DEHP Exposures During the Medical Care of Infants

A Cause for Concern

Prepared by
Ted Schettler MD, MPH
Science and Environmental Health Network

What is DEHP (di(2-ethylhexyl) phthalate)?

DEHP is one member of a family of chemicals called phthalates and it is used as a plasticizer of polyvinyl chloride (PVC) medical devices. Plasticizers provide PVC with flexibility, strength, and bondability. Most PVC medical devices contain 20-40% DEHP by weight, but PVC tubing may contain up to 80% DEHP.[1, 2] DEHP-plasticized PVC products are common in neonatal intensive care units (NICUs). Manufacturers use DEHP in bags that contain IV solutions, enteral formula, and blood products, and in tubing that delivers these fluids as well as TPN and oxygen.

DEHP-containing PVC medical products have been used for approximately 40 years. When the Food and Drug Administration (FDA) was authorized to regulate medical devices beginning in the mid-1970's, products made of material formulations that had been used previously were not tested to the same degree as new products that came to market after May, 1976. Any change in the status of older products or new products made of the same material must be based on a FDA conclusion that their use poses a significant risk of harm, rather than the manufacturer being required to demonstrate product safety.

How are patients exposed?

DEHP does not chemically bind to PVC. DEHP may therefore leach from plasticized PVC when a medical device comes into contact with fluids, lipids, and/or heat. DEHP is lipophilic and leaches preferentially into lipid-containing solutions. The rate of DEHP leaching also depends on storage conditions (e.g. temperature, contact time, agitation).

In general, medical procedures that require hours or days, like hemodialysis, blood transfusion, extracorporeal membrane oxygenation (ECMO), total parenteral nutrition (TPN), or enteral feeding, result in higher DEHP exposures than brief procedures. On a weight basis, neonates in the neonatal intensive care unit (NICU) are likely to be among the most highly DEHP-exposed patients because of the regular use of many different DEHP-containing PVC products in that setting.

What are the health effects of DEHP?

DEHP is a reproductive and developmental toxicant in laboratory animal testing. MEHP, the monoester metabolite of DEHP, is toxic to the Sertoli cells of the testes, causing cellular abnormalities and impairing proliferation. DEHP also interferes with testosterone synthesis. In rodents, developmental DEHP exposure causes general adverse effects on the structure and function of the male reproductive tract.[3] Effects on the developing male reproductive tract occur at far lower doses than are toxic to adult animals.[4, 5, 6] The testicular toxicity of DEHP has not been evaluated in immature, prepubertal primates, including humans. Based on developmental studies in animals, the Food and Drug Administration (FDA) and the National Toxicology Program's Center for Evaluation of Risks to Human Reproduction conclude that some medical procedures result in DEHP exposures that exceed the threshold NOAEL (no observable adverse effects level) in the developing male reproductive tract (NOAEL by oral route of exposure ~3.7-14 mg/kg/day) and exceed the FDA's estimated tolerable intake (TI), below which no adverse effects are expected.[7, 8]

In addition to effects on the developing male reproductive tract, questions have been raised about the effects of DEHP exposure on the liver and lungs. One prospective study found cholestasis in infants supported by ECMO.[9] The authors hypothesize that hemolysis during ECMO produces a large bilirubin load, the excretion of which is

Pub 3-06 This publication is part of *Going Green: A Resource Kit for Pollution Prevention in Health Care.* For additional copies of this or other publications included in the kit, or to find out how to get a complete kit, visit Health Care Without Harm on the Web at www.noharm.org/goinggreen.
This version: November 12, 2002

inhibited by inspissated bile and/or DEHP. Another study, however, did not find cholestasis after ECMO,[10] but DEHP plasma concentrations in the second study were substantially lower than in the first (estimated aggregate exposure levels 4.7-35 mg/kg vs. 42-140 mg/kg). Recently, renewed concerns have surfaced about a contributory role of DEHP in the genesis of hepatotoxicity frequently observed in infants receiving TPN.[11] Although this potential hazard has not been studied, larger quantities of DEHP leach from PVC tubing through which TPN solution is passed than were previously estimated. The authors of this study estimate that infant exposures from TPN may reach 10 mg/kg/day, which is more than one order of magnitude higher per kg than adult exposures from hemodialysis, and are experienced daily.

DEHP also leaches from PVC endotracheal tubes during use. One study documents a direct relationship between time of endotracheal tube use and DEHP leaching.[12] The authors hypothesize a link between DEHP exposure and the risk of bronchopulmonary dysplasia in premature newborns. This potential hazard has never been studied in infants. DEHP deposition in the infant lung, however, has been documented after ventilation with PVC tubing.[13]

The FDA also notes that DEHP leaching from PVC materials promotes platelet aggregation and complement activation, with the potential for adverse clinical consequences, including microemboli.[14]

Toxicokinetics of DEHP

Much of the DEHP administered via the gastrointestinal tract is converted to its monoester, mono-ethylhexyl phthalate (MEHP), by intestinal lipases before absorption into the systemic circulation. In adult primates, including humans and marmosets, a smaller proportion of DEHP is hydrolyzed and absorbed as the monoester [than in rats], apparently because of less lipase activity in primate intestine.[15] The degree of biotransformation of DEHP to MEHP is important since MEHP is generally agreed to be the testicular toxicant.

When DEHP is administered intravenously, less DEHP is converted to MEHP than if the exposure is via the intestinal tract.[16] In studies of patients, including infants, undergoing hemodialysis or exchange transfusions, however, significant levels of MEHP have been measured in blood after these parenteral exposures.[17] In a study of 11 patients undergoing maintenance hemodialysis for treatment of renal failure, concentrations of the metabolite, MEHP, ranged from about 1/3 to 6 times the DEHP concentrations.[18]

These data demonstrate that a significant amount of DEHP is converted to MEHP even after intravenous exposure to the parent compound. Humans and primates largely excrete the monoester via glucuronide conjugation, whereas rodents further hydrolyze MEHP into other intermediates.[19] The glucuronidation pathways of human children, however, do not mature until they are 3 months old.[20] Thus, this important clearance mechanism is not fully available to neonates and young infants.

What are the levels of DEHP exposure in the NICU?

Published reports of DEHP exposures from various sources in the neonatal intensive care unit are summarized in the table. For critically ill neonates, examining single sources of exposure may substantially underestimate total exposures. Babies who require ECMO, for example, also require multiple blood transfusions, parenteral feeding, medications, and IV fluids. Breast milk and enteral feeding formula may be administered through DEHP-containing PVC tubing. Loff, et al. note that, in infants receiving TPN, when infusions of other medications are also administered, the load can easily reach 10 mg DEHP/kg/day.[21] No studies have quantified exposure to DEHP from enteral feeding bags and tubing, nasogastric tubes, breast milk pumps and tubing, respiratory tubing, endotracheal tubes, oxygen masks, or all sources combined.

Summary

Neonates and infants who receive medical care that includes the use of plasticized PVC products may easily be exposed to DEHP at levels that are in excess of the no observed adverse effect level (NOAEL) in animal tests. For some medical therapies, these exposures also exceed the FDA-derived "tolerable intake" (TI). (see table) The FDA has concluded that total parenteral nutrition, enteral feeding, exchange transfusions, and ECMO can individually result in DEHP exposures that exceed the TI by 3-50 fold. Of course, multiple simultaneous medical procedures using DEHP-containing PVC products will more readily result in exposures in excess of the TI. DEHP toxicity in the developing male reproductive system is the greatest known risk, with additional concerns about thrombus formation, microemboli, and impacts on the liver and lungs. An expert panel convened by the National Toxicology Program's (NTP) Center for Evaluation of Risks to Human Reproduction concluded that:

> "[for DEHP] the available reproductive and developmental toxicity data and limited but suggestive human exposure data indicate that exposures of intensively-treated infants and children can approach toxic doses in rodents, which causes the panel serious concern that exposure may adversely affect male reproductive tract development."

The panel also expressed "concern that ambient oral DEHP exposures [primarily from general dietary contamination] to pregnant or lactating women may adversely affect the development of their offspring." DEHP exposures from medical therapy would, of course, add to ambient, dietary exposures.

The FDA characterizes their safety

Potential exposures to DEHP from medical procedures and nutrition in a neonatal intensive care unit

Source of DEHP Exposure	Exposure (mg DEHP/kg body weight)	Unit	Total Exposure or Concentration in Product	Source	TI/dose*
Artificial ventilation in preterm infants (PVC respiratory tubing; not polyethylene)	NR	Hour (inhalation)	0.001-4.2 mg(est. total exposure)	1	
Neonatal blood replacement transfusion; short-term, acute	0.3 (0.14-0.72)	treatment period	NR	2	2
Neonatal blood replacement transfusion; double volume; short term, acute	1.8 (0.84-3.3)	treatment period	NR	3	0.3
Platelet concentrates in newborns	1.9	treatment	NR	4	0.3
Extracorporeal oxygenation in infants	14-140	treatment	NR	5	0.04-0.004
Extracorporeal oxygenation in infants	4.7-34.9	Treatment	NR	6	0.12-0.02
Congenital heart repair (neonates)		1-4 hours	0.3-4.7 µg/mL/hr(change in level in whole blood during procedure)	7	
IV crystalloid solution	0.03	From tubing	NR	8	20
Total parenteral nutritional formula (TPN), with lipid	2.5	NR	3.1 µg/mL (concentration in TPN formula); more from tubing	9	0.2
TPN/IV Tubing	5	day	10 mg/2-kg baby/day	10	0.12
Multiple IV Sources: packed red blood cells, platelet rich plasma, fresh frozen plasma, and medications	5	day	10 mg/2-kg baby/day	11	0.12
Breast milk	0.0015-0.0165	Day	0.01-0.11 mg/kg (concentration in breast milk)	12	27-2.4
Infant formula	0.015	Day	0.004-0.06 mg/kg wet weight	13	2.6
Infant formula	0.0087-0.035	NR	0.33-0.98 mg/kg dry weight	14	4.5-1.1

NR = Not Reported *TI/dose: based on FDA's TI of 0.6 mg/kg/day for parenteral exposures and 0.04 mg/kg/day for intestinal exposures; TI/dose ratios < 1 imply that the TI has been exceeded for the given source of exposure

assessment of DEHP as entirely consistent with the NTP panel's concerns. In their public health notification, the FDA recommends that alternative devices that do not contain DEHP be used for procedures that may otherwise result in excessive DEHP exposures in susceptible patients.

Notes

1. NTP-CERHR expert panel report on di(2-ethylhexyl)phthalate. National Toxicology Program. US Dept of Health and Human Services; Oct, 2000.
2. DiGangi J. Phthalates in vinyl medical products. Washington DC: Greenpeace USA, 1999.
3. Gray E, Wolf C, Lambright C, et al. Administration of potentially antiandrogenic pesticides (procymidone, linuron, iprodione, chlozolinate, p,p'-DDE, and ketoconazole) and toxic substances (dibutyl- and diethylhexyl phthalate, PCB 169, and ethane dimethane suphonate) during sexual differentiation produces diverse profiles of reproductive malformations in the rat. Toxicol Ind Health 14: 94-118, 1999.
4. Lamb J, et. al. 1987. Reproductive effects of four phthalic acid esters in the mouse. Toxicol Appl Pharmacol 88: 255-269.
5. Arcadi R, Costa C, Imperatore C, et al. Oral toxicity of DEHP during pregnancy and suckling in the Long-Evans rat. Food Chem Toxicol 36:963-970, 1998.
6. Poon R, Lecavalier P, Mueller R, et al. Subchronic oral toxicity of di-n-octyl phthalate and DEHP in the rat. Food Chem Toxicol 35:225-239, 1997.
7. NTP-CERHR expert panel report on di(2-ethylhexyl)phthalate. National Toxicology Program. US Dept of Health and Human Services; Oct, 2000.
8. US FDA. Safety assessment of di(2-ethylhexyl)phthalate (DEHP) released from PVC medical devices. Sept, 2001.
9. Schneider B, Schena J, Truog R, et al. A prospective analysis of cholestasis in infants supported with extracorporeal membrane oxygenation. J Pediatr Gastroenterol Nutr 13: 285-89, 1991.
10. Karle V, Short B, Martin G, et al. Extracorporeal membrane oxygenation exposes infants to the plasticizer, di(2-ethylhexyl)phthalate. Crit Care Med 25:696-703, 1997.
11. Loff S, Kabs F, Witt K, et al. Polyvinylchloride infusion lines expose infants to large amounts of toxic plasticizers. J Pediatr Surgery 35(12): 1775-1781, 2000.
12. Latini G, Avery G. Materials degradation in endotrachael tubes: a potential contributor to bronchopulmonary dysplasia. Acta Pediatr 88(10):1174-5, 1999.
13. Roth B, Herkenrath P, Lehmann H, et al. Di-(2-ethylhexyl)-phthalate as a plasticizer in PVC respiratory tubing systems: indications of hazardous effects on pulmonary function in mechanically ventilated, preterm infants. Eur J Pediatr 147: 41-46, 1988.
14. US FDA. Safety assessment of di(2-ethylhexyl)phthalate (DEHP) released from PVC medical devices. Sept, 2001.
15. Pollack G, Li R, Ermer J, et al. Effects of route of administration and repetitive dosing on the disposition kinetics of di(2-ethylhexyl)phthalate and its mono-de-esterified metabolite in rats. Toxicol Appl Pharmacol 79:246-256, 1985.
16. Rubin R, Schiffer C. Fate in humans of the plasticizer, di-2-ethylhexyl phthalate, arising from transfusion of platelets stored in vinyl plastic bags. Transfusion 16:330-335, 1976.
17. Sjoberg P, Bondesson U, Sedin E, et al. Exposure of newborn infants to plasticizers: Plasma levels of di-(2-ethylhexyl) phthalate and mono-(2-ethylhexyl) phthalate during exchange transfusion. Transfusion 25(5):424-428, 1985.
18. Pollack G, Buchanan J, Slaughter R, et al. Circulating concentrations of di(2-ethylhexyl)phthalate and its de-esterified phthalic acid products following plasticizer exposure in patients receiving hemodialysis. Toxicol Appl Pharmacol 79:257-267, 1985.
19. Albro P, Corbett J, Schroeder J, et al. Pharmacokinetics, interactions with macromolecules and species differences in metabolism of DEHP. Environ Health Perspect 45:19-25, 1982.
20. Creistel T. Onset of xenobiotic metabolism in children: toxicological implications. Food Addit Contam 15:45-51, 1998.
21. Loff S, Kabs F, Witt K, et al. Polyvinylchloride infusion lines expose infants to large amounts of toxic plasticizers. J Pediatr Surgery 35(12): 1775-1781, 2000.

Table Sources

1. Roth B, Herkenrath P, Lehman H, et al. Di-(2-ethylhexyl)-phthalate as plasticizer in PVC respiratory tubing system: indications of hazardous effects on pulmonary function in mechanically ventilated, preterm infants. J Pediatr 147:41-46, 1988.
2. Sjoberg P, Bondesson U, Sedin E, et al. Exposure of newborn infants to plasticizers: Plasma levels of di-(2-ethylhexyl) phthalate and mono-(2-ethylhexyl) phthalate during exchange transfusion. Transfusion 25(5):424-428, 1985.
3. Sjoberg, 1985.
4. Huber WW, Grasl-Kraupp B, and Schulte-Hermann R. Hepatocarcinogenic potential of DEHP in rodents and its implications on human risk, Critical Reviews in Toxicology, 26: 365-481, 1996.
5. Schneider B, Schena J, Troug R, et al. Exposure to di(2-ethylhexyl)phthalate in infants receiving extracorporeal membrane oxygenation. New Engl J Med 320:1563, 1989.
6. Karle VA, Short Bl, Martin GR et al. Extracorporeal membrane oxygenation exposes infants to the plasticizer, DEHP, Critical Care Medicine, 25: 696-703, 1997.
7. Barry YA, Labow RS, Keon, WJ, et al. Perioperative exposure to plasticizers in patients undergoing cardiopulmonary bypass. J Thorac Cardiovas Surg, 97: 900-905, 1989.
8. Loff, S, Kabs F, Witt K, Sartoris J, et al. Polyvinylchloride infusion lines expose infants to large amounts of toxic plasticizers, J Ped Surg, 35: 1775-1781, 2000.
9. Mazur HI, Stennett DJ, and Egging PK. Extraction of diethylhexylphthalate from total nutrient solution-containing polyvinyl chloride babs. J Parenter Enter Nutr, 13:59-62, 1989.; Loff, S, Kabs F, Witt K, Sartoris J, et al. Polyvinylchloride infusion lines expose infants to large amounts of toxic plasticizers, J Ped Surg, 35: 1775-1781, 2000.
10. Loff, S, Kabs F, Witt K, Sartoris J, et al. Polyvinylchloride infusion lines expose infants to large amounts of toxic plasticizers, J Ped Surg, 35: 1775-1781, 2000.
11. Loff, S, Kabs F, Witt K, Sartoris J, et al. Polyvinylchloride infusion lines expose infants to large amounts of toxic plasticizers, J Ped Surg, 35: 1775-1781, 2000.
12. Pfordt J and Bruns-Weller E. 1999. Die Phthalsäureester als eine Gruppe von Umweltchemikalien mit endokrinen Potential. Niedarsächsisches Ministerium fhr Ernährung, Landwirschaft und Forsten.
13. Petersen J and Breindahl T. Plasticizers in total diet samples, baby food, and infant formulae, Food Additives and Contaminants, 17: 133-141, 2000.
14. MAFF. Food surveillance information sheet - Phthalates in infant formulae. Joint Food Safety and Standards Group: MAFF - UK, 1996.

Health Care Without Harm

1901 North Moore St.
Suite 509
Arlington, VA 22209
Phone: 703.243.0056
Fax: 703.243.4008
www.noharm.org
info@hcwh.org

This publication is part of *Going Green: A Resource Kit for Pollution Prevention in Health Care.* For additional copies of this or other publications included in the kit, or to find out how to get a complete kit, visit Health Care Without Harm on the Web at www.noharm.org/goinggreen.