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Chapter

Reducing Toxic Phthalate Exposures in Premature Infants

Randall Jenkins

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Abstract

Phthalates are a ubiquitous group of industrial compounds used as industrial solvents and as additives to plastics to make products softer avnd more flexible. Phthalates are found in a variety of products including medical devices, personal care products, flooring, and food packaging. Infants in the neonatal intensive care unit are exposed to phthalates both in the building materials, but more importantly in the medical supplies and devices. Toxicity from phthalates has been of concern to researchers for many decades. Toxicity concerns to neonates includes male reproductive toxicity, hepatotoxicity, cardiotoxicity (including hypertension), neurotoxicity, and neurodevelopmental abnormalities. Limited recommendations have been given for reducing phthalate exposures to premature infants. These include avoiding infusing lipids or blood products through intravenous tubing containing phthalates. Storage of blood in containers made with phthalates has been a strong recommendation and has largely been accomplished. A comprehensive plan for phthalate reduction has heretofore been missing. This chapter has the goal of identifying the problem of phthalate exposure in premature infants, with some practical solutions that can be done today, as well as suggestions for manufacturers to complete the work.

Keywords: phthalates, neonate, hypertension, toxicity, di-2-ethylhexyl phthalate (DEHP)

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1. Introduction

After the year 2000, we began observing a pattern of hypertension in premature infants [1]. In 2019, we reported on an evaluation of 97 premature infants revealing common features including near-universal low plasma renin activity, transient time course, and a good clinical response to treatment with spironolactone. Meanwhile, Trasande had recently shown an association with phthalate compounds and elevated blood pressure in children [2]. A few years earlier, Zhao proposed a possible mechanism for elevated blood pressure related to phthalates. Zhao documented in human microsomes how monoester phthalate metabolites cause sodium retention via inhibition of the enzyme 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2) [3]. This is the same enzyme responsible for licorice-related hypertension and the syndrome of apparent mineralocorticoid excess [4].

When considered together, these concepts led to a prospective study to evaluate the hypothesis that phthalates increase blood pressure in premature infants, and may cause the heretofore unexplained hypertension in this population [5]. The study showed phthalate exposure was associated with increased blood pressure and

hypertension in premature infants. Evidence was presented for activation of the mineralocorticoid receptor among hypertensive premature infants [5]. This experience raised our awareness of other potential toxic effects of phthalates in premature infants, and has spurred a more comprehensive examination of phthalates' effect on premature infants.

Phthalates are a ubiquitous group of industrial compounds related to phthalic acid [6]. These compounds are used as industrial solvents and additives to make plastic softer and more flexible. Phthalates are found in a variety of products including medical devices, personal care products, flooring, and food packaging [7]. Infants in the neonatal intensive care unit are exposed to phthalates in the room's construction materials, but more importantly in the department's medical supplies and devices [7, 8].

Toxicity from phthalates has been of concern to researchers since the 1970s. Research showing male reproductive toxicity in animals raised alarms for human exposures, especially as phthalates are known to be endocrine disruptors [9, 10]. Although steroidogenesis in rodents is quite different from that of humans, concerns have been validated for various endocrine effects of phthalates on developing humans [10]. Toxicity concerns to neonates include hepatotoxicity, hypertension, neurotoxicity, and neurodevelopmental abnormalities [7].

Limited actions have been recommended for reducing phthalate exposures to premature infants [11, 12]. These include avoiding infusions of lipids or blood products through phthalate-containing intravenous tubing, as well as avoiding blood storage containers which are comprised with phthalates [11–13]. Of these recommendations, only the proper storage of blood has been broadly adopted [13]. A comprehensive plan for phthalate reduction has heretofore been missing. This chapter's goal is to identify the problem of neonatal phthalate exposures and provide a blueprint for phthalate exposure reductions that can be achieved immediately, as well as suggest how manufacturers can further this work for the benefit of premature infants.

2. Phthalates: what are they?

Phthalates are a group of low-cost compounds which are used in the industrial production of commercial products [6, 7] In 2015, almost 8 million metric tons were produced [14]. Phthalates are used as solvents, and as a softening agent (plasticizer) in polyvinyl chloride (PVC). Phthalates are not covalently bound to the plastic and act by preventing the full polymerization of the PVC, thus imparting elasticity and flexibility to the plastic [15]. Phthalates are used in the production of vinyl flooring, wall coverings, food packaging, personal care products, toys, upholstery, fragrances, pharmaceuticals, fragrances, baby-care products, and medical supplies and devices [6, 7, 16–20]. PVC products may be comprised of up to 50% phthalates [16].

Di-2-ethylyhexyl phthalate (DEHP) is the most common phthalate used in the medical setting. DEHP is the only phthalate approved by the US Food and Drug Administration (FDA) for use in medical products. In the EU, where DEHP has been banned, alternative phthalate plasticizers are used, including di (isonyl) cyclohexane-1,2-dicarboxylate (DINCH), tris (2-ethylhexyl) trimellitate (TOTM), di (2-ethylhexyl) terephthalate (DEHT), di-(2-ethylhexyl) adipate (DEHA), acetyl tri-n-butyl citrate (ATBC), di-isodecyl phthalate (DiDP), di-isonlyl phthalate (DINP), and di (2-prophylheptyl) phthalate (DPHP) [21, 22]. DINCH and ATBC are both used for blood product storage as these prevent excessive hemolysis during storage [23]. Toxicity data is limited on many of these alternatives, making safety

determination difficult to ascertain [21, 24]. This chapter will focus primarily on DEHP, as it is the most-studied and most prevalent plasticizer in the world [7].

Humans are exposed to phthalates via food (from packaging), dermal absorption, and air inhalation [7, 15–20]. In the hospital setting, infants receiving respiratory therapy are exposed to phthalates through three primary means; from indwelling catheters and tubes, from intravenous fluid; and from the room's air [5, 7, 8, 11, 12, 16].

3. Metabolism and excretion of phthalates

Phthalates are quickly metabolized and excreted in urine [19, 24], making urine an ideal medium for monitoring phthalate exposures [7, 19, 24]. DEHP is metabolized to MEHP via pancreatic and other lipases. MEHP is the primary metabolite in urine along with two secondary metabolites, MEOHP and MEHHP. Further metabolic pathways are detailed by Koch et al. [19, 24], but include glucuronidation and excretion, leaving little tissue accumulation [20]. In adults, 44.2% of a DEHP exposure is excreted in 24 hours via these three metabolites [25]. This knowledge has allowed quantitative predictions of DEHP exposure based on urine metabolite measurements using an equation by David [26] as modified by Koch [24, 25]. It is not known how these predictions might vary when considering premature infants. Understanding the metabolic pathways is important, as there is ample evidence that the metabolites of DEHP are more toxic than the original compound [3, 8, 16].

Metabolism of DEHP is likely to be different in premature infants as compared to adults or older children [9]. Pancreatic enzymes are not full mature until 6–12 months of age [27, 28]. Glucuronidation activity is also not mature until three months of age, which may increase the half-life of MEHP in these infants [29].

Monitoring studies have found detectable levels of phthalates in almost all populations on the planet, with levels in children typically several times higher than in adults [7]. Zhang et al. showed that the median concentration of DEHP metabolites in children is 38.5 mcg/Liter, and 43.3 in adults [30]. This concentration can be double in pregnant women [31]. Premature infants, by virtue of their small size, and exposure to invasive medical products may have exposures that are more than 4,000 times the levels considered safe for reproductive toxicity [12]. Also, of great concern to premature infants, phthalates have been shown to cross the placenta, and have been measured in human amniotic fluid [32, 33].

4. Adverse effects from phthalates

4.1 Early animal studies on cancer and reproductive risks of DEHP exposures

Postnatal phthalate exposures have raised concerns of potential carcinogenic, mutagenic, reproductive, hepatic, and cardiotoxic effects [34–37]. Some of the first concerns raised from animal studies included carcinogenic risks. Rodents treated with DEHP had increased risk of hepatocellular carcinoma [38]. This risk prompted the EPA to classify DEHP as a possible human carcinogen [7]. As these studies were performed only in animals, it remains unclear as to the actual human carcinogenic risk from DEHP.

Other early animal (rodent) studies have shown that phthalate exposure can result in abnormal anogenital distance, pathologic changes in rodent testes, hypospadias and cryptorchidism, and reduced circulating testosterone [39]. Reviews of phthalate anti-androgenic reproductive toxicity are available [40–42]. Prenatal

exposures to phthalates have been associated with endocrine disruption, and have been reviewed by Martinez-Arguelles [10]. As steroidogenesis is different between rodents and humans, it remains unclear the magnitude of reproductive toxicity phthalates cause in humans.

4.2 Cardiovascular toxicity

Intrauterine DEHP exposure has been associated with cardiac malformations and alteration of key cardiac transcription factors in animals [43]. Both Wang and Snijder separately reported an increased risk of cardiac defects with increased parental exposure of phthalates [44, 45]. DEHP has been shown to inhibit gap junction intercellular communication in lung fibroblasts [46], sertoli cells [47], and cardiomyocytes [48].

DEHP exposure can decreased cardiac contractility in animals. Chick myositis exposed to 4 mg/ml of DEHP stopped beating after 30 minutes, and 97–98% of cardiomyocytes died after 24 hours of exposure [49]. DEHP exposures 6 times this level can be seen in children on ECMO [50]. Similar findings occurred when rat hearts were perfused with blood from blood bags containing DEHP [51]. Lastly, embryonic human cardiomyosites showed a decline in spontaneous beating after exposure to DEHP at 50 mg/ml [52]. A more complete summary of the effects of DEHP on electrophysiology and contractility was published in 2020 by Ramadan et al. [53].

In 2013, Trasande reported that DEHP exposures were associated with increased blood pressure in children [2]. Other reports showed the same in adults [54, 55]. Just a few years earlier, Zhao et al. provided a possible explanation how DEHP might raise blood pressure [3]. He demonstrated in human microsomes that MEHP (a DEHP metabolite) inhibits 11β-HSD2, the enzyme that converts cortisol into cortisone, the less potent mineralocorticoid. Excess cortisol activates the mineralocorticoid receptor, resulting in sodium retention. This is the mechanism of action for licorice-related hypertension, or the syndrome of apparent mineralocorticoid excess [4].

Our group reported that DEHP exposure in premature infants is associated with increased blood pressure and hypertension [5]. In a cohort of premature infants, we showed evidence of inhibition of 11B-HSD2 via changes in measurement of urinary cortisol/cortisone ratio which is a marker for 11β-HSD2. We also showed that markers of sodium channel activity were increased in infants exposed to DEHP. Hypertension in these neonates responded to treatment with spironolactone, and resolved over 10–20 weeks [5].

A subsequent study showed hypertension virtually disappeared when DEHP-containing intravenous fluid (for both mothers and infants) was removed for a two-year period [56]. Subsequently the DEHP-containing IV fluid returned and the hypertension returned to the same level prior to removal. There remain two large unknowns: first, it is unknown as to what is the crucial time period during which DEHP exposure might result in hypertension; second, it is unknown if prenatal DEHP exposure may have an epigenetic effect necessary for, or potentiating the development of subsequent hypertension in premature infants.

4.3 Metabolic and genetic toxicity

Phthalates can upregulate gene expression [57, 58]. One such gene which has been reported to upregulate after DEHP exposure is peroxisome proliferator-activated receptor alpha (as well as its cofactor) to increase utilization of fatty acid substrates in cardiomyocytes [57]. Aronson reported increased lactate levels and

lower ATP levels following DEHP exposure [51]. Martinelli suggested that DEHP exposure to animal skeletal muscle could disrupt glucose metabolism [58]. Amara showed that DEHP exposed mice have altered lipid profiles with higher triglycerides, cholesterol and high and low lipoproteins [59]. Human children aged 6–18 exposed to the metabolite MEHP had increased obesity, triglycerides, and increased blood pressure [60].

4.4 Immunity and oxidative stress effects

MEHP (the principal metabolite of DEHP), has been found in neonates to inhibit neutrophil apoptosis and chemotaxis [61]. Synthesis of integrin CD11b is doubled by exposure to DEHP at concentrations of 0.1–0.3 mg/L [62]. This integrin is involved in leukocyte adhesion and can thereby increase inflammation. Exposure of human neutrophils to MEHP can increase H2O2 content and inhibit apoptosis and chemotaxis [61]. Exposure of mice to inhaled MEHP results in a significant increase in lymphocytes, neutrophils and eosinophils in broncho-alveolar lavage fluid [63]. DEHP exposure has been linked to increased oxidative stress, both as indicated directly above, and also by increased malondialdehyde levels in infants and children receiving lipids and hyperalimentation fluid containing DEHP [64].

4.5 Pulmonary toxicity

Rat pups exposed to maternal DEHP during the final week of gestation showed marked enlargement in terminal airspaces, and a reduction in the number of airspaces, along with decreased surface area for gas exchange [65]. These findings closely resembled those seen with bronchopulmonary dysplasia. A similar study in rat pups also showed pathologic changes similar to BPD when analyzed during the postnatal period [66].

4.6 Hepatic toxicity

Rabbits were exposed to similar lipid infusions through IV tubing with and without DEHP. The non-DEHP tubing was made of polyethylene. After a three-week infusion of these lipids, only the DEHP exposed rabbits showed liver fibrosis, cell necrosis, and other features of oxidative stress. The conclusion was that DEHP was responsible for hyperalimentation-related cholestasis [67]. Von Rettberg et al. performed a similar study in human premature infants [68]. One group of 30 neonates receiving parenteral nutrition via DEHP-plasticized PVC tubing for three years. A second group of 46 neonates receiving parenteral nutrition via PVC-free tubing for three years. When comparing incidence of TPN-associated cholestasis they found that the incidence of cholestasis decreased from 50–13% after the change to PVC-free tubing. This translated to an increased risk of cholestasis with use of DEHP-plasticized PVC tubing by a factor of 5.6 [68].

4.7 Neurologic toxicity

Gestational and postnatal DEHP exposure has adverse effects on rat brain development and function [69]. Rat pups were exposed to intraperitoneal infusion of DEHP (10 mg/kg/day x 7 days) during the crucial time of hippocampal development. These pups at day 26 showed decreased innervation and neuronal density in specific hippocampal regions in males but not females exposed to the DEHP [70] In a similar study, the same abnormal hippocampal development was also seen only in males exposed to DEHP [71]. DEHP exposure in utero caused metabolic

disturbances of the lipid metabolome of the fetal rat brain, causing anomalous brain growth [69]. Other animal studies on DEHP and brain development are detailed in a review by Rowdhwal et al. [72].

Prenatal exposure to phthalates has been associated with poorer infant executive function, attention, and motor reflexes [73, 74]. In-utero DEHP exposure has also been associated with childhood impairments of cognitive dysfunction, motor function, executive function, as well as hyperactivity [75, 76], and autism spectrum [77] in term infants [75, 78]. Another study looked at IQ in 7-year-old children as a function of phthalate levels of pregnant mothers in their third trimester. IQ was 6–7 points lower in the mothers exposed to the highest levels of two phthalates, DnBP, and DiBP. Stroupstrup has begun a large study to study DEHP exposure in premature infants [79], given the similarity of the above abnormalities, and similar "preterm behavioral phenotypes" seen in premature infants as described by Montagna and Nosarti [80].

5. Exposures of DEHP in premature infants

Children and adults are exposed to phthalates primarily through ingestion of food, inhalation of dust, chewing or sucking on objects, inhalation of vapor, skin absorption from personal care products [7, 9] . In contrast, premature infants are exposed both trans-placentally before birth, and through exposure to medical devices after birth [5]. There are little data on the magnitude of trans-placenta transfer of phthalates. Data on postnatal phthalate exposure is much more robust, and dates back almost 50 years to 1973 and 1974 when DEHP was shown to be present in blood plasma and cryoprecipitate products [81, 82]. Of importance, DEHP is the only FDA-approved phthalate allowed in medical products for use in the USA.

5.1 Early determinations of DEHP exposures in premature infants (1980–2003)

In the late 1980s, Schneider et al. was one of the first to report high levels of DEHP exposure in ECMO circuits [83]. Also during this time, Barry et al. showed presence of DEHP in cardiac bypass circuits [84]. Roth et al. and Latini et al. also presented data showing presence of DEHP in respiratory tubing and endotracheal tubes in mechanically ventilated preterm infants [85, 86]. A few years later, Latini and Chellini showed that PVC endotracheal tubes were about 23% DEHP by weight, and that almost half of the DEHP can leach into the infant over several days time [87, 88]. Chellini et al. estimated the exposure to a 2 kg infant could be a mean of 49 mg/kg over several days-time [87].

In 2000, Loff et al. were the first to demonstrate that PVC IV infusion lines expose infants to large amounts of DEHP [89]. Several years later, Loff showed that when lipids were administered through PVC IV lines (containing DEHP) could leach about 6.5 mg/kg/day for a 24 hour lipid infusion [11]. Loff advised that PVC IV lines containing DEHP should be abandoned – this has not happened. Similarly, Kambia et al. demonstrated large DEHP exposure in patients receiving parenteral (IV) nutrition [90].

5.2 Quantitative DEHP exposures in the NICU

In 2004, Antonio Calafat et al. were the first to report quantitative evidence that premature infants receiving intensive medical treatment are actually exposed to higher concentrations of DEHP than the general population [8]. Calafat's group examined 33 urine samples from 6 premature infants between 4 and 92 days of age.

Most of the samples were obtained after the first month. Samples were analyzed for MEHP as well as the two principal oxidative metabolites, MEOHP and MEHHP. During the hospital stay, these infants were exposed to a variety of devices, but the data was not robust enough to show the effect of particular interventions or devices. DEHP metabolites were measureable in all 33 samples, demonstrating the ubiquity of DEHP exposure in this population. Metabolite levels varied widely from sample-to-sample—up to 100-fold. The median concentration of MEHP in these 6 premature infants was 129 ng/mL, which is about 26-fold higher that the US median of 3.43 ng/mL seen in children aged 6–11 years of age [91, 92]. Similar findings were seen for MEOHP and MEHHP levels in premature infants as compared with the US median for children, although these two oxidative metabolites are typically about 10-fold higher than that for MEHP across all samples [8].

A follow-up study was done soon thereafter by the same group, this time dividing 54 neonates (from two institutions) into low, medium, and high DEHP exposure [93]. The "low" DEHP exposure group was comprised of infants receiving bottle or gavage feeds with no other interventions. The "medium" group was comprised of infants who either had indwelling feeding tubes, parenteral nutrition, or were on continuous positive airway pressure devices. The "high" DEHP exposure group was comprised of infants intubated and on a mechanical ventilator while also receiving parenteral nutrition. As expected, infants in the "low" category showed urine DEHP metabolite levels only slightly more than the US averages noted above. Exposures as measured in the median group were about 7-fold higher, with exposures in the "high" group another 3-fold higher than seen in the "medium" group. Interestingly, urine metabolite levels varied greatly, with DEHP metabolite levels in one NICU being about 4-fold that of the other. This was speculated to be due to a difference in the frequency two DEHP-containing devices used: PVC endotracheal tubes and PVC umbilical catheters [93].

A year later, this group examined two other phthalates, dibutyl phthalate and monobenzyl phthalate, both used in personal care and construction products [94]. Metabolites of these two phthalates were detected in all 54 of the samples from the prior study, but these levels did not vary by gender, institution, or level of intensiveness of care. This information suggests that the premature infants are not only exposed to phthalates through medical products, but also from other parts of their environment, whether it be in the air, in their feedings, or in materials they contact.

Using a different approach, Mallow used data from the above-reported DEHP exposures in the NICU to estimate a typical daily DEHP exposure for a prototypical infant receiving blood, intravenous nutrition (including lipid infusions), mechanical ventilation, and a feeding tube [12]. Mallow estimated that a 2-Kg infant would receive 16.3 mg/day of DEHP while on all of this intervention.

5.3 A recent comprehensive quantitation of DEHP exposures in an NICU

Over more than twenty years since many of the potentially toxic exposures of DEHP have been reported, manufacturers have come out with some alternatives to DEHP, which include use of other polymers aside from PVC, as well as alternative phthalate plasticizers [95]. Braun, USA, markets DEHP-free intravenous fluid in the USA. We have observed that feeding tubes, IV administration tubing, and endotracheal tubes are readily available in DEHP-free material, although DEHP-containing products are still marketed. The only medical devices for which DEHP-free materials have not been observed are bags of sterile water for respiratory humidification, suction devices, urine collection bags, and most tubing for respiratory devices [5].

This last year, our group sought to examine the current state of DEHP exposure in a single large Northwestern US NICU [96]. This was accomplished both by

direct and indirect measurement of DEHP exposure in premature infants. For all intravenous products, including IV fluid, hyperalimentation fluid, lipid emulsions, and tubing sets, we directly measured the amount of DEHP leaching into IV fluid collected in a glass container at the "patient" end of sham IV circuits. Indirect measurement of DEHP exposure was based on urine metabolites collected in 12 premature infants receiving one specific respiratory therapy for two days or more (mean of 13 days). Koch's method was used to predict 24-hour DEHP intake based on a formula estimating 44.2% of DEHP intake is excreted in the three main metabolites (MEHP, MEHHP, and MEOHP) [24].

These results (**Table 1**) showed that IV DEHP exposures were zero when DEHP-free IV fluid was tested using DEHP-free tubing. Similarly, lipid emulsions (other than a fish-oil product) when administered through DEHP-free tubing DEHP exposure was measured at zero (below level of detection). Use of intravenous fluid gave varying DEHP exposures, magnified many-fold when administered through DEHP-positive tubing. Most striking was the enormous exposure related to hyperalimentation and lipid infusions when administered through DEHP tubing. In this case, DEHP daily exposures were in the range of 12 mg per day (range of 3.4–45 mg/day).

DEHP exposures from respiratory devices, including patients receiving no known DEHP exposures, are shown in **Table 2**. A wide range of exposures was observed. Most exposures were low, and not statistically different from "baseline" patients in room air who were not receiving any intravenous fluid (or any other known or suspected DEHP exposure). The "baseline" patients had a median DEHP exposure of 25.5 mcg per day. The baseline exposure was presumed to be related to environmental (likely air vapor) in the NICU. Among these "low-level" exposures, the DEHP exposures from mechanical ventilators appeared the highest at 61.4 mcg/day. Given the small numbers of tests, this was not statistically different from the baseline patients.

DEHP exposure related to continuous positive airway pressure (CPAP), specifically the bubble CPAP system, was remarkably higher than any other device tested. The median daily DEHP exposure was 7843 mcg per day, which is about 300-fold that seen in baseline patients. There was strong evidence that the bubble CPAP exposures were not spurious, given no significant variation was seen among six samples obtained in 4 patients, and tested at two unrelated laboratories. This report did not specifically test CPAP systems separate from bubble CPAP, but noted a 2019 study where two mask (non-bubble) CPAP patients had urine metabolite levels below the level of detection [5]. Lastly, no data is available for DEHP exposures from oscillator, jet ventilator, or non-invasive ventilation systems.

This study estimated DEHP exposure in 14 premature infants based on a chart review of all recorded IV and respiratory DEHP exposures. The value from the tables above were used to tabulate the daily DEHP exposure for each patient. **Table 3** shows the mean exposures for these 14 infants for each fluid or device. The mean DEHP exposure from IV fluid including hyperalimentation and lipid infusions was 4,039 mcg over the course of the NICU stay. The mean respiratory DEHP exposure was much higher than the intravenous exposures at 221,369, with 97% of that exposure attributable to bubble CPAP therapy. The total DEHP exposure for the NICU stay was a mean of 182,369 mcg/kg.

5.4 Determination of safe levels of DEHP exposure

Determination of safe levels of DEHP exposure has proved to be a complex and daunting task. One of the difficulties is that extrapolation of animal data to humans can be misleading. Animal studies may be done with different levels of exposure, and may differ in timing from human exposure (acute vs. chronic). For example,

Intravenous Product	Median	IQ Range	Range	Median	IQ Range	Range	Median	IQ Range	Range
	From Container			DEHP-Negative IV Set			DEHP-Positive IV Set		
DEHP-negative IVF	0.0	0.0	0–0.2	0.0	0.0	0–0	5.2[b]	12.1	2.4–15.0
DEPH-unlabeled IVF	27.0	—[a]	26–40	2.4	1.4	1.4–3.2	11.0[b]	16.2	2.3–26.0
DEHP-positive IVF	560.0	—[a]	560–620	32.0	24.1	7.6–40	15.0	24.8	4.4–38.0
HA fluid	5.1	—[a]	3.4–13.0	6.7	13.1	0–16	500.0[b]	1430	420–2300
Mixed lipid emulsion	1.9	4.4	0–5.9	0.0	0.0	0–0	9300[b]	4300	6100–13,000
Fish oil lipid emulsion	8.3	10.8	0–15	92.0	62.6	74–170	4000[b]	3350	2100–6900
Soybean lipid emulsion	0.0	0.0	0.0	0.0	0.0	0.0	12,000[b]	23,050	3400–45,000

[a]Unable to calculate interquartile range due to n = 3.
[b]Denoting signifant difference (p, 0.05) in median DEHP concentration between fluid without and with DEHP in the IV set using Wilcoxsen ranked sum test.
IV, intravenous; IVF, Intravenous fluid; DEHP, di-2-ethylhexyl phthalate; ND, not dectected; HA, hyperalimentation fluid, IQ, interquartile range. Reproduced from [96] 2021, Toxics.

Table 1.
DEHP content (mcg/L) in three types of IV fluid, one type of HA fluid, and three types of lipid emulsion.

Respiratory Device	*n*	Median (mcg/day)	IQ Range (mcg/day)
Bubble CPAP	5	7843.5[b]	6500.5
Room Air (baseline)	5	25.5	42.5
HFNC	5	21.6	20.3
LFNC	1[a]	7.3	NA
Ventilator with DEHP-negative ETT	5	61.4	174.1

[a]*Four samples excluded due to additional IVF received by the patient.*
[b]*Signifant difference ($p < 0.05$) in median DEHP exposure between the baseline and other respiratory device using Wilcoxsen ranked sum test.*
Reproduced from [96] 2021, toxics.
CPAP, continuous positive airway pressure; HFNC, high-flow nasal cannula; IQ, interquartile range; LFNC, low-flow nasal cannula; DEHP, di-(2-ethylhexyl phthalate); ETT, endotracheal tube; NA, not able to calculate an interquartile range when N = 1.

Table 2.
Daily DEHP estimated exposures of respiratory therapy device based on urine metabolites of DEHP.

Mean cumulative DEHP exposure by IV product or respiratory device	Quantity (mL-days)	Mass (mcg)	Totals (mcg/Kg)
Conventional intravenous fluid	454 mL	5	
Starter (initial) hyperalimentation	133 mL	67	
Hyperalimentation fluid	2283 mL	1141	
Lipid emulsions	274 mL	2847	
Total intravenous DEHP		4039	
Mechanical ventilator[a]	23 days	6616	
Bubble CPAP	28 days	219,338	
NIPPV	2 days	127	
Low flow nasal cannula	1 day	4	
High flow cannula	3 days	69	
Mean respiratory DEHHP		221,369	
Mean IV + respiratory DEHHP		230,207	
Mean IV + respiratory DEHHP per Kg			182,369

[a]*Using non-DEHP endotracheal tube.*
All IV tubing was DEHP-positive in these patients. Reproduced from [96] 2021, toxics.
DEHP, Di-2-ethylhexyl phthalate; VLBW, Very low birth weight; IV, Intravenous; CPAP, Continuous positive airway pressure; NIPPV, Noninvasive positive pressure ventilation.

Table 3.
Mean cumulative DEHP exposures for 14 VLBW infants based on actual IV and respiratory exposures using above derived values for DEHP exposure for each device.

early work in animals suggesting that DEHP was a carcinogen, and that it might result in injury to male testicular tissue with resultant fertility reduction [7]. These problems have not occurred thus far in children.

Cardiac contractility and viability may only be affected by the extreme exposures, such as with cardiac bypass or extracorporeal membrane oxygenation circuits [50]. Still, increased blood pressure can be seen with much lower levels [2]. Hypertension has been seen with actual and currently occurring DEHP exposures [5]. It is usually seen in patients with substantial postnatal DEHP exposures, although the contribution of prenatal phthalate exposures remains unknown, and safe levels of postnatal DEHP exposure is unknown.

Liver problems, however, related to actual DEHP exposure were substantiated as cholestasis in premature infants was markedly reduced when DEHP IV tubing was avoided [68]. In this case, animal studies may also be relevant. Mallow showed daily intake of DEHP exposure was 162,459 times that deemed as acceptable by the U.S. Consumer Product Safety Commission [12].

The US Environmental Protection Agency (EPA) established an estimate called the DEHP reference dose (RfD), as the estimate of safe daily intake of DEHP. This was set in 2003 at 20 mcg/kg/day [91]. A Canadian study in 1994 estimated DEHP exposure in infants at 9 mcg/kg/day [92]. A more recent study in a subset of the U.S. estimated that typical exposure is 0.71 mcg/kg/day [97]. The mean U.S. DEHP level associated with this exposure was 2.7 ng/mL [97].

The Consumer Product Safety Improvement Act was passed by the US Congress in 2008. This act limited the concentration of six phthalates including DEHP to a limit of 0.1% for toys and childcare products [98]. In 2007, the European Union effectively banned DEHP from use in medical products [99]. Despite this directive, when evaluating European infusion fluid labeled DEHP-free, only two of nine devices were indeed DEHP-free [22]. Concern was also raised that the alternative phthalate plasticizers have not been fully studied as to risk of adverse effects in humans [22, 99].

France, in 2015, banned used of DEHP-containing tubes in neonatal, pediatric, and maternal units [100]. The FDA in the US limits phthalate use in medical products to just DEHP. The FDA has not yet set a limit for DEHP, or designated safe levels of DEHP use in the US, leaving decisions about use of products containing DEHP to providers and hospital administrators. Our experience is this effectively leaves the decision up to manufacturers and distributors, as toxicity concerns are rarely raised by either hospital staff, providers, or administrators.

6. Actions to reduce DEHP exposures in premature infants

Since premature infants are so small and are still in the midst of development it would seem prudent to avoid potential toxicants whenever possible. At a minimum, one should strive to reduce neonatal exposure to less than 20 mcg/day, the estimated safe limit set by the EPA. Lower levels of exposure should be achieved if possible. In the past, arguments were made that the benefits of life-saving medical devices outweigh the unknown and ill-defined risks [9]. Now, much of the exposure can be eliminated by choice of products currently available by manufacturers.

The easiest step to take would be to not use IV administration sets containing DEHP, especially for administration of blood products, hyperalimentation fluid, or lipid emulsions. DEHP-free infusion sets are readily available, with little cost differential.

The second step would be to use only DEHP-free IV fluid, at least for premature infant and maternal use. DEHP-free commercial IV fluid is available in the US and abroad.

The third, and potentially the most crucial step would be to limit exposure to respiratory devices found to have very large DEHP exposures. We tested only one bubble CPAP system, and currently have no data on that from other manufactures of bubble CPAP. Advice on CPAP alternatives is beyond the scope of this publication, but modification of current bubble CPAP, or providing CPAP using either a ventilator device or with a linear pressure generator might be preferred from a toxicity viewpoint. Specific testing of suspected high-exposure devices may be helpful in assessing the risk/benefit ratio for clinical use.

These changes in medical products should result in marked reductions in DEHP exposure, but one has to be vigilant about: 1.) New products that contain DEHP and may not be labeled concerning its phthalate content. 2.) Supplies that change on a daily basis without providers' and staff's knowledge. This author has seen this occur on many occasions. 3) Current products in clinical use which do not have available testing data (such as oscillator or jet ventilators).

We suggest periodic checking of IV supplies used in maternal units, and all supplies used in the NICU for products labeled to contain DEHP. It may also be prudent to have some system for checking a random patient's urine for DEHP metabolites, as a screen for unexpected DEHP exposure. Lastly, building materials (primarily flooring and wall coverings) should be selected to minimize phthalate environmental exposure in the NICU.

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Acronyms and abbreviations

DEHP	di-(2-ethylhexyl) phthalate
PVC	polyvinyl chloride
IV	intravenous
NICU	newborn intensive care unit
MR	mineralocorticoid receptor
11β-HSD2	11β-hydroxysteroid dehydrogenase type 2
AME	apparent mineralocorticoid excess
MEHP	mono-(2-ethylhexyl) phthalate
PRA	Plasma renin activity
MEHHP	mono-(2-ethyl-5-hydroxyhexyl) phthalate
MEOHP	mono-(2-ethyl-5-oxohexyl) phthalate

Author details

Randall Jenkins
Oregon Health and Sciences University, Portland, Oregon, USA

*Address all correspondence to: jenkinra@ohsu.edu

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