

SPECIAL FEATURE

Phthalates and critically ill neonates: device-related exposures and non-endocrine toxic risks

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OBJECTIVE: To assess the types and magnitudes of non-endocrine toxic risks to neonates associated with medical device-related exposures to di(2-ethylhexyl)phthalate (DEHP).

STUDY DESIGN: Dose-response thresholds for DEHP toxicities were determined from published data, as were the magnitudes of DEHP exposures resulting from neonatal contact with polyvinyl chloride (PVC) devices. Standard methods of risk assessment were used to determine safe levels of DEHP exposure in neonates, and hazard quotients were calculated for devices individually and in aggregate.

RESULT: Daily intake of DEHP for critically ill preterm infants can reach 16 mg/kg per day, which is on the order of 4000 and 160,000 times higher than desired to avoid reproductive and hepatic toxicities, respectively. The non-endocrine toxicities of DEHP are similar to complications experienced by preterm neonates.

CONCLUSION: DEHP exposures in neonatal intensive care are much higher than estimated safe limits, and might contribute to common early and chronic complications of prematurity. Concerns about phthalates should be expanded beyond endocrine disruption.

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INTRODUCTION

Flexible plastic devices in the neonatal intensive care unit (NICU) are most commonly made of polyvinyl chloride (PVC). Pliability of PVC is conferred by the incorporation of the plasticizer di(2-ethylhexyl)phthalate (DEHP), which is the only phthalate approved for medical use in the United States. DEHP does not bind covalently to the PVC polymer, and migrates from the plastic into surrounding fluids and tissues.^{1,2} DEHP is hydrolyzed to form the more toxic mono(2-ethylhexyl)phthalate (MEHP), which undergoes hepatic metabolism to form several renally excreted oxidation products.^{1–3} Preterm infants have immature enzyme systems and impaired renal clearance, and are less able to metabolize and eliminate DEHP and MEHP.⁴ Infants in the NICU may have intensive and prolonged contact with a wide range of PVC tubing and catheters. Clinical studies of preterm neonates have shown that levels of urinary DEHP metabolites correlate strongly with acuity of care.^{4–7}

DEHP and other phthalates are anti-androgens, and prenatal exposure in rodents results in a well-defined set of male urogenital anomalies, termed the phthalate syndrome.^{1,3,8} Evidence exists for these effects in human infants as well.^{8,9} Concern about phthalates has centered primarily on their role as endocrine disruptors. However, they also exhibit a wide range of non-endocrine toxicities which may have implications for newborns requiring intensive care.

STUDY DESIGN

To determine the range of DEHP's known toxicities and toxic thresholds, as well as magnitudes of neonatal exposures by various routes and PVC devices, the literature was reviewed using PubMed and a flexible approach. Initial search terms were general, in order to

identify the extended literature covering experimental and clinical research related to DEHP, its non-endocrine toxicities, and pertinence to neonatal care. Papers found and deemed relevant had their reference lists reviewed for additional such articles, and citations identified were retrieved via PubMed. Related articles were also suggested by PubMed. For the risk analysis, articles were chosen based on quality of experimental design, data collection, statistical rigor and potential relevance to neonatal diseases. The wide range of DEHP's effects, as well as the diversity of experimental models and protocols, precluded a meta-analysis. The use of published data for conducting a chemical risk assessment is standard practice, and is the approach used by the US Environmental Protection Agency, the US Food and Drug Administration and the Consumer Product Safety Commission (CPSC). The risk assessment did not incorporate data published prior to 2000.

In accordance with federal guidelines for risk assessment, toxic thresholds for specific DEHP effects were integrated with calculated neonatal exposures from individual PVC device types. Appropriate safety factors were applied to calculate acceptable daily intakes, and hazard quotient analysis¹⁰ was performed for all DEHP sources, individually and in aggregate.

NON-ENDOCRINE TOXICITIES OF DEHP

Effects on immunity

Phthalates induce inflammation and inhibit its resolution.¹¹ The integrin CD11b is involved in leukocyte adhesion and degranulation, and its synthesis *in vitro*, in both human and rat neutrophils, is doubled at nanomolar DEHP concentrations (0.1 to 0.3 mg/l).¹² Exposure of human neonatal neutrophils to 500 μ M MEHP strongly increases cellular H₂O₂ content and rate of production, and inhibits apoptosis and chemotaxis.¹¹

DEHP and MEHP, in nanomolar concentrations, induce IL-8 production in cultured human umbilical vein endothelial cells.¹³ Production of IL-6 and IL-8 in human lung epithelial cells is stimulated by MEHP at a concentration of approximately 250 μM .¹⁴

DEHP and other phthalates have pronounced adjuvant effects in rodents^{15–18} when administered subcutaneously,¹⁷ as an aerosol,^{15,19} or intraperitoneally,¹⁸ along with the stimulatory antigen ovalbumin. Exposure of mice to prolonged inhalation of MEHP at concentrations of 0.03 mg/m³ and 0.4 mg/m³, in combination with aerosolized ovalbumin, results in a significant and dose-dependent increase of lymphocytes, neutrophils and eosinophils in bronchoalveolar lavage fluid.¹⁵

Oxidative stress

Oxygen radicals are an important contributor to tissue injury during inflammation, and DEHP has been shown to increase oxidative stress. As described above, MEHP increases H₂O₂ production in neutrophils.¹¹ The influence of intravenous lipid infusion on serum levels of malondialdehyde, a product of free radical-induced polyunsaturated fatty acid degradation, was investigated in a group of seven infants and children receiving hyperalimentation via PVC tubing.²⁰ Despite a small sample size, there was a strongly significant relationship between the amount of lipids administered and plasma levels of DEHP ($P=0.008$), and between plasma DEHP levels and malondialdehyde levels ($P=0.002$). This demonstrates that a global marker for free radical production correlates with DEHP exposure.

Effects on lung development

To evaluate the effects of DEHP on lung development, rat pups were exposed to maternally administered DEHP in the final week of gestation.²¹ Lung sections at postnatal day 2 showed marked enlargement of terminal airspaces, along with a reduction in the number of airspaces, and a reduced overall surface area available for gas exchange. This pathology closely resembled bronchopulmonary dysplasia (BPD) of preterm human infants.²¹

In a similar study, rat pups were exposed to DEHP during pregnancy and nursing, and lung tissue was analyzed at 2, 7 and 14 days postnatally, encompassing the entire duration of alveolarization.²² Again, lung histology showed a substantial enlargement of airspaces and a reduction of respiratory surface area, similar to BPD.

Gastrointestinal effects

Enteral feedings extract significant amounts of DEHP from PVC feeding tubes.²³ Thus, onset of tube feeding should be expected to increase intestinal luminal exposure to DEHP. The role of either enteral or parenteral DEHP in the etiology of gastrointestinal inflammatory conditions such as necrotizing enterocolitis is unknown.

A clinical study found an association between intravenous DEHP exposure and hyperalimentation-associated cholestasis.²⁴ During a period of 3 years, 30 infants undergoing intensive care received hyperalimentation via PVC tubing containing DEHP, and 15 (50%) developed cholestasis. In a subsequent 3-year period, 46 infants received hyperalimentation using non-DEHP containing, non-PVC tubing, and only 6 (13%) developed cholestasis. The relationship between the incidence of cholestasis and the use of PVC infusion tubing was strongly significant ($P=0.0004$).

The effects of DEHP on liver structure were investigated in rabbits using a protocol simulating lipid infusions in human infants.²⁵ Pre-pubertal rabbits weighing between 1.0 and 1.5 kg received intravenous lipid emulsion continuously for 21 days. In the experimental group, PVC tubing was used, and the amount of DEHP extracted by the lipids and infused was approximately 1 mg/kg per day. A control group received an identical lipid infusion, but

through polyethylene tubing containing no DEHP. After 3 weeks, liver tissue from only the DEHP-exposed animals showed fibrosis, cell necrosis, bile duct proliferation, and features characteristic of oxidative stress. The authors concluded that DEHP is the agent most likely responsible for hyperalimentation-associated cholestasis, a condition responsible for considerable morbidity among infants requiring prolonged intravenous nutrition.

Neurological effects

The effects of DEHP on hippocampal development were assessed in rat pups given 10 mg/kg per day DEHP via intraperitoneal injection, from postnatal day 16 through 22, the critical period for hippocampal neuronal proliferation and migration.²⁶ Analysis of brain tissue at day 26 showed significant reductions of innervation and neuronal cell density in specific hippocampal regions in DEHP-exposed males. Hippocampal maturation in rats is associated with increased spatial ability.²⁷ The minimum threshold for the observed effect is unknown; however, the dose of DEHP used in this study is a realistic exposure for a critically ill preterm infant, as shown below.

Effects on retinal vascularization

To investigate the effects of prenatal DEHP exposure on retinal development, pregnant rats were fed DEHP in the final week of gestation and for 2 weeks postpartum.²⁸ Retinal specimens from rat pups were examined microscopically at 7 and 14 days postnatally. At both time points, retinas displayed features of disordered vascular development, including marked variation in the caliber of arterioles and venules; hypoperfused arteriolar segments indicating the presence of abnormal shunts; and irregular development of capillary networks. No vascular extensions into the vitreous were observed. These findings share features with retinopathy of prematurity, and suggest that it would be appropriate to investigate DEHP exposure as a potential factor in the cause or progression of this disease.

DEHP SOURCES, AND ESTIMATES OF EXPOSURE

Blood products

PVC bags have been used for the storage of blood products since the 1940s.²⁹ DEHP leached from bags increases lipid peroxidation in red blood cells, yet it also stabilizes cell membranes, protecting against hemolysis during storage.^{29,30} The amount of DEHP leached into blood products is related to time in storage,¹³ and can reach quantities that result in large single transfusion exposures, and considerable longer-term exposure with repeated transfusions.

In a study of the DEHP content of neonatal transfusions, a wide range of DEHP concentrations was found within each blood product type.³¹ This may have resulted from variations in length of storage, as fresher products contain less DEHP.²⁹ Fresh frozen plasma (FFP) contained considerably more DEHP than either platelets or packed red blood cells. Table 1 summarizes DEHP concentration data and shows calculated DEHP exposure ranges for 15 ml/kg transfusions of each product type, after passage through PVC infusion tubing. FFP extracted the most DEHP from tubing. DEHP measurements in blood products may underestimate actual risk, since the more toxic MEHP is also present as a result of spontaneous hydrolysis of DEHP during storage.

Intravenous tubing

To investigate the amount of DEHP leached from intravenous tubing, a 20% lipid emulsion was perfused through 2.25 meter lengths of a standard PVC infusion tubing at 27 °C (80.6 °F) and 33 °C (91.4 °F), close to room and incubator temperatures,

Table 1. Concentrations of di(2-ethylhexyl)phthalate in blood products after passage through PVC infusion tubing; calculated exposure ranges resulting from 15-ml/kg transfusions of each product (adapted from Loff *et al.*³¹)

Product	n	Concentration range (µg/ml)	Mean	Exposure (mg/kg) from a 15-ml/kg transfusion
Packed red blood cells	14	6.4–29.0	16.6	0.10–0.44
Fresh frozen plasma	14	27.6–405.4	168.4	0.41–6.08
Platelets	10	34.2–61.4	46.4	0.51–0.92

respectively.³² Extraction of DEHP from the tubing was substantial at both temperatures, and the effect was strongly temperature dependent, with nearly 30% greater extraction at 33 °C. The authors calculated that intravenous exposure to DEHP for a 2-kg infant, from tubing alone during a 24-h lipid infusion, could reach 6.5 mg/kg at 33 °C.

Endotracheal tubes

Most neonatal endotracheal tubes (ETTs) are made from PVC. Tubes removed from the airway are often less flexible than fresh ones, a result of phthalate leaching.³³ In a recent study, 10 ETTs were analyzed for DEHP content after having been used in infants for durations of 18–168 h.³⁴ Of these, seven had been in place for >24 h (one of 3.0 mm internal diameter, five of 3.5 mm and one of 4.0 mm). From these seven tubes, estimates of the potential range of ETT-related DEHP exposures can be made. These are summarized in Table 2, along with calculated exposure values for a 2-kg infant, based on a 3.5-mm PVC ETT, inserted to a depth of 8 cm,³⁵ and weighing³⁶ 0.11 gm/cm.

The investigators observed that most leaching of DEHP from an ETT occurs in the first 24 h of use. Thus, multiple boluses of DEHP may result from frequent reintubations with fresh tubes. It can be expected that leaching occurs via direct tissue contact, as well as into intraluminal condensate and secretions which could then enter the lungs. DEHP also evaporates from the tube and can reach the airways as a vapor.³⁷

Feeding tubes

The extraction of DEHP from neonatal PVC feeding tubes in gastric juice was studied *in vitro*.²³ Mean loss of DEHP over 7 days, for 20 identical 5-cm tubing samples (size 8F) at 37 °C, was 0.847 mg (range of 0.635–1.043 mg). From these results, an estimate of exposure can be made. Using the greatest leached quantity of 1.043 mg per 5 cm (0.209 mg/cm), and assuming that 19 cm of an orogastric feeding tube resides within the body of a 2-kg infant,³⁸ this yields an exposure of 1.98 mg/kg over 7 days, or 0.28 mg/kg per day. Only the distal portion of a feeding tube lies within the stomach, and the proximal portion contacts the oropharynx (or nasopharynx) and esophagus. However, since direct transfer of DEHP from tubing to tissue occurs readily, the above estimates should be nearly correct. In practice, feeding tubes are often replaced more frequently than every 7 days. This could result in greater DEHP exposure if most leaching occurs early after tube placement, as was observed for ETTs.

Other devices

Umbilical catheters, nasal cannulas and continuous positive airway pressure (CPAP) fittings are often made from materials free of DEHP, such as polyurethane and silicone elastomer. Although not a subject of published studies, PVC chest tubes are similar to ETT with respect to length and diameter, and might yield similar DEHP

Table 2. DEHP losses from PVC endotracheal tubes (ETTs), and resulting infant exposures. Used ETTs were *in situ* >24 h. (Adapted from Chiellini *et al.*³⁴)

DEHP exposure	DEHP in unused ETT (%)	DEHP in used ETT (%)	DEHP loss (%)	DEHP loss, mg/g ETT	Exposure for a 2-kg infant (mg/kg) ^a
Least	17.9 ^b	12.5 ^c	30.2	54	23.8
Greatest	24.4 ^d	9.6 ^e	60.7	148	65.1
Mean	21.9 ^f	10.7 ^g	51.1	112	49.3

Abbreviations: DEHP, di(2-ethylhexyl)phthalate; PVC, polyvinyl chloride.
^aAssumes 0.88 g ETT internal to the patient (8 cm × 0.11 gm/cm for a 3.5 mm I.D. ETT).

^bLowest content of three unused ETTs (measured in a 3.0-mm tube).

^cHighest content of seven used ETTs (measured in a 3.5-mm tube, at 127 h).

^dHighest content of three unused ETTs (measured in a 3.5-mm tube).

^eLowest content of seven used ETTs (measured in a 4.0-mm tube, at 100 h).

^fMean content of three unused ETTs.

^gMean content of seven used ETTs (duration of use: mean = 86 h, median = 96 h, range = 29–169 h).

exposures. Exchange transfusions, cardiopulmonary bypass, and extracorporeal membrane oxygenation all result in substantial exposures, but are outside the scope of this risk assessment. Other PVC products (e.g., suction catheters, gloves, oxygen masks) have only brief contact with patients, and their contributions to daily DEHP intake are likely small.

EXPOSURE SUMMARY

Exposures to DEHP for a 2-kg infant, from principal sources as detailed above, are shown in Table 3.

RISK ASSESSMENT

The US CPSC in 2010 established acceptable daily intakes (ADIs) for DEHP, for specific populations, based on a comprehensive review of the literature describing dose-response characteristics for DEHP toxicities.³ ADIs were categorized according to exposure duration: acute (≤14 days), intermediate (15 to 364 days) and chronic (≥365 days). Table 4 summarizes these values. In accordance with federal guidelines³⁹ and CPSC practice,³ ADIs are derived by dividing experimental exposures by safety factors of 100 or 1000 as follows: No observed adverse effect levels (NOAELs) are divided by 10 for interspecies differences, and again by 10 for intraspecies (human) variation; lowest observed adverse effect levels (LOAELs) are divided further by another factor of 10, given their greater uncertainty for a lowest exposure threshold for adverse effects. A hazard quotient (HQ) is then calculated by dividing the estimated daily intake by the ADI; a larger number implies increased risk, and a value of <1 is desired.

Our analysis included an additional safety factor of 10 for infants, since they may not be protected sufficiently by the factor of 10 for human variability (which accounts for variation among adults). This approach was recommended by the National Research Council Committee on Pesticides in the Diets of Infants and Children,⁴⁰ and its use by the US Environmental Protection Agency was then mandated by the Food Quality Protection Act of 1996.⁴¹ This safety factor compensates for an absence of studies establishing toxicity thresholds in infants, and the fact that infants are expected to be more sensitive to chemical exposures than the general population. It is logical to apply these concepts to the case of DEHP exposures in neonatal care. One could also propose additional safety factors for illness and prematurity, to account for those patients who may have greater multisystem and

Table 3. Estimated DEHP exposures from principal sources

Source	Route	Exposures for a 2-kg infant (mg/kg)
Lipid emulsion	24-h infusion	6.5 ^a
PRBC	15 cc/kg transfusion	0.10–0.44
FFP	15 cc/kg transfusion	0.41–6.08
Platelets	15 cc/kg transfusion	0.51–0.92
Endotracheal tube	<i>In situ</i> contact ^b	49.3 ^c
Feeding tube	<i>In situ</i> contact ^b	1.98 ^d

Abbreviations: DEHP, di(2-ethylhexyl)phthalate; ETT, endotracheal tube; FFP, fresh frozen plasma; PRBCs, packed red blood cells.

^aPer 24 h, for a 20% emulsion at 3 gm/kg per day.³²

^bExposure is for one tube, over its duration *in situ*.

^cMean estimate, from Table 2.

^d19 cm * (0.209 mg DEHP/cm)/2 kg.

Table 4. Acceptable daily intakes (ADIs) for DEHP, per US Consumer Product Safety Commission

	Acute	Intermediate	Chronic
General population	0.1 mg/kg per day ^a	0.024 mg/kg per day ^b	0.0580 mg/kg per day ^c
Male reproduction	–	0.037 mg/kg per day ^d	0.0058 mg/kg per day ^e
Development	–	0.011 mg/kg per day ^f	–

Abbreviations: DEHP, di(2-ethylhexyl)phthalate; LOAEL, lowest observed adverse effect level; NOAEL, no observed adverse effect level.

^aNOAEL/100. Increased liver weights and enzymes in young rats.

^bLOAEL/1000. Increased liver weights in adult male rats.

^cNOAEL/100. Increased liver weights in adult rats.

^dNOAEL/100. Vacuolization of Sertoli cells in adult male rats.

^eLOAEL/1000. Aspermatogenesis in adult male rats.

^fLOAEL/1000. Male rat offspring with phthalate syndrome.

developmental vulnerabilities. In the interest of simplicity, such factors were not used in this analysis.

Of the ADI values in Table 4, the one most relevant to infants is that of 0.037 mg/kg per day, for male reproductive effects (vacuolization of Sertoli cells). This is an intermediate duration exposure, as are most exposures in the NICU. We can obtain an infant ADI (ADI_{inf}) of 0.0037 mg/kg per day by dividing the ADI of 0.037 mg/kg per day by the additional safety factor of 10 for infants.

As discussed above, liver toxicity was observed in prepubertal rabbits following intravenous administration of DEHP via lipid emulsion for 21 days, an intermediate duration exposure.²⁵ The exposure, of 1 mg/kg per day, yielded a toxic response at a dose lower than in any study considered in the CPSC report, and is a LOAEL, since a threshold for toxicity was not established. Using the approach of the CPSC, an ADI of 0.001 mg/kg per day can be calculated by dividing the LOAEL of 1 mg/kg per day by 1000. Dividing further by the safety factor of 10 for infants yields an ADI_{inf} of 0.0001 mg/kg per day.

Table 5 shows calculated daily DEHP intakes, as well as hazard quotients for male reproductive (testicular) and liver toxicities, for a hypothetical critically ill, intubated, 2-kg infant, based on exposure data from Table 3. Daily intakes exceed ADI_{inf} values by multiples of 4391 and 162,459 for male reproductive and hepatic effects, respectively. These results are based on reasonable assumptions for the use of blood products and tubes, as detailed in Table 5.

Exposures could be higher for sicker infants, for whom ETTs may be changed, and blood products administered, more frequently.

Note: an exposure is a NOAEL (no observed adverse effect level) if it is the highest value tested—among a graded series of increasing exposures—at which no adverse effects are seen. Thus, toxicity is not expected at lower exposures, but might occur at higher values. A LOAEL (lowest observed adverse effect level) is the lowest exposure observed to result in toxicity, and is usually the lowest value tested. Therefore, toxicity might still occur at levels lower than a LOAEL. For the purposes of risk assessment, the NOAEL provides greater certainty with respect to the lower bound on toxic thresholds. For this reason, an additional safety factor of 10 is used when calculating an ADI from a LOAEL.

DISCUSSION

Infants undergoing intensive care may receive substantial amounts of DEHP from direct and indirect contact with PVC devices. Total daily exposure for an intubated 2-kg critically ill infant is in the range of 16 mg/kg per day. Hazard quotient analysis based on toxicity thresholds shows this level of intake to be on the order of 4000 and 160,000 times higher than desired to avoid male reproductive and hepatic toxicities, respectively. These calculations incorporated a safety factor of 10 for infants, but did not include additional safety factors for illness and prematurity. If these had been used, hazard quotient values would have been substantially higher. Therefore, we consider our derived hazard quotients to be conservative from the standpoint of standard risk assessment methods. We recognize that the calculated ADI_{inf} values are quite low: 3.7 μ g/kg per day and 0.1 μ g/kg per day, for reproductive and liver toxicities, respectively. Given the ubiquity of DEHP as an environmental contaminant and a component of a wide range of consumer products, these values might be difficult to achieve in practice. If we had chosen smaller (nonstandard) safety factors, the ADI_{inf} values would have been higher (and hazard quotients lower), but the final conclusions would have been the same: that infants in the NICU receive DEHP exposures orders of magnitude higher than acceptable values, and that actual intakes are in excess of amounts demonstrated to cause a range of toxicities. It must be noted that even without the use of safety factors, the mean daily intake of DEHP is still 16 times higher than the 1 mg/kg per day exposure that caused liver damage experimentally.²⁵

The non-endocrine toxic profile of DEHP suggests that exposures in the NICU might contribute to the cause and severity of common complications of prematurity. DEHP is proinflammatory via several mechanisms, and most neonatal morbidities have inflammation-mediated tissue injury as a central feature. DEHP-induced disruption of lung development is similar to BPD. We propose that a lesser exposure to DEHP may be one reason that ventilation strategies using nasal CPAP instead of endotracheal intubation can result in better lung outcomes.⁴²

Infants in the NICU are exposed to a wide range of natural and synthetic antigens which may incite local (e.g., pulmonary, gastrointestinal) or systemic reactions. Adjuvant effects of DEHP and MEHP could, in principle, augment this process. Existing evidence for an association between environmental phthalate exposure and childhood asthma⁴³ suggests that DEHP could be a potential contributor to the reactive airway component of BPD.

Contamination of lipid emulsions by DEHP results in a complex pattern of liver injury and may be a principal cause of hyperalimentation-associated cholestasis. Experimental and clinical data show that DEHP increases oxidative stress. DEHP exposure during a critical period of brain development results in neuronal defects experimentally, and epidemiologic studies suggest that prenatal and childhood exposures to phthalates are associated with cognitive and behavioral deficits.^{44,45} Finally, perinatal DEHP exposure in a

Table 5. Estimated daily DEHP exposures for a critically ill 2-kg infant; hazard quotients calculated for each DEHP source using a reproductive ADI_{inf} of 0.0037 mg/kg per day, and liver toxicity ADI_{inf} of 0.0001 mg/kg per day.

Source	Daily exposure, 2-kg infant ^a (mg/kg per day)	Hazard quotient (HQ) ^b	
		Reproduction ^c	Liver ^d
Lipid emulsion	6.5	1757	65,000
PRBC	0.15 ^e	40	1467
FFP	0.87 ^e	235	8686
Platelets	0.18 ^e	50	1840
Endotracheal tube	8.22 ^f	2221	82,167
Feeding tube	0.33 ^g	89	3300
Total	16.3	4391	162,459

Abbreviations: ADI_{inf}, acceptable daily intake for infants; DEHP, di(2-ethylhexyl)phthalate; ETT, endotracheal tube; FFP, fresh frozen plasma; LOAEL, lowest observed adverse effect level; NOAEL, no observed adverse effect level; PRBCs, packed red blood cells.

^aBased on values from Table 3, and the following assumptions: one PRBC transfusion every 3 days; one platelet transfusion every 5 days; one FFP transfusion every 7 days; ETT and feeding tubes are replaced every 3 days; for ETT and feeding tubes, 50% of DEHP loss occurs in the first 3 days (daily exposure = total exposure (from Table 3) × 50% loss ÷ 3 days).

^bHQ = actual daily exposure divided by ADI_{inf} (Desired value is <1).

^cCalculated ADI_{inf} = NOAEL/1000 = 0.0037 mg/kg per day.

^dCalculated ADI_{inf} = LOAEL/10,000 = 0.0001 mg/kg per day.

^eDaily exposure per kg = upper bound estimates for each blood product (from Table 3) divided by respective assumed transfusion interval.

^f(49.3 mg/kg) [from Table 3]/3 * 0.5.

^g(1.98 mg/kg) [from Table 3]/3 * 0.5.

newborn animal model results in a marked disruption of retinal vascular development resembling retinopathy of prematurity.

Replacing DEHP-containing PVC medical devices with existing alternative products⁴⁶ would be the most effective initial step in reducing phthalate exposures during intensive care. Further reductions would be attained by addressing other sources of phthalates, such as materials used in NICU construction (e.g., flooring, wall coverings, paints, adhesives); complex hardware (e.g., ventilators, respiratory circuits, incubators); breast milk; hand soaps, lotions, cosmetics and fragrances used by staff and visitors; and soaps, lotions and powders used for baby care.

The Consumer Product Safety Improvement Act, passed by Congress in 2008, established a maximum legal limit for specific phthalates, including DEHP, in toys and consumer childcare products.⁴⁷ This value is set at a total content of 0.1%, due to concerns regarding endocrine disruption. No similar rule exists for PVC medical devices, yet these contain high percentages of DEHP, their modes and duration of contact ensure that substantial leaching and exposures occur, and—for critically ill and preterm infants—the exposed population is especially vulnerable. To address these hazards, France has enacted a ban, effective July 2015, on the use of DEHP-containing tubes in neonatal, pediatric, and maternity units.⁴⁸

CONCLUSION

DEHP exposures in the NICU can exceed estimated safe levels by 3 to 5 orders of magnitude. A diverse toxicology literature shows the non-endocrine adverse effect profile of DEHP to be similar to the range of acute and chronic complications occurring in critically ill infants. Accordingly, concern regarding DEHP and other phthalates

in neonatal care should be expanded beyond their role as endocrine disruptors.

Reduction of DEHP exposures can be accomplished by substituting already available DEHP-free products. Further development of such devices by manufacturers, along with greater demand by caregivers and hospitals, could result in a transition away from DEHP in neonatal units. Restrictions on the use of phthalates in medical settings could provide wider protections.

As we strive to provide care appropriate to the sensitivities of sick and preterm infants, the devices used in their management should be considered as potential contributors to illness. Causes of most neonatal complications are multifactorial and incompletely understood. The role of the highly synthetic NICU environment in these conditions remains a promising, yet largely unexplored, frontier.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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