effects of phthalates might be mediated by interactions with muscarinic receptors, whereas disrupted gap junction intercellular connections can cause slowed electrical conduction. Importantly, gap junction uncoupling exists in other organ systems (such as the male reproductive tract and liver) exposed to phthalates.

It is too late to put this genie back in its plastic bottle, and whether these experimental results fully extrapolate to humans is still uncertain. Given the pervasiveness of plastics, future collaborative endeavours are needed to bridge the gap between experimental, epidemiological and clinical investigations to resolve the effect of plastics on cardiovascular health.

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