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Bisphenols and phthalates: Plastic chemical exposures can contribute to adverse cardiovascular health outcomes

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Abstract

Phthalates and bisphenols are high production volume chemicals that are used in the manufacturing of consumer and medical products. Given the ubiquity of bisphenol and phthalate chemicals in the environment, biomonitoring studies routinely detect these chemicals in 75–90% of the general population. Accumulating evidence suggests that such chemical exposures may influence human health outcomes, including cardiovascular health. These associations are particularly worrisome for sensitive populations, including fetal, infant and pediatric groups—with underdeveloped metabolic capabilities and developing organ systems. In the presented article, we aimed to review the literature on environmental and clinical exposures to bisphenols and phthalates, highlight experimental work that suggests that these chemicals may exert a negative influence on cardiovascular health, and emphasize areas of concern that relate to vulnerable pediatric groups. Gaps in our current knowledge are also discussed, so that future endeavors may resolve the relationship between chemical exposures and the impact on pediatric cardiovascular physiology.

Keywords

BPA; cardiotoxicity; DEHP; endocrine-disrupting chemical; environmental; heart

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CONFLICT OF INTEREST

Nothing to disclose.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

1 | INTRODUCTION

Over a lifetime, individuals are exposed to a variety of environmental chemicals that can contribute to nonhereditary components of health and disease. Environmental toxicology research can provide an understanding of how these chemical exposures influence human health. Of all the chemical exposures that individuals experience, phthalate and bisphenol chemicals have emerged as two potential contributors to cardiovascular dysfunction (Gao & Wang, 2014; Han & Hong, 2016; Lind & Lind, 2012; Mariana, Feiteiro, Verde, & Cairrao, 2016; Posnack, 2014). Phthalates and bisphenols are high production volume chemicals that are widely used in the manufacturing of consumer and medical-grade plastics. Due to their broad use in both industrial and consumer products, >2 billion pounds of bisphenol-A (BPA) and di-2-ethylhexyl phthalate (DEHP) are produced globally each year (Halden, 2010; Shelby, 2008). BPA is a synthetic monomer that is commonly used as a building block in polycarbonate plastic products, an epoxy resin for food packaging (e.g., canned goods), or in thermal printing applications (e.g., receipt paper). BPA polymers can degrade under normal conditions of use, and this deterioration is increased when subjected to elevated temperatures or mechanical stress (Krishnan, Stathis, Permuth, Tokes, & Feldman, 1993). DEHP is a high molecular weight phthalate that is frequently employed as a plasticizer in polyvinyl chloride (PVC) products, including medical devices and food packaging. Given the rigidity of PVC materials, phthalate plasticizers impart flexibility and elasticity to PVC products by embedding in between polymer segments to disrupt complete polymerization (National Research Council (U.S.) Committee on the Health Risks of Phthalates, 2008). Since phthalate plasticizers are not covalently bound to the PVC matrix, these chemical additives are susceptible to leaching (Tereshchenko & Posnack, 2019). Given the ubiquity of bisphenol and phthalate chemicals in the environment, biomonitoring studies routinely detect these chemicals in 75–90% of the general population, likely from multiple routes of exposure (ATSDR, 2019; Calafat, Ye, Wong, Reidy, & Needham, 2008; Hoppin, Brock, Davis, & Baird, 2002; Kato et al., 2004; Koch, Drexler, & Angerer, 2003; Koch, Rossbach, Drexler, & Angerer, 2003; Silva et al., 2004; Vandenberg et al., 2010; Y. Wang, Zhu, & Kannan, 2019; Zota, Calafat, & Woodruff, 2014).

Despite the benefits of plastics, their relative abundance in both the environment and clinical setting has raised concerns pertaining to human health. BPA and DEHP are both classified as endocrine-disrupting chemicals (EDCs) due to their ability to interfere with hormone homeostasis (La Merrill et al., 2020). BPA is considered a xenoestrogen because of its interactions with estrogen receptors (Ben-Jonathan & Steinmetz, 1998; Krishnan et al., 1993), whereas DEHP is broadly considered an antiandrogen due to its inhibitory effects on androgen receptors (Borch, Metzдорff, Vinggaard, Brokken, & Dalgaard, 2006; Swan, 2008). Although, it is important to note that both chemicals exert biological effects through multiple mechanisms of action. Once inside the body, bisphenol and phthalate chemicals may interact with nuclear receptors, hormone receptors, transcription factors, ion channels and disrupt intracellular signaling pathways (Ben-Jonathan & Steinmetz, 1998; Ito, Kamijima, & Nakajima, 2019; Jaimes et al., 2019; La Merrill et al., 2020; MacKay & Abizaid, 2018; Mariana et al., 2016; Moriyama et al., 2002; Nadal et al., 2000; Rowdhwil & Chen, 2018; Singh & Li, 2012; Sohoni & Sumpter, 1998; Soriano et al., 2016; Wetherill et

al., 2007; Ye et al., 2017). Many of these interactions can result in acute and rapid consequences. Unsurprisingly, exposure to EDCs, including phthalates and bisphenols, is associated with a variety of adverse human health outcomes, including hypertension, myocardial infarction, angina, atherosclerosis, diminished heart rate variability, impaired neurodevelopment, and inflammatory conditions (Casals-Casas & Desvergne, 2011; Halden, 2010; Mallow & Fox, 2014; Mariana et al., 2016; Schug, Blawas, Gray, Heindel, & Lawler, 2015; Verstraete et al., 2016; Yi et al., 2010). These health associations are particularly worrisome for sensitive populations, including fetal, infant and pediatric groups (Beszterda & Fra ski, 2018; Braun & Hauser, 2011; Braun, Sathyanarayana, & Hauser, 2013). Young children have an underdeveloped metabolic system, which can prolong exposure to EDCs and secondary metabolites (Beszterda & Fra ski, 2018; Lu & Rosenbaum, 2014). Early life exposures can also precipitate lasting effects on sensitive organ systems that are still developing (Meeker, 2012). Further, critically ill neonatal and pediatric patients often undergo multiple medical interventions that employ plastic materials, which can increase their cumulative exposure to levels that are 10–10,000 fold higher than observed in healthy populations (ATSDR, 2019; Calafat et al., 2009; Calafat, Needham, Silva, & Lambert, 2004; FDA, 2002; Mallow & Fox, 2014). In response to these health concerns, the U.S. Food & Drug Administration has recommended minimizing phthalate exposure to newborn boys during high-risk medical procedures—but refrained from taking further action (FDA, 2002). To date, patients continue to be inundated (inadvertently) with plastic chemicals that can distribute to sensitive organs, including the heart (Chu et al., 1978; Hillman, Goodwin, & Sherman, 1975; Jarosova, Harazim, Suchy, Kratka, & Stancova, 2009; Kim et al., 2004; Oishi & Hiraga, 1982; Shin et al., 2004; VandeVoort et al., 2016). Cardiovascular and autonomic function are highly susceptible to xenobiotic toxicity, and as such, exogenous chemical exposures may contribute to adverse health outcomes (Mlad nka et al., 2018; Rahm, Lugenbiel, Schweizer, Katus, & Thomas, 2018).

In the presented article, we aimed to review the literature on environmental and/or clinical exposures to bisphenols and phthalates, with a focus on potential cardiovascular outcomes and sensitive pediatric populations (Figure 1). We summarize (a) biomonitoring studies that have quantified environmental and clinical exposures, (b) experimental evidence of adverse cardiovascular effects and potential mechanisms, (c) epidemiological associations between chemical exposure and cardiovascular health, and (d) highlight the need for future studies to discern the risk to human health.

2 | BISPHENOL-A

2.1 | Environmental and clinical exposure to BPA

Bisphenols, including BPA, are used in the manufacturing of polycarbonate plastics and epoxy resins, including food and drink containers, water pipes, and thermal printed paper products (Vandenberg, Hauser, Marcus, Olea, & Welshons, 2007). Due to its ubiquitous use in consumer and medical products, human exposure to BPA is nearly continuous and biomonitoring studies routinely detect BPA in >90% of the population, including both children and adults (Calafat et al., 2005, 2009, 2008; Vandenberg et al., 2010; Woodruff, Zota, & Schwartz, 2011) (Supporting Information Table 1). Since BPA is a nonpersistent

chemical, urinary samples are often preferred in biomonitoring studies as the chemical concentration is higher (as compared to plasma or serum) (Koch & Calafat, 2009), and there is concern for environmental BPA contamination that can lead to erroneous results when blood samples are used for these measurements (Teeguarden et al., 2011; Teeguarden, Twaddle, Churchwell, & Doerge, 2016). Although some investigators note that assay contamination is well controlled in most laboratories, and argue that human BPA exposure is significantly understated (Taylor et al., 2011; vom Saal & Welshons, 2014). Accordingly, serum BPA levels remain actively debated, with reports ranging widely (Aris, 2014; Y. J. Lee et al., 2008; Padmanabhan et al., 2008; Schönfelder et al., 2002; Vandenberg et al., 2010; T. Zhang, Sun, & Kannan, 2013). For urinary samples, population-based studies have reported BPA concentrations that range from undetectable to 9.3 µg/L in relatively healthy adults and children (Vandenberg et al., 2007, 2010). One study suggested that high urinary and plasma concentrations may be partly explained by sublingual BPA absorption, which bypasses first-pass metabolism, while another group has refuted this suggestion using different sites of blood collection (Gayrard et al., 2013; Teeguarden et al., 2015).

It is important to note that the degree of BPA exposure can range dramatically depending on socioeconomic factors, lifestyle choices, medical status, and route of exposure. Oral exposure to BPA is considered the most prevalent, with exposure levels linked to dietary choices, including use of canned beverages with BPA liners (Bae & Hong, 2015; Cao, Corriveau, & Popovic, 2010). Skin absorption and/or inhalation can be associated with higher levels of circulating unconjugated or biologically active BPA that may persist for longer periods of time, as compared to ingestion which is subject to first-pass metabolism (Mattison, Karyakina, Goodman, & Lakind, 2014). In plasma, reports suggest that nearly 90% of BPA is bound to serum proteins and is considered inactive (Teeguarden, Waechter Jr., Clewell III, Covington, & Barton, 2005). Studies have also shown that BPA can penetrate and accumulate in the human placenta at higher levels than detected in maternal plasma, as placental enzymes may deconjugate BPA to its active form (Nishikawa et al., 2010; Schönfelder et al., 2002). Further, studies suggest that unconjugated or active BPA can readily pass across the placenta into fetal circulation (Gerona et al., 2016), and the expression of metabolizing enzymes responsible for BPA glucuronidation to its inactive form are reduced during the prenatal period (R. N. Hines, 2008). Additional studies are needed to fully understand the extent of fetal and infant exposure to bisphenols, and the potential downstream effects on pediatric health.

While environmental exposure to BPA is continuous at a relatively low dose (Koch & Calafat, 2009; Vandenberg et al., 2007, 2010)—clinical (Calafat et al., 2009; Duty et al., 2013; Gaynor et al., 2018) and occupational (C. J. Hines et al., 2018; Ribeiro, Ladeira, & Viegas, 2017) environments can result in higher BPA exposures (Table 1) (Calafat et al., 2009; Duty et al., 2013; Gaynor et al., 2018; Huygh et al., 2015). BPA has been detected in 60% of neonatal intensive care unit (ICU) supplies, and experimental studies have identified estrogenic activity in >25% of extracts from these items (Iribarne-Durán et al., 2019). Clinical exposure can result in heightened and/or prolonged exposure to BPA, particularly in neonatal and pediatric patients with an underdeveloped metabolic system (Calafat et al., 2009). Premature infants in the NICU setting had urinary BPA levels that ranged from 1.6–946 µg/L (Calafat et al., 2009). Clinical BPA exposure is associated with high-intensity

medical treatment, as premature infants requiring multiple (≥ 4) medical devices had higher urinary concentrations (36.6 µg/L) compared with those who required fewer devices (0–3 devices, 13.9 µg/L) (Duty et al., 2013). Collectively, premature infants undergoing intensive care had BPA exposures that were 16–32-fold higher than infants and children in the general population (Calafat et al., 2009; Duty et al., 2013). For comparison, an average 2–2.6 µg/L BPA (females, males) was detected in healthy infants not requiring invasive medical interventions (Mendonca, Hauser, Calafat, Arbuckle, & Duty, 2014). Considering the numerous sources of environmental BPA exposure during pregnancy (Joe M. Braun et al., 2011; Gerona et al., 2016), additional studies are warranted to understand prenatal exposure and risk (C. J. Patel et al., 2014). Similar results have been reported in adult intensive care patients undergoing invasive procedures including hemofiltration and circulatory support, which resulted in elevated urinary (6–680 µg/L) and serum BPA concentrations (2.6–255 µg/L) (Huygh et al., 2015). The latter underscores the importance of investigating inadvertent hospital-based chemical exposures, and the potential contribution to patient health outcomes.

The Environmental Protection Agency's reference dose for BPA is 0.05 mg kg⁻¹day⁻¹—which signifies an “estimate of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime” (U.S. Environmental Protection Agency, 1988). Although, it is important to note that this value was last updated in 1988—and additional experimental and epidemiological studies have highlighted a nonmonotonic dose response for BPA (Gore et al., 2015; Liang, Gao, Chen, Hong, & Wang, 2014; Vandenberg, 2014). Similar to other natural hormones, a nonmonotonic dose response has been observed in 20–30% of experimental BPA studies (Vandenberg, 2014). These findings suggest that risk assessments are needed for both “low” and “high” dose exposures, given the potential for a U-shaped dose response curve. Further, an increasing number of studies have shown negative health outcomes associated with BPA exposure, manufacturers have begun to replace BPA with structural analogs, including bisphenol-F (BPF) and bisphenol-S (BPS) (Moon, 2019; Moreman et al., 2017; Rochester & Bolden, 2015). Reference doses are not yet available for these structural analogs, as these other bisphenols have not been studied as thoroughly. Biomonitoring studies have compared urine concentrations of these three chemicals, and found that BPA remains the most prevalent, followed by BPF and BPS (Lehmle, Liu, Gadogbe, & Bao, 2018; Y. X. Wang, Liu, et al., 2019). Additional studies are needed to understand the degree of cumulative bisphenol exposure (e.g., BPA, BPS, BPF) and the potential risk to maternal, fetal and pediatric health across a range of concentrations (Figure 1).

2.2 | Effects of BPA on intercellular junctions

Cardiomyocytes are connected to neighboring myocytes via intercalated disks, a highly organized structure comprised of mechanical (desmosomes, adherens, and tight junctions) and electrical connections (gap junctions) (Vermij, Abriel, & van Veen, 2017). Intercalated disks integrate electrical and mechanical function across the myocardial tissue, and disruption of intercalated disk protein expression or their localization has been associated with cardiac arrhythmias (Kleber & Saffitz, 2014; Rampazzo, Calore, van Hengel, & van

Roy, 2014). Accordingly, environmental chemicals that disrupt cell–cell communication can have adverse effects on intercellular signaling and stability. To the best of our knowledge, experimental work addressing the potential effects of BPA-treatment on intercalated disk and sarcomeric proteins in cardiac preparations is limited (Belcher, Gear, & Kendig, 2015; Chapalamadugu, VandeVoort, Settles, Robison, & Murdoch, 2014). However, a number of studies have examined key protein targets in alternative cell types. As an example, experimental studies often employ a “bisphenol-a model” to induce tight junction and gap junction disassembly at the blood-testis barrier and/or in Sertoli cell lines (Li, Mruk, Lee, & Cheng, 2009, 2010). Using a supraphysiological concentration of BPA (200 μM), Li et al. reported that BPA exposure caused a transient disruption of tight junction permeability and reduced the expression of key proteins in tight junctions (occludin, junctional adhesion molecule A), adherens junctions (N-cadherin, β -catenin, α -catenin), desmosomal (desmoglein-2), and gap junctions (connexin-43) using Sertoli cells (Li et al., 2009). Similarly, Fiorini et al. noted that the expression of three connexin-43 isoforms were reduced in BPA-treated Sertoli cells, with a lesser effect on occludin and N-cadherin levels (Fiorini, Tilloy-Ellul, Chevalier, Charuel, & Pointis, 2004). Lee et al. also noted a reduction in connexin-43 expression in epithelium cells, which was mediated via nongenomic mechanisms (I.-K. Lee & Rhee, 2007). *in vivo* BPA exposure (2.4 mg kg⁻¹ day⁻¹) has also been shown to reduce connexin-43 expression in neonatal male rats at two time points tested (postnatal Days 45 and 90), as well as increase the expression of N-cadherin and zonula occludens-1 in the testes (Salian, Doshi, & Vanage, 2009). In cardiac tissue, the formation of mechanical junctions is considered a prerequisite for gap junction intercellular connections in cardiomyocytes (Rampazzo et al., 2014), and a similar disruption of key structural proteins could impair electrical conduction in the heart. Of interest, postoperative intestinal barrier dysfunction is commonly observed in children with congenital heart disease requiring cardiopulmonary bypass (Typpo et al., 2015). Cardiopulmonary bypass is known to precipitate an inflammatory response that can contribute to intestinal barrier dysfunction, yet, it is still unknown whether BPA exposure from tubing circuits may contribute to these effects.

2.3 | Effects of BPA on ion channels and electrophysiology

Ion channels play an important role in the generation of the cardiac action potential and electrical propagation, wherein disruption of ion channel localization, expression or function can precipitate cardiac dysrhythmias (Grant, 2009). Electrophysiology studies performed in HEK cells showed that BPA blocks hNav1.5 (IC₅₀ = 25 μM), the fast voltage-gated sodium channel subtype responsible for the action potential upstroke (Supporting Information Table 2) (O'Reilly et al., 2012). Results suggest that BPA inhibits sodium current by interacting directly with a binding site that is shared by local anesthetics, including mexiletine. In cardiac tissue, such an effect on sodium channel current is expected to reduce the rate of depolarization and slow cardiac conduction velocity. BPA exposure has also been shown to inhibit sodium channel current in isolated mouse dorsal root ganglion neurons—including both TTX-sensitive (IC₅₀ = 40 μM) and TTX-resistant (IC₅₀ = 70 μM) sodium currents (Q. Wang et al., 2011). BPA-inhibition was rapid, but reversible, with a dose–response relationship. Notably, these effects were blocked by protein kinase C (PKC) and protein kinase A (PKA) inhibitors, suggesting that BPA may act through a protein kinase-dependent

pathway. This result is in agreement with Gao et al., which found that BPA-induced effects on ryanodine receptors were mediated through an estrogen receptor beta (ER β) and PKA signaling pathway (Gao, Liang, Chen, & Wang, 2013).

BPA exposure has also been shown to inhibit calcium channel current, which is important for nodal cell depolarization, atrioventricular conduction, and the plateau phase of the cardiac action potential (phase 2). Using an HEK cell line, Michaela et al. demonstrated that BPA inhibits calcium current via T-type channels in a concentration-dependent manner with an IC₅₀ = 6–33 μ M, depending on channel subtype (Michaela, Mária, Silvia, ůbica, & L'ubica, 2014). Nanomolar concentrations did not affect voltage dependence or channel gating kinetics, but micro-molar concentrations accelerated the kinetics of current decay and inhibited calcium current amplitude. These findings suggest that BPA modifies channel gating and acts as a calcium channel antagonist at higher concentrations. In a separate study, Deutschmann et al. reported that BPA was a potent blocker of multiple voltage-gated calcium channels (Deutschmann, Hans, Meyer, Häberlein, & Swandulla, 2013). BPA rapidly and reversibly inhibited calcium current through native L-, N-, P/Q-, and T-type channels in rat endocrine cells, mouse dorsal root ganglion neurons or cardiac myocytes, and recombinant human R-type calcium channels expressed in HEK cells. In the latter, BPA was found to interact with the extracellular part of the channel protein without dependence on intracellular signaling pathways or voltage, and without affecting channel gating. Since channel gating was unaffected, this suggests a second mechanism by which BPA can directly interact with calcium channels externally, in its resting state. Similar inhibitory effects on L-type calcium channels have also been observed in rat aortic preparations (Feiteiro, Mariana, Glória, & Cairrao, 2018).

Estrogenic chemicals, like BPA, have also been shown to affect other ion channels, but the results are less conclusive (Soriano et al., 2016). Estrogenic agents can exert fast-acting stimulatory or inhibitory effects on big conductance calcium, L-type calcium, and voltage-activated potassium channels (Kow & Pfaff, 2016). As an example, BPA-treatment was shown to alter the gene expression of voltage-gated sodium, voltage-gated potassium, inward rectifier potassium channels and solute carrier transporters in cardiac tissue in a sex-specific manner (Belcher et al., 2015). The latter is attributed to the estrogenic effects of BPA, which can differ in males versus females due to disparate estrogen-receptor profiles (Hutson et al., 2019; Pugach, Blenck, Dragavon, Langer, & Leinwand, 2016). Asano et al. also reported a decrease in voltage-gated calcium and potassium channel activity in coronary smooth muscle cells treated with BPA (Asano, Tune, & Dick, 2010). Although, to the best of our knowledge, the direct effects of BPA on ion channel currents have not been measured in cardiomyocyte preparations.

The inhibitory effects of BPA on sodium and calcium channel currents (Soriano et al., 2016) can result in notable changes in cardiac electrophysiology, which has been observed in both ex vivo and in vivo experimental models. BPA-exposure can result in sinus bradycardia and delayed electrical conduction in rodent models, including prolonged P-wave duration, PR interval and QRS duration (Belcher et al., 2015; B. B. Patel, Raad, Sebag, & Chalifour, 2015; Posnack et al., 2014; Valokola et al., 2019). Patel et al. noted an exaggerated effect on electrical conduction in female BPA-treated animals in response to catecholamine challenge

(B. B. Patel, Raad, et al., 2015). In comparison, Belcher et al. observed heart rate slowing in BPA-treated male mice only, but noted exaggerated heart rate slowing in BPA-treated female mice in response to phenylephrine (Belcher et al., 2015). Using an ex vivo isolated heart model, we observed conduction slowing in response to acute BPA exposure that followed a dose response relationship (Posnack et al., 2014). In addition to BPA-induced effects on calcium current, which can directly impair cardiac automaticity and electrical conduction, Belcher et al. proposed that BPA may also slow heart rate by altering autonomic regulation (Belcher et al., 2015). The latter was supported by differential mRNA expression of beta-adrenergic receptors in BPA-treated animals, and may also explain increased sensitivity to beta-adrenergic agonists. Using isolated ventricular myocytes from female mice, Yan et al. reported that BPA rapidly induced arrhythmogenic triggered activities, which were exacerbated in the presence of isoproterenol (beta adrenergic agonist) and estradiol (Yan et al., 2011). The authors demonstrate that these triggered activities may be calcium mediated, as BPA altered protein phosphorylation to increase the likelihood of calcium leak from the sarcoplasmic reticulum. Notably, ryanodine inhibition suppressed spontaneous after-contractions that were induced by BPA or BPA + estradiol. Ultimately, there is evidence for BPA-induced effects on cardiac electrophysiology, but additional studies are needed to understand remaining questions about sex-specificity, dose-response relationships, direct versus intracellular signaling mechanisms, and the role of BPA exposure on developing hearts.

2.4 | Effects of BPA on calcium handling

As demonstrated in the described electrophysiology studies, a commonly reported effect of BPA-treatment is a disruption in calcium signaling (Supporting Information Table 3). Following acute BPA exposure, our laboratory reported alterations in intracellular calcium handling in neonatal rat cardiomyocytes (Ramadan et al., 2018), which can result in reduced cardiac contractility and left ventricular developed pressure in isolated, whole rat heart preparations (Posnack, Brooks, et al., 2015). The observed effects were rapid, and included smaller calcium transient amplitudes, prolonged calcium transient duration time, and an increased propensity for calcium amplitude alter-nans (Ramadan et al., 2018). Notably, the observed effects on calcium were largely reversible, similar to reports by others (Deutschmann et al., 2013), suggesting that these effects are mediated by either direct interactions with calcium channels and/or rapid posttranslational modifications of calcium-handling proteins (Gao et al., 2013).

Studies suggest that the effects of BPA on (adult) cardiomyocyte calcium handling are female-specific, due to BPA's interaction with estrogen receptors. Rapid exposure to low-dose BPA (1 nM) increased the incidence of ventricular arrhythmias following ischemia-reperfusion injury in female rat hearts, but these effects were not observed in male cardiac preparations (Yan et al., 2013). As previously noted, physiologically-relevant BPA concentrations can promote calcium-leak from the sarcoplasmic reticulum and increase the propensity of triggered activity in adult cardiomyocytes isolated from female rats (Yan et al., 2011). The pro-arrhythmic effects of BPA were negated when cardiomyocytes were pretreated with an estrogen receptor (ER) antagonist, or when applied to cardiac preparations from an ER β knockout model. Follow-up studies indicated that BPA-treatment

exerts monotonic effects via ER β signaling, but collectively the disruption on multiple intracellular calcium handling targets can result in a global nonmonotonic dose–response curve (Liang et al., 2014). Mechanistic studies revealed that BPA exposure alters intracellular signaling pathways, namely through PKA and calcium/calmodulin-dependent protein kinase II (Gao et al., 2013). In cardiac preparations, BPA exposure can alter the phosphorylation of ryanodine receptors and phospholamban, key regulators of calcium release and reuptake into the sarcoplasmic reticulum. In mouse hearts, BPA exposure was also shown to alter the expression of the sarcoplasmic reticulum calcium ATPase (SERCA) with decreased protein expression in both males and females, plus reduced phospholamban and sodium/calcium exchanger expression in females (B. B. Patel, Raad, Sebag, & Chalifour, 2013). It is important to note that BPA-induced cardiac effects may be mediated by ER and PKA signaling mechanisms, particularly at low exposure levels, whereas direct inhibitory effects on cardiac ion channels may occur at higher concentrations.

The combined effects of BPA on ion channels and calcium handling are particularly concerning for pediatric populations—as the immature heart can be sensitive to toxins, electrolyte disturbances, and alterations in calcium handling. Immature myocytes have rudimentary t-tubules, inefficient excitation–contraction coupling—with a greater dependence on sarcolemmal calcium flux and diffusion (Louch, Koivumäki, & Tavi, 2015). To date, the downstream effects of BPA on post-translational modifications of calcium handling proteins (e.g., phospholamban, ryanodine) or antagonism of T-type or L-type calcium in immature cardiomyocytes is largely unknown. Future studies are warranted to understand the role of BPA exposure in developing cardiomyocytes—and also to investigate potential mitigation strategies. Indeed, recent reports have highlighted progesterone pretreatment as a protective measure to block the effects of BPA on phospholamban and prevent BPA-induced arrhythmogenesis in female (adult) cardiomyocytes (Ma, Hong, & Wang, 2017).

2.5 | Effects of BPA on inflammation and remodeling

Pathological remodeling refers to changes in the heart that occur in response to injury, and may include cardiomyocyte hypertrophy, fibrosis, and changes in the extracellular matrix (Cohn, Ferrari, Sharpe, & Remodeling, 2000). Recent experimental studies suggest that chronic BPA exposure can also precipitate cardiovascular dysfunction by promoting cardiac remodeling and inflammation (Supporting Information Table 4). In one study, which examined pregnant mice and their progeny during chronic BPA exposure, sex-specific phenotypic changes included increased collagen extracellular matrix, increased fibrosis and modest cardiac remodeling (Belcher et al., 2015). In a follow-up study, as part of the Consortium Linking Academic and Regulatory Insights on BPA Toxicity (CLARITY-BPA) initiative, pregnant mice and offspring were chronically exposed to a full range of BPA concentrations (2.5–25,000 $\mu\text{g kg}^{-1} \text{ day}^{-1}$) (Gear, Kendzierski, & Belcher, 2017). BPA-exposed female offspring were at increased risk for cardiomyopathy, and both male and female offspring were prone to myocardial degeneration with signs of inflammatory cell infiltration. Rasdi et al. also reported an increase in maternal and fetal cardiac fibrosis following intrauterine BPA exposure (Rasdi et al., 2020). At higher BPA concentrations (50,000 $\mu\text{g kg}^{-1} \text{ day}^{-1}$), focal inflammation was observed in the cardiac tissue of pregnant

mice, which coincided with slowing of cardiac electrical conduction and increased systolic and diastolic pressure relative to vehicle control (Valokola et al., 2019). The authors noted an attenuation of BPA-induced effects when an anti-inflammatory agent was administered. These long-term studies highlight the potential adverse outcomes that perinatal BPA exposure can have on both maternal and fetal health.

In other cases, BPA exposure was found to exacerbate cardiac injury. To mimic plastic chemical exposure during cardiac surgery, Shang et al. exposed mice to a cocktail of BPA and phthalates as they recovered from myocardial infarction (Shang et al., 2019). Rodents exposed to plastic chemicals had increased cardiac dilation, increased immune cell infiltration, and impaired recovery. In a separate study, the authors also found that bisphenol exposure (25 ng/ml BPA or BPS) significantly impaired cardiac healing following myocardial infarction, with an increased inflammatory response and adverse cardiac remodeling (B. B. Patel, Kasneci, et al., 2015). Of interest, the effects of BPA exposure were significantly attenuated in ER β -knockout mice, which suggests that inflammation and cardiac remodeling may be attributed to the estrogenic activity of BPA (Kasneci et al., 2017). Additional injury studies have found that BPA exposure increases myocardial inflammation, fibrosis and elevated pro-inflammatory markers following viral infection (Bruno et al., 2019)—and that BPA exposure exacerbated the cardiotoxic effects of a chemotherapeutic agent, by increasing the production of pro-inflammatory interleukins in cardiomyoblasts (Quagliariello et al., 2019). These in vivo studies demonstrate how bisphenol exposure from medical procedures may impair patient recovery, particularly in populations susceptible to systemic inflammation from cardiopulmonary bypass or extracorporeal membrane oxygenation procedures.

2.6 | Effects of BPA on blood pressure regulation and cardiovascular disease

Inflammation and oxidative stress can contribute to the development of hypertension, cardiac remodeling, and cardiovascular disease (Cohn et al., 2000; González, Valls, Brito, & Rodrigo, 2014). Saura et al. noted a dose-dependent increase in angiotensin II and oxidative stress markers in BPA-treated animals (Saura et al., 2014). Pharmacological manipulations revealed that BPA-treated animals had an increase in blood pressure, which was mediated by AngII/CAMKII uncoupling of endothelial nitric oxides synthase. Of interest, population-based studies have also noted an association between BPA exposure, inflammation, and oxidative stress markers (Kataria et al., 2017; Steffensen et al., 2020; Y. X. Wang, Liu, et al., 2019; Yang et al., 2009)—including elevated F2-isoprostane levels in children. Accordingly, inflammation and oxidative stress are potential mediators of elevated blood pressure and hypertension in adults and children with higher BPA exposures (Aekplakorn, Chailurkit, & Ongphiphadhanakul, 2015; Han & Hong, 2016; Jiang et al., 2020; A. Shankar & Teppala, 2012). In pregnancy, preeclamptic women were found to have significantly higher BPA concentrations in placental tissue, compared to normotensive pregnant women (Leclerc, Dubois, & Aris, 2014). In another study, Philips et al. reported an association between BPA exposure and subclinical changes in placental hemodynamics that warrant additional study, but did not find a significant link to maternal blood pressure (Philips et al., 2019). Cross-sectional studies have also reported a link between maternal BPA exposure and elevated diastolic blood pressure in children (Bae et al., 2017; Warembourg et al., 2019). Whereas,

urinary BPA levels were associated with elevated blood pressure in children, with a greater effect in young boys compared with girls (Bae et al., 2017; Khalil et al., 2013; Sol et al., 2020). Accumulating evidence suggests that these associations are directly linked to BPA exposure, as demonstrated in a randomized trial (Bae & Hong, 2015). Specifically, Bae et al. found that urinary BPA concentrations increased by >1,600% in adult participants after consuming canned beverages containing BPA-liners. This increase in urinary BPA level was associated with an acute 4.5 mmHg increase in blood pressure. A follow-up study also found a positive association between urinary BPA concentrations and hypertension in elderly participants, and a negative association with heart rate variability (Bae, Kim, Lim, Park, & Hong, 2012). The latter may also be mechanistically linked to alterations in sympathetic tone and autonomic regulation, as previously described in experimental models (Belcher et al., 2015). BPA is largely considered an estrogen agonist, yet, recent work has highlighted that estrogenic activity can induce either vasodilation or vasoconstriction—depending on the product of nitric oxide synthase (nitric oxide vs. superoxide) (Fardoun et al., 2020). This is an area of research that requires additional attention—as BPA exposure has been shown to both increase (B. B. Patel, Raad, et al., 2015; Rasdi et al., 2020) and decrease (Belcher et al., 2015) blood pressure in rodent models. Although this discrepancy may be attributed to experimental design, which include different doses, treatment duration, and animals of differing age.

A few studies have also reported a relationship between BPA exposure and peripheral and/or coronary artery disease. Shankar et al. reported a positive association between BPA exposure and peripheral artery disease in a U.S. adult population (A. Shankar, Teppala, & Sabanayagam, 2012). Similarly, Melzer et al. reported that urinary BPA levels were associated with an increased risk of myocardial infarction and coronary artery disease (D. Melzer, Rice, Lewis, Henley, & Galloway, 2010). Follow-up studies highlighted that BPA exposure was also associated with severity of coronary artery stenosis and future risk of coronary artery disease in the adult population (Melzer, Osborne, et al., 2012; Melzer, Gates, et al., 2012). Although not directly applicable to pediatric populations, future longitudinal studies could investigate the link between early life exposure to BPA and cardiometabolic health later in life (Philips, Jaddoe, & Trasande, 2017).

3 | DI-2-ETHYLHEXYL PHTHALATE

3.1 | Environmental and clinical exposure to DEHP

Due to its low-cost of production and superior chemical properties for the manufacturing of flexible plastic products, DEHP remains the most widely used plasticizer in PVC products. Human exposure to DEHP can occur through contaminated drinking water, as widespread use can result in environmental contamination at waste sites, industrial locations, and/or landfills (ATSDR, 2019; Wowkonowicz & Kijeska, 2017). More commonly, daily exposure to phthalates occurs through inhalation, ingestion, or dermal contact with phthalate-containing personal care products and/or food packaging (ATSDR, 2019; Guo & Kannan, 2013; Koch et al., 2013; Rowdhwal & Chen, 2018; Wormuth, Scheringer, Vollenweider, & Hungerbühler, 2006). Indeed, dietary DEHP intake closely correlates with the daily variation of DEHP metabolites in urine samples (Fromme et al., 2007) and higher urinary phthalate

levels are associated with consuming food from plastic packaging (Giovanoulis et al., 2016). Accordingly, human biomonitoring studies have reported DEHP metabolites in 75–90% of biological samples collected from the general population, including both adults and children (Hoppin et al., 2002; Kato et al., 2004; Silva et al., 2004; Zota et al., 2014). Since DEHP is a nonpersistent chemical, biomonitoring studies often use urine samples for these measurements (Koch & Calafat, 2009). Although historical work focused on measuring the parent chemical (DEHP), more recent biomonitoring studies have quantified the sum of DEHP metabolites in urine or blood samples. DEHP is rapidly hydrolyzed to its monoester (MEHP, mono-ethylhexyl phthalate), which is further metabolized into secondary metabolites (MEHHP, 5OH-mono-2-ethylhexylphthalate; MEOHP, 5oxo-mono-ethylhexylphthalate; MECPP, 5carboxy-mono-2-ethylhexylphthalate [Kato et al., 2004]). This approach improves the accuracy of measurements, reduces the likelihood of environmental artifacts, and is biologically important—as studies suggest that DEHP's metabolites are more toxic than the parent chemical (Koch & Calafat, 2009; Latini, 2005) (Supporting Information Table 5). Recently, Zhang et al. demonstrated that median urinary DEHP concentrations is 38.5 µg/L in children (<18 years old) and 43.3 µg/L in older adults (X. Zhang et al., 2020). In pregnant females, the sum of DEHP metabolites can be even higher, ranging from 78.1–93.7 µg/L (Nassan, Gunn, Hill, Williams, & Hauser, 2020; Watkins et al., 2017).

In addition to consumer goods, phthalates are frequently used in PVC-based medical products, given their low cost, flexibility, strength, and suitability for steam sterilization (FDA, 2002; Tickner, Schettler, Guidotti, McCally, & Rossi, 2001). In the final product, DEHP can contribute up to 40% of the finished weight of plastic medical products (e.g., intravenous fluid bags, blood storage bags), and up to 80% of the weight of flexible medical tubing (Halden, 2010; Jaeger & Rubin, 1973, 2010; Plonait, Nau, Maier, Wittfoht, & Obladen, 1993). Since phthalates are not covalently bound to PVC, these chemical additives are known to leach or migrate into surrounding solutions, including blood (Table 2) (Barry et al., 1989; D'Alessandro et al., 2019; Demirel et al., 2016; Gaynor et al., 2018; Green et al., 2005; Kaestner et al., 2020; Karle et al., 1997; Mallow & Fox, 2014; Münch et al., 2020; Peck et al., 1979; Rael et al., 2009; Sjöberg, Bondesson, Sedin, & Gustafsson, 1985; Sjöberg et al., 1985; Stroustrup et al., 2018; Su et al., 2012; Takatori et al., 2008; van der Meer et al., 2014). Moreover, DEHP leaching is exacerbated under conditions of prolonged use, mechanical stress, higher temperature and/or in the presence of lipid-containing fluids. As an example, Karle et al. estimated that extracorporeal membrane oxygenation circuits leach DEHP at a rate of 0.32–0.57 µg ml⁻¹ hr⁻¹ in nonheparinized circuits (Karle et al., 1997), which corresponds to an exposure level that is 20–70× higher than reported for other invasive procedures. In another simulation study, Loff et al. reported that DEHP leaching was temperature dependent, with 30% greater leaching observed during lipid infusion at warmer temperatures (33 vs. 27°C). The authors noted that a 24-hr lipid infusion would result in a 2-kg infant receiving a DEHP exposure of 6.5 mg/kg. Similarly, Takatori et al. reported that enteral nutrition circuits (9–32% DEHP by weight) can result in considerable phthalate exposure in neonatal patients (148 µg kg⁻¹ day⁻¹ DEHP, 4 µg kg⁻¹ day⁻¹ MEHP). (Takatori et al., 2008).

In addition to tubing circuits, substantial phthalate leaching into stored blood products has also been reported (Cole, Tocchi, Wye, Villeneuve, & Rock, 1981; Luban, Rais-Bahrami, & Short, 2006; Peck et al., 1979; van der Meer et al., 2014). In red blood cell units, phthalate concentrations range from 5,300 to 38,100 $\mu\text{g/L}$ for DEHP and 800 to 14,800 $\mu\text{g/L}$ for its primary metabolite, mono-2-ethylhexyl phthalate (MEHP) (Münch et al., 2020). Notably, phthalate concentrations accumulate over time in stored red blood cell units—with DEHP levels increasing from 34.3 μM (± 20.0 *SD*) on Day 1 to 433.2 μM (± 131.2 *SD*) on Day 42, a 12.6-fold increase (Rael et al., 2009). Similarly, MEHP levels increase from 3.7 μM (± 2.8 *SD*) on Day 1 to 74.0 μM (± 19.1 *SD*) on Day 42, a 20.2-fold increase. Based on these measurements, Rael et al. estimated that a single red blood cell unit transfused close to expiry (42 days) would result in a circulating level of 740 nM MEHP and 4,330 nM DEHP (Rael et al., 2009). This estimate is in agreement with phthalate exposure measurements in neonates following an exchange transfusion, which resulted in 2.3–19.9 $\mu\text{g/ml}$ DEHP and 1.1–15.6 $\mu\text{g/ml}$ MEHP in blood samples (Sjoberg et al., 1985). With more than 3,000,000 infants admitted to the neonatal ICU each year in the United States, phthalate exposure from medical products is a considerable concern during this developmentally vulnerable period (FDA, 2002; Stroustrup et al., 2018). Neonatal and pediatric ICU patients can be exposed to multiple DEHP-containing plastic devices, which can result in a cumulative phthalate exposure of 16 mg/kg per day (Mallow & Fox, 2014). Such exposures can precipitate adverse health outcomes, including the cardiotoxic effects described in this review.

3.2 | Effect of DEHP on heart development and intercellular coupling

As previously described, cardiomyocytes are connected to neighboring myocytes via intercalated disks, a highly organized structure comprised of mechanical and electrical connections (Vermij et al., 2017). Intercalated disks integrate electrical and mechanical function across the myocardial tissue, and as such, disruption of these intercellular junctions can increase the incidence of cardiac arrhythmias (Kleber & Saffitz, 2014; Rampazzo et al., 2014). Accordingly, environmental chemicals that disrupt cell–cell communication can have adverse effects on intercellular signaling and stability. In rodents, DEHP-treatment has been shown to induce hepatocellular carcinomas (Klaunig, Ruch, DeAngelo, & Kaylor, 1988), which may be a consequence of DEHP's inhibition of gap junction intercellular communication—akin to tumor promoters (Isenberg et al., 2000; Kamendulis et al., 2002). Of interest, follow-up studies noted that in the liver, the loss of gap junctions was limited to mice and rats, suggesting a species-specific effect (Isenberg et al., 2000; McKee, 2000; Pugh et al., 2000). Notably, other groups have found a similar effect, with DEHP-treatment resulting in the inhibition of gap junction intercellular communication in other cell types, including lung fibroblasts (Cruciani, Mikalsen, Vasseur, & Sanner, 1997; Malcolm & Mills, 1989), Sertoli cells (Kang, Lee, Kim, & Kim, 2002) and cardiomyocytes (Gillum et al., 2009; Posnack, Idrees, et al., 2015). Loss of gap junction intercellular coupling can result in slowed electrical conduction in heart cells, which was reported in neonatal cardiomyocytes following phthalate treatment (Gillum et al., 2009). We reported that DEHP exposure slowed electrical conduction in cardiomyocyte layers in a dose-dependent manner (1–50 $\mu\text{g/L}$), with increased exposure resulting in an arrhythmogenic phenotype (Gillum et al., 2009). Additional studies are necessary to determine the role of phthalates in cardiomyocyte coupling, using in vivo models.

In addition to intercellular coupling, intrauterine DEHP exposure has been associated with cardiac malformations. Tang et al. reported that maternal DEHP exposure (250 mg/kg—1 g/kg) led to congenital heart defects and altered the expression of key cardiac transcription factors in mice (MEF2C, GATA4, CHF1) (Tang et al., 2018). These transcription factors are essential to cardiac development and the expression of sarcomere genes (Estrella & Naya, 2014; Suluba, Shuwei, Xia, & Mwanga, 2020). Of interest, Wang et al. reported that parental occupational exposure to phthalates was associated with an increased risk of congenital heart defects, including patent ductus arteriosus, atrial and ventricular septal defects (C. Wang et al., 2015). A similar result was reported by Snijder et al., which reported an association between paternal phthalate exposure and ventricular septal defects in children (Snijder et al., 2012). Little is known about the direct effects of environmental chemical exposures on cardiac development, but additional studies are warranted to investigate this link.

3.3 | Effect of DEHP on electrophysiology and contractility

DEHP exposure has been shown to directly affect cardiac electrophysiology and contractile performance in experimental models (Supporting Information Table 6). Multiple studies have reported a rapid cardiodepressive effect following DEHP (or MEHP) exposure. Rubin et al. reported that 4 µg/ml DEHP treatment completely stopped the spontaneous beating activity of chick cardiomyocytes after 30 min, and resulted in 97–98% cell death with 24 hr treatment (Rubin & Jaeger, 1973). Importantly, this dose is within the range of clinical exposure, as DEHP levels in children on extracorporeal membrane oxygenation can reach 24 µg/ml (Karle et al., 1997). A similar cardiodepressive effect was observed by Aronson et al., in which excised, Langendorff-perfused, rat hearts were treated with a DEHP dose similar to that reported in stored blood bags (250 µM) (Aronson, Serlick, & Preti, 1978). The authors noted a dramatic decrease in heart rate, coronary flow and systolic tension—all of which increased in severity throughout the duration of study (60 min total). Further, atrioventricular conduction and repolarization time were significantly slowed in hearts perfused with DEHP-containing buffer (Aronson et al., 1978). We reported a similar effect on human cardiomyocyte automaticity, in which the spontaneous beating rate of embryonic stem cell derived cardiomyocytes declined with 72-hr DEHP treatment (50 µg/ml)—underscoring the potential applicability to humans (Posnack, Idrees, et al., 2015).

To further characterize the effect of phthalates on cardiac electrophysiology, our laboratory selected a dose of MEHP (60 µM) comparable to patient plasma levels after exchange transfusion for isolated, Langendorff-perfused heart studies (Jaimes et al., 2019; Sjöberg et al., 1985). In this study, we observed that MEHP-treatment slowed sinus node recovery time, increased atrioventricular conduction time, and slowed epicardial conduction velocity (Jaimes et al., 2019). Effects on conduction time may be partly attributed to inhibitory effects on voltage-gated sodium channels, as voltage-clamp studies in HEK 293 cells revealed a reduction in fast and late sodium current, albeit at relatively high MEHP concentrations (IC₅₀ 874 and 231 µmol/L, respectively). Slowed conduction velocity may also be attributed to impaired gap junction intercellular coupling and reduced connexin-43 expression, which has been reported in neonatal cardiomyocytes following phthalate treatment (Gillum et al., 2009). Indeed, we reported that DEHP exposure slowed cardiomyocyte conduction velocity in a dose-dependent manner (1–50 µg/L), starting 24 hr

after exposure (Gillum et al., 2009). After prolonged treatment (72 hr), cardiomyocyte uncoupling resulted in an arrhythmogenic phenotype, which may be attributed to decreased connexin expression and/or localization.

Relatively few studies have examined the mechanistic underpinnings of phthalate chemicals on cardiac ion channels and calcium handling that may explain the observed changes in cardiac electrophysiology and contractility. Using microarray analysis, our laboratory reported that DEHP-treatment alters the mRNA expression of ion channel and calcium-handling genes in neonatal cardiomyocytes (Posnack, Lee, Brown, & Sarvazyan, 2011). Specifically, DEHP treatment decreased the expression of calcium handling genes, including calponin, troponin C, and calsequestrin 2—and increased the expression of ryanodine receptor 2, cardiac calcium transporting ATPase, triadin, voltage-dependent L-type calcium channel, phospholamban, sodium/potassium transporting ATPase. Such changes in global gene expression may explain some of the phenotypic observations in both cardiomyocytes and heart tissue, as both nodal cell automaticity and myocardial contractility are sensitive to changes in calcium ion homeostasis. As an example, our group reported that human embryonic stem cell-derived cardiomyocytes are sensitive to DEHP-treatment, which reduced the spontaneous beating rate, decreased the calcium transient amplitude and altered calcium transient kinetics (Posnack, Idrees, et al., 2015). DEHP-treated cells also displayed triggered activity following external pacing, which can be calcium-mediated. These results align with those of Barry et al., which reported decreased contractility in human atrial trabeculae in response to MEHP exposure (Barry, Labow, Keon, & Tocchi, 1990). The authors suggested that MEHP may act on cholinergic receptors, as atropine blocked its cardiodepressive effects. Alterations in calcium current have also been reported in other cell types. Mariana et al. found that DEHP-treatment inhibited L-type calcium channel current in vascular smooth muscle cells (Mariana, Feiteiro, & Cairrao, 2017). Future studies are warranted to fully elucidate the mechanistic effect of phthalates on calcium flux, cardiac electrophysiology, and contractility—including the relative timing required for these effects.

Finally, phthalate exposure has been shown to inhibit potassium ion channels that are important for establishing cardiac repolarization (Phase 3) and the resting membrane potential (Phase 4, cardiac action potential). Wu et al. reported that DEHP-treatment suppressed the amplitude of ether-a-go-go-related-gene potassium current (IK[erg]) in a pituitary cell line, in a concentration-dependent manner ($IC_{50} = 16.3 \mu M$) (Wu, Yang, Yeh, & Huang, 2012). It is important to note that the human ether-a-go-go-related gene (hERG) has been implicated in cardiac arrhythmias, as hERG channel inhibition delays repolarization (Phase 3) and presents as QT prolongation on electrocardiograms (Sanguinetti & Tristani-Firouz, 2006). DEHP exposure has also been shown to alter potassium current in hippocampal cells. Ran et al. reported that high phthalate concentrations (100–300 μM DEHP) reduced the frequency of mini excitatory postsynaptic currents, increased the firing threshold needed to induce neuronal action potentials, and reduced the outward current through voltage-gated potassium channels (Kv current) (Ran, Luo, Gan, Liu, & Yang, 2019). As previously mentioned, cardiac repolarization is largely determined by outward potassium current. To the best of our knowledge, the direct effect of phthalates on potassium current have not been measured in cardiomyocyte preparations—however, our group did observe a

dose–response relationship between increased DEHP exposure (1–50 µg/ml) and decreased potassium channel gene expression (Posnack et al., 2011).

3.4 | Effects of DEHP on metabolism

EDCs, including DEHP, have been shown to interact with nuclear receptors to modulate gene expression (Casals-Casas & Desvergne, 2011). Our laboratory previously reported that DEHP exposure upregulates PPAR α (peroxisome proliferator-activated receptor alpha) and its coactivator, PGC1 α (peroxisome proliferator-activated receptor gamma, coactivator 1alpha) to increase the utilization of fatty acid substrates in cardiomyocytes (Posnack, Swift, Kay, Lee, & Sarvazyan, 2012). Importantly, both PPAR α and PGC1 α act as sensors to modulate metabolic activity (Lopaschuk, Ussher, Folmes, Jaswal, & Stanley, 2010). We also reported that myocardial reliance on fatty acid oxidation resulted in an inhibition of glucose oxidation and an accumulation of lactate. Using an ex vivo Langendorff-perfused heart model, Aronson et al. reported a 400% increase in lactate levels, 50% decrease in ATP production and depressed contractile function following DEHP exposure (Aronson et al., 1978). Similarly, Martinelli et al. reported an accumulation in the skeletal muscle of DEHP-treated animals (Martinelli, Mocchiutti, & Bernal, 2006), which further supports the notion that DEHP disrupts glucose metabolism. Notably, PPAR α overexpression in mice leads to an unexpected phenotype with increased plasma glucose/insulin levels and glucose/insulin intolerance (B. Finck et al., 2005). Cardiac-specific PPAR α overexpression in mice leads to lipid accumulation, reduced glucose utilization, insulin resistance, and signs of cardiomyopathy (B. N. Finck et al., 2002).

Given its interaction with PPAR nuclear receptors, this is one potential mechanism by which DEHP exposure can disrupt energy metabolism and contribute to metabolic disorders. Indeed, Amara et al. reported that DEHP exposure (5–200 mg/kg) altered the serum lipid profile of mice by increasing total cholesterol, triglycerides, low and high density lipoproteins (Amara et al., 2019). The authors also reported an increase in inflammatory and oxidative stress markers, which coincided with increased myocardial injury in DEHP-treated animals. Similar findings have been observed in children with increased MEHP exposure, which was associated with obesity, elevated triglycerides and increased blood pressure in children age 6–18 years old (Amin et al., 2018). Most recently, a meta-analysis study by Golestanzadeh et al. concluded that phthalate exposure was associated with increased cardiometabolic risk factors in children (Golestanzadeh, Riahi, & Kelishadi, 2019).

3.5 | Effects of DEHP on blood pressure regulation

Early life exposure to phthalates can lead to vascular adaptations that increase the risk of cardiovascular disease later in life (Sol et al., 2020; Trasande et al., 2013). Cross-sectional studies have found an association between higher urinary phthalate levels and a propensity for elevated systolic blood pressure in children (Trasande et al., 2013; Trasande & Attina, 2015) (Supporting Information Table 7). Specifically, the work of Trasande et al. has highlighted a link between phthalate exposure and increased blood pressure in children (aged 8–19 years), while an observational cohort study by Jenkins et al. found a similar association in premature infants subjected to clinical phthalate exposure (Jenkins et al., 2019; Trasande et al., 2013). Experimental work indicates that the mechanisms responsible

for phthalate-induced prehypertension are multifactorial, but may be related to increased cortisol: cortisone levels and mineralcorticoid receptor-mediated sodium retention (Jenkins et al., 2019; Zhao et al., 2010). Other studies suggest that DEHP-induced oxidative stress may be responsible for increased systolic blood pressure (K. Ferguson, Loch-Caruso, & Meeker, 2011; Hong et al., 2009). Human urinary DEHP-metabolite levels have been associated with increased serum C-reactive protein, an inflammatory marker (K. Ferguson et al., 2011), and the oxidative stress markers gamma glutamyltransferase (K. Ferguson et al., 2011) and malondialdehyde (Hong et al., 2009; Kambia et al., 2011). The latter is a biomarker of free radical production, which may alter arterial tone and increase blood pressure (Kambia et al., 2011). Additional studies have found an association between maternal urinary phthalate levels and 8-isoprostane, a biomarker of oxidative stress, in children (14 years of age) (Tran et al., 2017) and women with preterm birth (K. K. Ferguson, McElrath, Chen, Mukherjee, & Meeker, 2015). Increased oxidative stress during the vulnerable period of development could alter fetal programming and increase the risk of cardiovascular disease later in life (Giussani et al., 2012; Warembourg et al., 2019).

The downstream effects of maternal DEHP exposure on the developing fetus remain less clear. Valvi et al. and Vafeiadi et al. have reported that maternal DEHP exposure is associated with a decrease in systolic blood pressure in children aged <7 years (Vafeiadi et al., 2018; Valvi et al., 2015). Similarly, Sol et al. reported that maternal phthalate exposure was associated with a decrease in systolic and diastolic blood pressure in girls, but not boys (mean age 9.7 years) (Sol et al., 2020). It has been suggested that the endocrine-disrupting properties of DEHP results in impaired adrenal function, which is a potential mechanism for this decrease in blood pressure. Indeed, some experimental studies have reported a decrease in blood pressure following maternal DEHP-treatment ($100\text{--}300\text{ mg kg}^{-1}\text{ day}^{-1}$), which may be related to altered adrenal function that decreases aldosterone production and angiotensin II expression (Martinez-Arguelles et al., 2014, 2013; Martinez-Arguelles, Guichard, Culty, Zirkin, & Papadopoulos, 2011). Yet, others have reported that maternal DEHP exposure ($0.25\text{--}30\text{ mg/kg}$) impairs renal function and decreases endothelial nitric oxide synthase activity, resulting in increased blood pressure in rodent offspring (K.-I. Lee et al., 2016; Wei et al., 2012). Differing conclusions between studies may be partly attributed to variable dosing regimens, which can lead to significant differences in circulating phthalate levels. Additional mechanistic studies are needed to fully understand the effects of phthalate exposure during prenatal and postnatal development, and the potential impact on cardiovascular health later in life.

4 | CONCLUSION

We aimed to review the literature on environmental and clinical exposures to BPA and DEHP—two high production volume chemicals that have emerged as potential contributors to cardiovascular dysfunction. Our current understanding of BPA and DEHP cardiovascular toxicity is a product of epidemiological and experimental studies. Epidemiological studies are useful in identifying the extent of chemical exposures and their association with adverse health conditions, whereas experimental studies are necessary to identify causation and pinpoint potential mechanisms. Collaborative efforts are needed between investigators with expertise in epidemiology, clinical, and basic science to fully address cardiovascular health

concerns related to “plastic” exposure. Future areas of interest include: (a) epidemiological or clinical research with additional cardiovascular endpoints—including electrocardiogram or echocardiogram measurements; (b) clinical and experimental work that focuses on vulnerable patient populations—including those with congenital heart defects, cardiomyopathies, or cardiac arrhythmias, as chemical exposures may contribute to cardiovascular dysfunction; (c) clinical and experimental work focused on neonatal, infant and pediatric populations—as cardiac, autonomic and metabolic systems continue to develop and mature after birth; (d) use of (nonrodent) experimental models that better replicate human electrophysiology; (e) studies that explore the effects of bisphenol and phthalate mixtures (or studies that take into account a pediatric patient’s “exposome”); and finally, (f) comparative studies that examine the cardiac safety profile of alternative chemicals. The latter is particularly important as we move toward adopting BPA and DEHP substitutes, without a thorough understanding of their safety or impact on cardiovascular health (M. Ferguson, Lorenzen-Schmidt, & Pyle, 2019; Gao, Ma, Chen, & Wang, 2015; Lozano & Cid, 2013; Trasande, 2017; van der Meer et al., 2014). Through comprehensive examination of bisphenol and phthalate toxicity in vulnerable populations, protective measures or mitigation strategies may be revealed and implemented.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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FIGURE 1. Phthalate and bisphenol chemical exposures from medical devices and consumer products may contribute to adverse cardiovascular outcomes. Image designed using resources from Biorender and [Freepik.com](https://www.freepik.com)

TABLE 1

Bisphenol-A, clinical exposure

Description	Biological sample	Mean concentration, µg/L (range)	Reference
Preoperative infants (5.4 ± 3.8 days)	Urine	9.8 (7.3–13.3)	Gaynor et al., 2018
Postoperative infants (5.4 ± 3.8 days)		13.9 (10.8–18.0)	
NICU infants (<44 weeks)		30.3 (1.6–946)	Calafat et al., 2009
Breastfed NICU infants (27–40 weeks)		23.3 (12.8–40.7) (median)	Duty et al., 2013
Formula-fed NICU infants (27–40 weeks)		13.1 (9.2–40.6) (median)	
NICU infants using >4 medical devices		36.6 (17.2–47.3) (median)	
NICU infants using <4 medical devices		13.9 (9.2–35.1) (median)	
Adult, ICU		1.3 (<LOD—203.3)	Huygh et al., 2015
Adult, venovenous hemofiltration		3.9 (<LOD—17.8)	
Adult, ECMO		11.2 (1.6–17)	

TABLE 2

Di-2-ethylhexylphthalate, clinical exposure

Description	Biological sample	Mean concentration, µg/L (range)	Reference
<i>Patient samples</i>			
NICU patients RBC exchange transfusion	Plasma	DEHP 5.8–19.6 µg/ml MEHP 5 µg/ml (maximum)	Sjoberg, Bondesson, Sedin, & Gustafsson, 1985
NICU patients RBC exchange transfusion	Plasma	DEHP 2.3–19.9 µg/ml (range) MEHP 1.1–15.6 µg/ml (range)	Sjoberg et al., 1985
Infants, bypass Age range: 2 months to 2 years	Whole blood	DEHP 1.10–5.06 µg/ml (range) MEHP 0.06–2.66 µg/ml (range)	Barry, Labow, Keon, Tocchi, & Rock, 1989
NICU patients, ECMO	Plasma	DEHP 0–24.18 µg/ml (range)	Karle et al., 1997
NICU patients High exposure group	Urine	MEHP 86 (median)	Green et al., 2005
NICU patients, w/o IV injections Median	Urine	MEHP 73.3 (38.8–157) MEHHP 62.8 (18.7–833) MEOHP 49.7 (17.1–261) DEHP 155 (78.0–1,203)	Su et al., 2012
NICU patients, with IV injections Median		MEHP 178 (48.9–1,273) MEHHP 393 (41.5–10,225) MEOHP 266 (27.1–9,268) DEHP 805 (160–20,766)	
NICU patients (preterm) Gestational age range: 28.9 ± 1.5 weeks	Urine	DEHP 5.8 (0–163.7) MEHP 13 (0–1,234.3) MEOHP 239.6 (0–5,841.5) MEHHP 319.5 (0–5,068.6) MEHHP 6.9–240.5	Demirel et al., 2016
NICU patients (preterm) Feeding tube only		MEHHP 9.2–255.3	
NICU patients (preterm) Ongoing intervention			
Infants (preoperative) Age range: 5.4 ± 3.8 days	Urine	MECPP 58.5 (29.4–116.5) MEHHP 10.7 (5.7–20.0) MEOHP 7.2 (3.9–13.2) MEHP 1.7 (0.8–3.9)	Gaynor et al., 2018
Infants (postoperative) Same patients as preoperative		MECPP 1166.1 (576.7–2,357.9) MEHHP 229.0 (119.6–438.4) MEOHP 148.6 (72.2–305.6) MEHP 27.2 (14.9–49.5)	
NICU patients (preterm) Median	Urine	MEHP 7.12 (0.5–72.39) MECPP 49.72 (0.2–304.95) MEHHP 11.84 (0.56–164.58) MEOHP 11.95 (55.0–148.57)	Stroustrup et al., 2018

Description	Biological sample	Mean concentration, µg/L (range)	Reference
NICU patients (preterm) Lowest exposure group Median (25th–75th percentile)		DEHP 68.4 (31.0–107.7)	
NICU patients (preterm) Highest exposure group Median (25th–75th percentile)		DEHP 134.0 (80.0–199.7)	
Adult ICU patients on ECMO 20–72 years old Median	Blood	DEHP 156.0 (31.5–1,009), MEHP 15.9 (<LOD to 475),	Kaestner et al., 2020
Adult ICU patients w/ 2+ ECMO cannulas, 20–72 years old Median	Blood	DEHP 338 (median) MEHP 114.9 (median)	
Adult ICU patients w/ >1 ECMO membranes, 20–72 years old Median	Blood	DEHP 535 (median) MEHP 114.9 (median)	
Adult ICU patients on ECMO w/o urine output, 20–72 years old Median	Blood	DEHP 823 (median) MEHP 214 (median)	
<i>Blood/other samples</i>			
Simulated neonatal exposure, Enteral nutrition	Nutrition	DEHP 148 µg kg ⁻¹ day ⁻¹ (maximal) MEHP 3.72 µg kg ⁻¹ day ⁻¹ (maximal)	Takatori et al., 2008
Packed RBC storage bags Day 1	RBC supernatant	DEHP 34.3 µM (±20.0 SD) MEHP 3.7 µM (±2.8 SD)	Rael et al., 2009
Packed RBC storage bags Day 42		DEHP 433.2 µM (±131.2 SD) MEHP 74.0 µM (±19.1 SD)	
DEHP exposure in blood products Following passage through PVC tubing	Plasma	DEHP 6.4–29 µg/ml (packed red blood cells) DEHP 27.6–405 µg/ml (fresh frozen plasma) DEHP 34.2–61.4 µg/ml (platelets)	Mallow & Fox, 2014
Unwashed RBC units Median storage time: 8 days	RBC unit blood	DEHP 5.3–38.1 mg/L (range) MEHP 0.8–14.8 mg/L (range)	Münch et al., 2020
Washed RBC units Average storage time: 31.2 ± 8.8 days		DEHP 18.0 ± 2.0 mg/L [SD] MEHP 1.0 ± 0.7 mg/L [SD]	