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Risk Assessment of Di(2-Ethylhexyl) Phthalate (DEHP) and Bisphenol A (BPA) Exposure to Infants Undergoing Heart Defect Surgery

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in

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by

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Abstract

Background: Di(2-Ethylhexyl) phthalate (DEHP) and bisphenol A (BPA) are common anthropogenic chemicals used to manufacture plastics. Humans are typically exposed to DEHP and BPA from industrial and consumer products, often by chemicals leaching into food and drinks. Exposures in health-care environments also occur from leaching into IV fluids, directly into blood, or other body fluids from plastic medical equipment. Exposure to DEHP and BPA raise health concerns because they are endocrine disruptors and have been linked to adverse health outcomes including poorer airway functioning, preterm birth, altered puberty timing, delayed mental and motor development, or cancer risk, among other outcomes. Newborns undergoing congenital heart defect (CHD) surgery are particularly vulnerable due to their young age and elevated exposures from medical products.
Objective: The objective of this study was to evaluate potential health risks from BPA and DEHP exposure in 18 infants who underwent heart defect surgery.
Methods: Specifically, 1) we applied a reverse-dosimetry method to estimate infant dose based on urinary BPA and DEHP metabolites concentrations postoperative, and 2) we then compared the exposure-doses to chronic reference doses.
Results: The median hazard quotients for BPA were 0.28, with a maximum of 0.8 (SD =0.2) among the infants after heart defect surgery. The median hazard quotient for DEHP was 51.2 (SD=86.8), with a maximum of 353.4 among infants after heart defect surgery.
Significance: Exposures of DEHP and BPA are likely to remain elevated as long as the infants are supported by medical interventions, which may last weeks depending on the length of recovery time required. We observed elevated postoperative exposure and potential health risks from DEHP and BPA in neonates undergoing cardiac operations that may have long-term impacts on child well-being.

Keywords: DEHP, BPA, phthalate, infant, heart defect surgery, environmental exposure

Introduction

Di(2-Ethylhexyl) phthalate (DEHP) and bisphenol A (BPA) are common anthropogenic chemicals used to manufacture plastics.[1] Humans are typically exposed to DEHP and BPA from industrial and consumer products, often by chemicals leaching into food and drinks.[1,2] Exposures to DEHP and BPA are common in the United States (U.S.). For example, BPA and DEHP have been detected in 96% and 98% of urine samples from participants in the National Health and Nutrition Examination Survey (NHANES), respectively.[3]

Multiple studies have reported associations between DEHP exposure and adverse health effects, including immunoglobin airway remodeling in the lungs affecting airway responsiveness, increased risk of asthma, preterm birth, altered puberty timing, delayed mental, and motor development.[1,4–10] Hepatic effects from exposure to DEHP have been reported to include increased serum enzyme levels, hepatocellular hypertrophy, increased liver weight, induction of hepatic enzymes, centrilobular necrosis and inflammation, hepatocyte cytoplasmic eosinophilia, bile duct lesions, and altered foci.[1,11,12] Renal effects may include increased albumin to creatinine ratio (ACR) in urine.[1] Reproductive effects of DEHP exposure include decreased testosterone, sperm motility, and fertility.[1,3] The long-term impacts of early life exposure are uncertain, but several studies raise concerns about reduced neurodevelopmental outcomes.[10,13,14] Epidemiological studies have demonstrated that DEHP has adverse effects on the reproduction and development of humans.[10,15–17] Moreover, several studies indicate that phthalates, and specifically DEHP, can stop thyroid hormone signaling; disruption of this hormone can lead to effects on growth and also development and differentiation, particularly in the developing brain, suggesting specific mechanisms of toxicity underlying the epidemiologic findings.[18,19] DEHP is classified as an endocrine disruptor by the European Chemicals Agency (ECHA)[20] and identified by the U.S. Environmental Protection Agency (U.S. EPA) as a liver toxicant and a probable human carcinogen[21] and as a carcinogen and a reproductive toxicant under California's Proposition 65.[22]

BPA is weakly estrogenic and binds to estrogen receptors.[23] There are concerns regarding BPA's potential adverse impacts on children's health, especially reproduction systems, early and adolescent development, and behavior.[24] At high exposures, BPA is a known respiratory irritant and health hazard.[25] BPA has been shown to be associated with numerous health effects including reproductive, cancer risk, hyperthyroidism, hypothyroidism, immunosuppression, and is associated with a wide range of neurodegenerative diseases.[26] The reproductive effects of exposure to BPA may include increased uterine weight, changes in epithelial tissue, accelerated development of the mammary gland, early onset of puberty, spermatogonia, and changes to testosterone level.[26] BPA may increase cancer risk because it can interfere with cellular process.[26] BPA is listed under California's Proposition 65 as a reproductive toxicant.[2]

In the U.S., it is estimated that nearly 1% of children born each year are born with coronary heart defects (CHDs).[27] Approximately 1 in 4 children with a critical CHD will need a surgery or other medical procedure within the first year of their life.[28] DEHP is

used to impart flexibility and temperature tolerance to polyvinyl chloride (PVC) while BPA is used to manufacture polycarbonate,[7,29] both of which are used in the cardiopulmonary bypass (CPB) circuit and other critical medical equipment used to support the infants during CHD surgery.[3]

Newborns undergoing CHD surgery are exposed to DEHP and BPA post-surgery by the leaching of these chemicals from endotracheal tubes, blood storage bags, or medical devices used for the administration of drugs such as peripheral and central venous access catheters, infusion lines, feeding tubes, IV bags and tubing, and also blood and airway management devices such as extracorporeal membrane oxygenation (ECMO) machines.[3,30,31] These findings are consistent with studies that have shown that plasticizers such as DEHP can move from the PVC matrix into drug solutions, thereby exposing patients.[32] These routes of exposure to DEHP and BPA differ from the typical U.S. population exposures, which are primarily through ingestion of contaminated food or drinks.

A growing literature has demonstrated that very young children are more vulnerable to toxicants compared with older children and adults because of their immature and rapidly changing body systems.[3,4,8,17,33–37] The fetal and neonatal periods are especially critical windows of development that are prone to the effects of endocrine disruptors[32]. Newborns undergoing CHD surgery are a particularly vulnerable population; they are more likely to have increased vulnerability to DEHP exposure and BPA due to the many and intensive surgical-related interventions, resulting in higher exposures, and their impaired inability to excrete xenobiotics such as phthalates.[3,4,34,36–39] Several studies show that CHD infants often have poorer neurodevelopment outcomes, but that the severity of these outcomes cannot be fully explained by surgery-related trauma such as hypoxia.[3,10,14,30,40]

Given the young age of infants with CHD and the trauma caused by cardiac surgeries, exposure to DEHP and BPA may have a greater adverse impact on the life of these children. Research on the health impacts of infant exposure to DEHP and BPA from cardiac operations remains scarce; however, preliminary information suggests that high medical-related exposures could impact later health.[41] Given the prevalence of CHD in children and the widespread use of plastic materials in medical care environments, understanding the plastic-related exposures and health risks to infants with CHD is critical to identify potentially modifiable factors to reduce infant exposures.

Biomonitoring, which is the measurements of toxicants or their metabolites in biological media such as blood and urine, has become a standard approach to assess human environmental exposures.[42] Biomonitoring has many advantages as a tool to assess chemical exposures because the measurements integrate all routes of exposure – inhalation, dermal absorption, and ingestion – and this provide a direct measure of what is actually in the body. Historically, biomonitoring has been used to characterize population-level exposures and evaluate temporal trends. For example, biomonitoring has shown that blood lead levels have decreased in the last 50 years since lead was banned from gasoline. Biomonitoring measurements have also been used to characterize

exposure for epidemiologic studies. More recently, U.S. EPA and other groups have attempted to use biomonitoring as tool to assess risk based on regulatory standards. These methods involve back-calculating individual dose on a mg/kg basis which can then be compared to a regulatory standard such as a reference dose.[43] Several methods have been developed to back-calculate dose, often called dose-reconstruction or reverse-dosimetry. For example, physiologically-based pharmacokinetic (PBPK) models, which are based on absorption, perfusion, excretion, and metabolic transformation rates, are often used to relate toxicant levels measured in urine to intake.[44] Other approaches standardize urinary toxicant metabolites to creatinine levels, which is assumed to be excreted at a constant rate each day; information on estimated 24 hour creatine excretion is available in the medical literature for different populations and can be used to back calculate dose.[45] For example, if a toxicant in urine was measured at 1 mg/g-creatinine in a child, and the literature indicates that children typically excrete 5 grams of creatinine a day, then we can assume the child was exposed to 5 mg of toxicant.

Because we had extensive medical record information for this paper, it was not necessary to use a PBPK model or creatinine adjustment to estimate exposure. Specifically, we had detailed information on 24-hour urine output. Thus, it was possible to calculate total excretion on a mass basis and assume that when went out was equal to what went in, with adjustment for information in the literature about how well specific DEHP and BPA urinary metabolites represent intake. For BPA it is assumed that the amount excreted is equal to the amount exposed, whereas for DEHP, adjustments were made since there is not one hundred percent representation of what has entered the body; this is further explained in the methods section.[45–50]

In this paper, we assessed the potential risks from BPA and DEHP exposure in 18 infants undergoing heart defect surgery at the Children's Hospital of Philadelphia (CHOP). Specifically, 1) we applied a reverse dosimetry approach to estimate the child dose based on levels of urinary BPA and DEHP metabolites postoperative, and 2) we then compared the estimated dose to health benchmarks. This information may be used to inform regulatory authorities and medical equipment manufacturers on strategies to prevent these exposures and health risks.

Methods

Participants and Sample Collection

Detailed information for the parent study can be found in Gaynor et, al., 2019.[3] In summary, this risk assessment study focused on previously reported measurements of DEHP metabolites and BPA in 18 infants who underwent CHD surgery at the Children's Hospital of Philadelphia (CHOP).[3] Specific details of participant selection, demographics, urine collection, laboratory methods, and quality control, such as inclusion criteria are discussed in Gaynor et al. 2019.[3] Infants with an identified genetic syndrome, major extracardiac anomaly, or family language other than English spoken in the home were not included in the parent study.[41] All procedures were reviewed by the CHOP committee for

the protection of human subjects and written informed consent was obtained from the parents. These criteria resulted in the inclusion of 19 infants, and a total of 18 infants underwent CHD surgery. Information collected about the children included gestational age, birthweight, age at surgery, body weight at surgery, and urine excretion volume. Urine samples were collected from cotton placed in the diaper, a urine collection bag, or a Foley catheter collection bag. These samples were then frozen and shipped for analysis to the Centers for Disease Control in Atlanta, GA.

DEHP and BPA Metabolism

DEHP: DEHP ($C_{24}H_{38}O_4$) has a molecular weight of 390.6g/mol.; log Kow of 7.60, and a vapor pressure of 1.32 mmHg, and an estimated half-life in humans of 2.75 days [51]. DEHP is a colorless and nearly odorless oily liquid that has a pale-yellow color.[51] DEHP is soluble in blood and fluids containing lipoproteins, but not soluble in water.[13] The initial step of DEHP metabolism yields monoethylhexyl phthalate (mEHP) and 2-EH through hydrolytic cleavage.[3] The catalysts of this reaction are DEHP hydrolases, which are found in the pancreas, liver, kidneys, lungs, skin, plasma, and testes. Pancreatic tissue lipase secretion contributes to DEHP hydrolase activity in the contents of the small intestine, which plays a vital role in the metabolism of DEHP. Further metabolism occurs in the gut through the help of enzymes that convert DEHP to mEHP before absorption of DEHP occurs. In organ tissues other than the pancreas, such as the liver or plasma, esterase activity contributes to the complete hydrolysis of DEHP before the chemical appears in the plasma.[52] mEHP can be further metabolized to 2-Ethyl-5-hydroxy-hexylpthalte (mEHHP), 2-Ethyl-5-oxy-hexylphthalate (mEOHP), and 2-Ethyl-5-carboxy-pentylphthalate (mECPP), all of which can be measured in urine.[14] Aggregated, these metabolites reflect 53% of excreted DEHP, with mEHP, mEHHP, mEOHP, and mECPP reflecting 5%, 19%, 11%, and 18% of excreted DEHP, respectively.[53]

BPA: BPA ($C_{15}H_{16}O_2$) has a molecular weight of 228.3 g/mol and a half-life in humans of 1.9 days.[25] BPA is a white to light brown solid flakes or powders and gives a weak medicinal or phenolic odor.[25] BPA is soluble in water, ethanol, ether, benzene, alkali, and acetic acid.[25] BPA is metabolized and excreted in urine, representing 100% of BPA intake.[3,25]

Reference Dose Information

Table 1 shows the Reference Dose (RfD), Point of Departure (PoD), cancer slope factor, Maximum Allowable Dose Level (MADL) (Prop 65), and No Significant Risk Level (NSRL) (Prop 65) from both the U.S. EPA and the California Office of Environmental Health Hazard Assessment (OEHHA). [21,54–56]

Table 1: DEHP and BPA health-based benchmarks from EPA and OEHHA guidelines.

	DEHP	**BPA**
EPA		
Non-Cancer		
RfD (Oral)	2 x 10^{-2} mg/kg-day	5 x 10^{-2} mg/kg-day
PoD	LOAEL : 1.9 x 10^{1} mg/kg-day (Hepatic)	LOAEL : 5 x 10^{1} mg/kg-day (reduced body weight in rodents)
RfD (Inhalation)	Not yet assessed	Not yet assessed
Cancer		
Oral Cancer Slope Factor	1.4 x 10^{-2} per mg/kg-day (Hepatocellular carcinoma and adenoma)	Not yet assessed
Inhalation Cancer Slope Factor	Not yet assessed	Not yet assessed
OEHHA		
Non-Cancer		
Maximum Allowable Dose Level (MADL)	• 42 x 10^{-1} mg/day (intravenous- adult) • 6 x 10^{-1} mg/day (intravenous- infant boys, age 29 days to 24 months) • 21 x 10^{-2} mg/day (intravenous- neonatal infant boys, age 0 to 28 days)	3 x 10^{-3} mg/day (dermal exposure from solid materials)
Oral Maximum Allowable Dose Level (MADL)	• 41 x 10^{-2} mg/day (adult) • 58 x 10^{-2} mg/day (infant boys, age 29 days to 24 months) • 2 x 10^{-2} mg/day (neonatal infant boys, age 0 to 28 days)	Not yet assessed
Cancer		
Oral Slope Factor	3.0 x 10^{-3} mg/kg-day	Not yet assessed
Inhalation Slope Factor	8.4 x 10^{-3} mg/kg-day	Not yet assessed
No Significant Risk Level (NSRL) - adult	3.1 x 10^{-1} (adult) mg/day	Not yet assessed
No Significant Risk Level (NSRL) - child	3.1 x 10^{-2} (child) mg/day	Not yet assessed

U.S. EPA reference doses are computed as the PoD, usually a no observed adverse effect level (NOAEL) or lowest observed adverse effect level (LOAEL), divided by safety factors.[47] The PoD is the point on a dose-response curve that is used as the cut point to calculate a reference dose; safety factors, usually factors of 10, are applied to the PoD to account for uncertainties such as extrapolating results from animal studies to humans.[57] OEHHA, under Proposition 65, publishes maximum adverse dose levels (MADLs) for reproductive toxicants. The MADL is a special case of a reference dose that is solely based on reproductive outcomes and uses 1000 as a safety factor.[58]

The EPA calculated the BPA oral RfD as 0.005 per mg/kg per day using a LOAEL as 50 mg/kg per day as the PoD. Inhalation RfD and cancer slope factors have not yet been assessed.[55] OEHHA computed only the MADL for BPA, which was calculated at 3mg/day for dermal exposure.[56] Other BPA benchmarks have not yet been assessed by OEHHA.[56] Exposure to DEHP has been evaluated by both the EPA and OEHHA more extensively compared to BPA.[21,59]

For DEHP, the EPA established an oral RfD of 0.02 per mg/kg per day based on a LOAEL of 19 mg/kg per day, and an oral cancer slope factor of 0.014 per mg/kg per day.[55] U.S. EPA has not established an inhalation RfD or inhalation cancer slope factor for DEHP.[60]

Unlike BPA, OEHHA has fully assessed DEHP.[21,56] OEHHA has recognized the potential for exposure from medical equipment, and developed an intravenous MADL, determined for adults at 4.2 mg/kg-day, for infant boys, age 29 days to 24 months, at 0.6 mg/kg per day, and for neonatal infant boys, age 0 to 28 days, at 0.02 mg/kg per day. This benchmark is based solely on reproductive outcomes, but is identical to the EPA RfD.[21] OEHHA established an oral MADL for adults at 0.41 mg/kg per day, for infant boys aged 29 days to 24 months at 0.058 mg/kg per day, and for neonatal infant boys. The NSRL is the lifetime intake associated with a lifetime cancer risk of one in a hundred thousand (10^{-5}). During early life, OEHHA has determined that young children have a higher cancer risk for a given unit of exposure at young ages and recommends that the cancer slope factor be increased by a factor of 10 to adjust the risks of exposures at early ages.[21,56] Thus, in this study, the child-specific no significant risk level (NSRL) was calculated for children at 0.031 mg/kg per day ($NSRL_{adult}/10$).

Infant Dose Estimates and Risk Assessment

We applied a reverse-dosimetry method to estimate peri-operative exposures to BPA and DEHP on a mg/kg basis. Specifically, we assumed that the amount of BPA and DEHP metabolites measured in the urine samples were representative of levels in the infant's twenty-four-hour urine output on the day the samples were collected (Table 2). We then computed the urinary BPA and DEHP concentrations on a molar basis. Calculations were completed on a spreadsheet using Microsoft Excel, 2022.

For BPA, it is estimated that the amount of BPA at intake is equivalent to that excreted, therefore we assumed that 100% of the excreted mols represent 100% of intake. We then used this information and assumed the total molar intake was equal to the output and computed intake on a mass (mg) basis.

Based on Angerer et.al., 2011, the total mols of the DEHP urinary metabolites we measured represent 53% of the total intake,[53] therefore we assumed that 53% of the excreted mols represent 53% of intake. We then used this information and adjusted the total molar intake and computed intake on a mass (mg) basis.

The estimated intake on a dose basis (mg/kg-body weight) was then divided by infant body weight (kg) to estimate dose (mg/kg-body weight). To calculate the non-cancer hazard quotient, the estimated dose was then divided by the RfD.

As noted above, OEHHA has calculated NSRLs for adult populations and they recommend that an age-specific sensitivity factor of 10 be applied for children aged two years and younger; this recommendation is reflecting their judgement that young children are 10 times venerable to a carcinogen to compared to adults. We additionally computed a hazard quotient comparing the estimated DEHP dose to the child-specific NSRL.

Results

Population

Table 2 presents the descriptive characteristics of the infants, including urine output, hours between pre-op sample and surgery, hours between post-op sample and surgery and body weight (kg). The 18 infants undergoing CHD surgery were 44 weeks post-conception or younger and weighed an average of 3 kgs (SD=0.5).[3] At the time of surgery, the childrens' mean age was 5.4 days; the mean 24 hour urine output was 246.3 mls on the day the childrens' urine was sampled for laboratory analysis.

Table 2. Characteristics of participating children.

Variable	Mean	SD	25th percentile	50th percentile	75th percentile	Max
Urine output (ml)*……..	246.3	53.3	226	252	277	371
Hours between pre-op sample and surgery**……..	43.3	86.2	1	2	54	340
Hours between post-op sample and surgery***……..	5.2	7.2	1	2	5.75	24
Body weight (kg)……	3.0	0.5	2.6	3.1	3.4	4

**Urine output refers to the 24 hours output the day of surgery*

***The number of hours between the pre-operative sample and heart defect surgery*

****The number of hours between the post-operative sample and heart defect surgery*

Risk Characterization

Table 3 shows the range of DEHP and BPA concentrations in the infants both pre-operative and post-operative. The post-operative levels are substantially higher than the pre-operative concentrations, especially for DEHP metabolites, which are over an order of magnitude higher. These levels are also higher than what is reported by NHANES; more information can be found in Gaynor et. al.[3]

Table 3. Urinary concentrations of BPA (µg/L) and DEHP (µg/L) in pre-operative and post-operative samples (N=18).

Variable	Mean (µg/L)	SD	25th percentile	50th percentile	75th percentile	Max
Pre-Operative						
Phenols						
BPA	10	4.2	7	9.6	11.7	21
Phthalate metabolites[1]						
mEHP	5.6	13.1	0.4	1.5	5	53.5
mEOHP	18.6	43	2.6	4.9	15.9	178
mEHHP	25.2	51.6	3.5	8.9	25.1	215
mECPP	180.1	444	20.5	45.85	140.7	1830
Post-Operative						
Phenols						
BPA	17	9.5	9.9	14.7	25	37.1
Phthalates metabolite[1]						
mEHP	46.8	38.4	11.8	36.9	82.5	126
mEOHP	573.2	1213.4	41.7	90.2	621	5060
mEHHP	691.1	1203.8	75.6	156	818	4340
mECPP	3129.1	4213.8	440	1023	6350	14500

1. The initial step of DEHP metabolism yields monoethylhexyl phthalate (mEHP) and 2-EH through hydrolytic cleavage.[3] MEHP can be further metabolized to 2-Ethyl-5-hydroxy-hexylpthalte (MEHHP), 2-Ethyl-5-oxy-hexylphthalate (mEOHP), and 2-Ethyl-5-carboxy-pentylphthalate (mECPP), all of which can be measured in urine.[14] Aggregated, these metabolites reflect 53% of excreted DEHP, with mEHP, mEHHP, mEOHP, and mECPP reflecting 5%, 19%, 11%, and 18% of excreted DEHP, respectively.[53]

Table 4 presents the estimated infant doses. The mean BPA dose was 0.0014 mg/kg, with a maximum of 0.004 mg/kg and standard deviation (SD) of 0.009 mg/kg; the mean DEHP dose was 1.02 mg/kg, with a maximum of 7.07 mg/kg and SD of 1.74 mg/kg.

Table 4. BPA and DEHP post-operative dose estimates (mg/kg) in infants undergoing heart defect surgery.

Leachate	Mean (*n*= 18)	SD	75th percentile	Max
BPA	0.001	0.001	0.002	0.004
DEHP	1.02	1.74	1.96	7.07

Table 5 presents the non-cancer hazard quotients for the estimated BPA and DEHP post-operative exposures. The median hazard quotient for BPA were 0.28, with a

maximum of 0.8 (SD =0.2) among the infants after heart defect surgery. The median hazard quotient for DEHP was 51.2 (SD=86.8), with a maximum of 353.4.

Table 5. BPA and DEHP non-cancer hazard quotients for infant exposure after heart defect surgery.

Leachate	Mean (*n*= 18)	SD	75th percentile	Max
BPA	0.28	0.2	0.4	0.8
DEHP	51.2	86.8	97.8	353.4

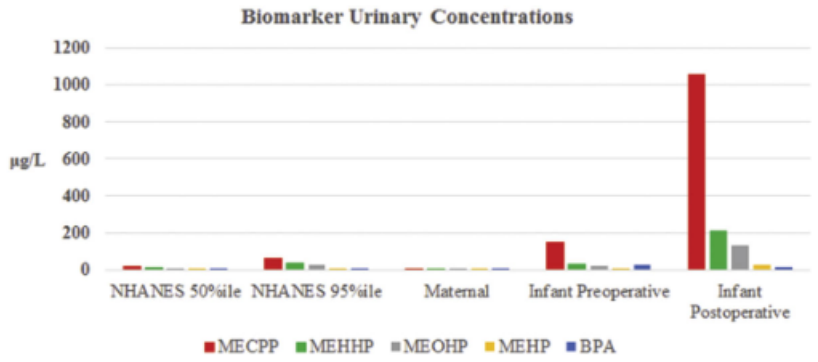
Discussion

Overall, we found that post-operative exposures to DEHP, but not BPA, were above health-based benchmarks developed by the U.S. EPA and other agencies. Although BPA metabolite concentrations exceeded U.S. normative trends[3], computed doses did not exceed the U.S. reference dose. The DEHP exposures also exceeded California Office of Environmental Health Hazard Assessment adult and child-specific cancer "no significant risk levels" (NSRLs), a threshold for lifetime exposure that result in cancer risks greater than one in one hundred thousand.

These high hazard quotients for DEHP--over two orders of magnitude above health-based benchmarks--indicates that there may be an increased risk for long-term adverse health effects among infants undergoing CHD surgery, such as poorer mental and psychomotor development.

To date, we have not identified other studies that have attempted to reconstruct BPA and DEHP dose from CHD surgery and evaluate risk against health-based benchmarks; however, our results are consistent with several studies that have shown infants with high plasticizer exposure in healthcare environments.[3–5,29,37,61,62] In this study, we used peri-operative exposure data from Gaynor et al. 2019), which are significantly higher than BPA and DEHP exposures the U.S. general population reported by NHANES (Figure 1).[3] These findings are consistent with exposures reported by Bernard et al. 2014 that showed increased plasticizer exposure in infants undergoing extracorporeal membrane oxygenation (ECMO).[3,63] Overall, several recent investigations demonstrate the occurrence of plasticizers in medical devices and high exposures to infants in NICU and other healthcare environments,[63–66] underscoring concerns about the long-term impacts of these exposures.

Figure 1. Comparison of geometric mean maternal and infant DEHP metabolite and BPA concentrations to U.S. general population concentrations for all females.



Source: Gaynor JW, Ittenbach RF, Calafat AM, et al. Perioperative Exposure to Suspect Neurotoxicants From Medical Devices in Newborns With Congenital Heart Defects. *Ann Thorac Surg*. 2019;107(2):567-572.

The BPA concentrations in our population were only somewhat higher (~a factor to two) than the US population as whole[3] and the estimated doses did not exceed EPA reference doses. Similarly, Aylward et. al., 2013, estimated likely urinary concentrations when exposures occur at exactly the reference dose (known as biomonitoring equivalents[42,44]) and found that general U.S. population BPA exposures were substantially below the EPA reference dose.[42,44] For DEHP the NHANES geometric mean was well below a hazard quotient of 1 while the 95th percentile hazard quotient was >1, suggesting that some general U.S. population DEHP exposures exceed the EPA reference. [44]

Strengths and Limitations

This study has several strengths and limitations. Although children likely experienced elevated exposures prior to, during, and after surgery for an extended period, we estimated dose for a single time period postoperatively. We likely captured the period of high exposure, but our analysis did not assess trends in exposure over the entire CHD care period as the intensity of care decreased upon recovery. For example, during heart surgery, infants may be connected to 50 or more devices.[3] As the children recover, the number of connections will decrease and device-related exposures will also decrease. However, intensive medical care, including pre-operative care for respiratory and cardiac abnormalities and the use of IV drips--a known source of DEHP exposure[30,67]--may persist for weeks, resulting in relatively long exposures. According to ISO 10993, The time-frames for evaluating the biocompatibility of medical devices are defined as "short term" (<24 hours), "prolonged" (2-30 days), and "permanent" (>30 days).[47] It is likely that some infants undergoing heart defect surgery may experience elevated health-care related exposures for >30 days, and thus fall into the "permanent" exposure category.[47]

Future studies should evaluate infant exposure during pre-, peri-, and post-operative periods and during recovery through discharge from the hospital.

Additionally, we compared exposures to EPA reference doses, which are based on rodent oral-feeding toxicological studies. Ingested xenobiotics are usually transported to the liver, where they may be metabolized into less toxic metabolites, a process known as the "first-pass effect".[46] Thus, the EPA health-based benchmarks may not reflect the higher toxicity of exposures directly into blood, resulting in higher organ-specific exposures.

Our analysis included a small sample size and therefore the results are not generalizable to all children undergoing CHD. This study also focused on just two common leachates from plastic medical equipment. Infant exposures to other plasticizers and volatile organic compounds have also been documented in health care environments[16,19,29,34,37,40,61,68], indicating that the children are exposed to chemical mixtures which may pose risks that are not reflected in our analysis. Finally, we did not characterize the specific type of medical devices used for each child. Despite these limitations, our study has several strengths. It is one of the first to examine the risks of plasticizer exposure in infants undergoing invasive CHD surgery. We were able to use crucial information from the medical record, including total urinary output, to directly calculate dose, rather than relying on PBPK models or creatine-based methods that have not been validated for newborns.[42-47]

Future Research

Future studies are needed to fully characterize the magnitude and pattern of exposure to DEHP and BPA and other care-related toxicants over the entire hospitalization period. Future studies should also examine the potential health effects of these exposures which, at least for DEHP, can be up to 2 orders of magnitude higher than health-based benchmarks. Lastly, to come to a firm conclusion about the suitability of certain plasticizers for medical devices, regulatory agencies should evaluate the applicability of current health-based benchmarks to the actual route of exposure to highly vulnerable newborn infants with severe heart defects.[69]

Public Health Implications

Our study has several public health implications. A growing literature demonstrates that young children are more vulnerable to adverse effects of toxicants compared with adults.[9,35,70–72] As noted above, it is possible that care-related exposures may cause long-term health impacts to children. Thus, medical equipment manufacturers should consider developing products with lower potential to leach xenobiotics that will subsequently enter the human body during treatment. One step the U.S. can take is to following the lead of European Regulation N°2017-45, which introduces a quantitative restriction on the use of plastic additives (plasticizers) that are classified as carcinogenic, mutagenic, reproductive toxicants and/or have proven endocrine disruption effects.[73] In this regulation, the mass of DEHP in PVC medical devices should not exceed 0.1% by mass of the plasticized materials.[73] Overall, these steps have helped limit DEHP use and

exposure in the European Commonwealth. There may be trade-offs in the functionality of new products, and care should be taken to ensure that alternative products work equally well as older models. A key tenant of ISO 10993 risk assessment guidelines is that the benefits of life-saving medical equipment should always be considered against possible risks resulting from product use. Clearly, ECMO and other vital medical equipment saves children's lives.

Conclusions

This study demonstrated significant postoperative exposure to DEHP and BPA in neonates undergoing cardiac operations that in some instances exceeded health-based benchmarks. When modifiable, efforts to reduce this exposure should be implemented. More research is needed to further understand the risks posed by DEHP and BPA among infants undergoing heart defect surgery.

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