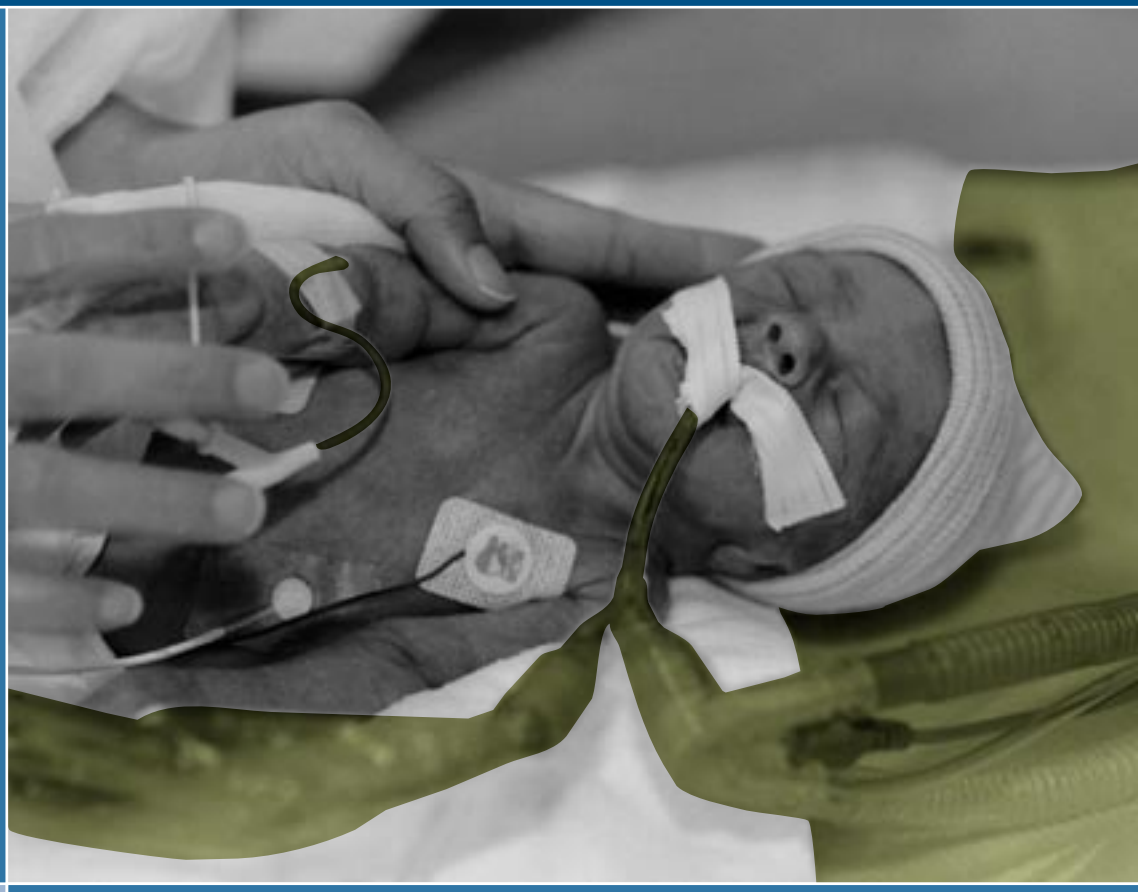
Neonatal Exposure to DEHP (di-2-ethylhexyl phthalate) and Opportunities for Prevention



Mark Rossi

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Health Care Without Harm

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PHOTOGRAPHS

The yellow coloring in the photographs represents potential sources of DEHP-plasticized PVC in a neonatal intensive care unit.

ACKNOWLEDGEMENTS

We are deeply indebted to those who reviewed the report. Their insightful comments have strengthened the final document. Thank you Cynthia Bearer, MD, Dan Billman, MD, Charlotte Brody, RN, Jackie Hunt Christensen, Lilian Corra, MD, Tracey Easthope, MPH, Sherwin Kevy, MD, Patty Lovera, MS, Michael McCally, MD, Peter Orris, MD, Ted Schettler, MD, Hollie Shaner, RN, MSA, Joel Tickner, ScD, and Rich Whate. Their review of the report does not constitute an endorsement of the findings or conclusions and any errors that persist are my responsibility.

PREFACE

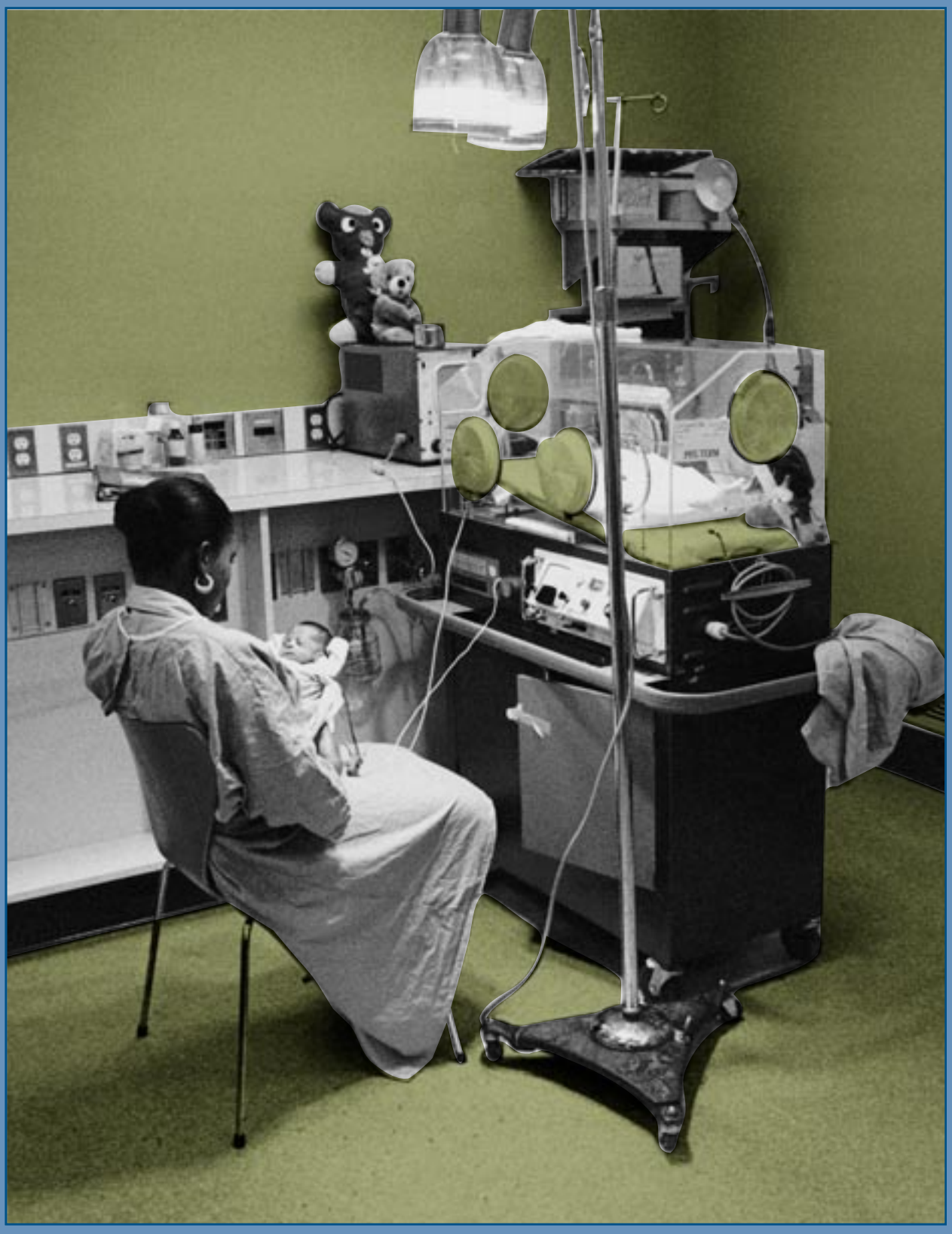
When Health Care Without Harm first published this report in October 2000 we concluded that the hospital patient most vulnerable to the effects of di-2-ethylhexyl phthalate (DEHP) was the infant born prematurely and receiving care in a neonatal intensive care unit (NICU). We based this conclusion on three observations:

1) peer-reviewed laboratory animal studies that demonstrate the particular vulnerability of the developing fetus and immature organism to DEHP toxicity and evidence that those studies are relevant to humans;
2) documented high DEHP exposures from medical treatments involving polyvinyl chloride (PVC) plasticized with DEHP under certain circumstances; and
3) knowing that neonates often receive multiple treatments with DEHP-containing medical devices during the course of their care.

In the two years since HCWH first published *Neonatal Exposure to DEHP and Opportunities for Prevention*, the US Food and Drug Administration, the Center for the Evaluation of Risks to Human Reproduction at the National Toxicology Program, and an expert advisory panel to Health Canada have all concluded that neonates may be exposed to levels of DEHP known to cause harm in laboratory animals and that those animal studies are relevant for predicting impacts in humans. Each of the review panels has explicitly noted the lack of any human data addressing the impacts of DEHP exposure on the developing male reproductive tract, which is the most sensitive endpoint.

Since alternative products that do not leach DEHP are widely available, health care providers can protect the fetus, neonates, pre-pubertal children, and other vulnerable patients from exposure to DEHP by insisting on DEHP- and PVC-free products.

Charlotte Brody, RN
Health Care Without Harm



EXECUTIVE SUMMARY

Human exposure to DEHP occurs throughout life. The exposure to this toxic chemical begins in the womb, rises dramatically for premature infants and newborns requiring intensive care in a neonatal unit, and declines with their removal from intravenous, enteral feeding and oxygen therapy systems and their arrival at home. Pre-term babies, especially low-weight babies, may require many of the medical treatments that use DEHP-plasticized PVC products including blood infusions, respiratory therapy, infusions of electrolytes, sugars, and medications, total parenteral (intravenous) nutrition, enteral (directly to the intestine) feedings, blood exchange transfusions and extracorporeal membrane oxygenation (ECMO).

DEHP (di-2-ethylhexyl phthalate) is part of a family of chemicals called phthalates (pronounced "THA' lates"). These chemicals are used to make polyvinyl chloride (PVC) plastic soft and flexible. Because it does not bind with the plastic, DEHP can leak out of the PVC product. The general population is being exposed to DEHP and other phthalates that act in a similar fashion through the skin and in air, water, and food as a result of phthalate leaching and off-gassing from a wide variety of common products and emissions from industrial facilities. Human exposure to DEHP and other phthalates begins while the child is still in the mother's womb as phthalates cross the placenta.

DEHP is also used in PVC medical products. As in other products, DEHP can leach out of flexible PVC medical devices into the solution or medication it contains and subsequently into the patient.

Animal studies have shown DEHP to be particularly harmful to the developing fetus. Adverse effects in the reproductive system include changes in the testes, reduced fertility, changes in sperm production in males and ovarian dysfunction and decreased hormone production in females. Respiratory distress and changes in kidney and liver function have also been linked to DEHP exposure. Although some of the effects occur only after relatively large exposures, the developing male reproductive system is particularly susceptible to low level exposures, similar to those that can occur during medical care with DEHP-containing equipment.

While no studies have looked directly at the effects of DEHP on the developing human reproductive system, animal studies that are relevant for predicting human risk suggest likely toxic effects in humans. Thus, it is of particular concern that human exposures are the highest for very small and underdeveloped babies when reproductive and other organs are developing.

A baby's contact with DEHP continues, though at a lower level, upon arrival at home. DEHP is found not only in indoor air but in baby formula, baby food, and in breast milk as well.

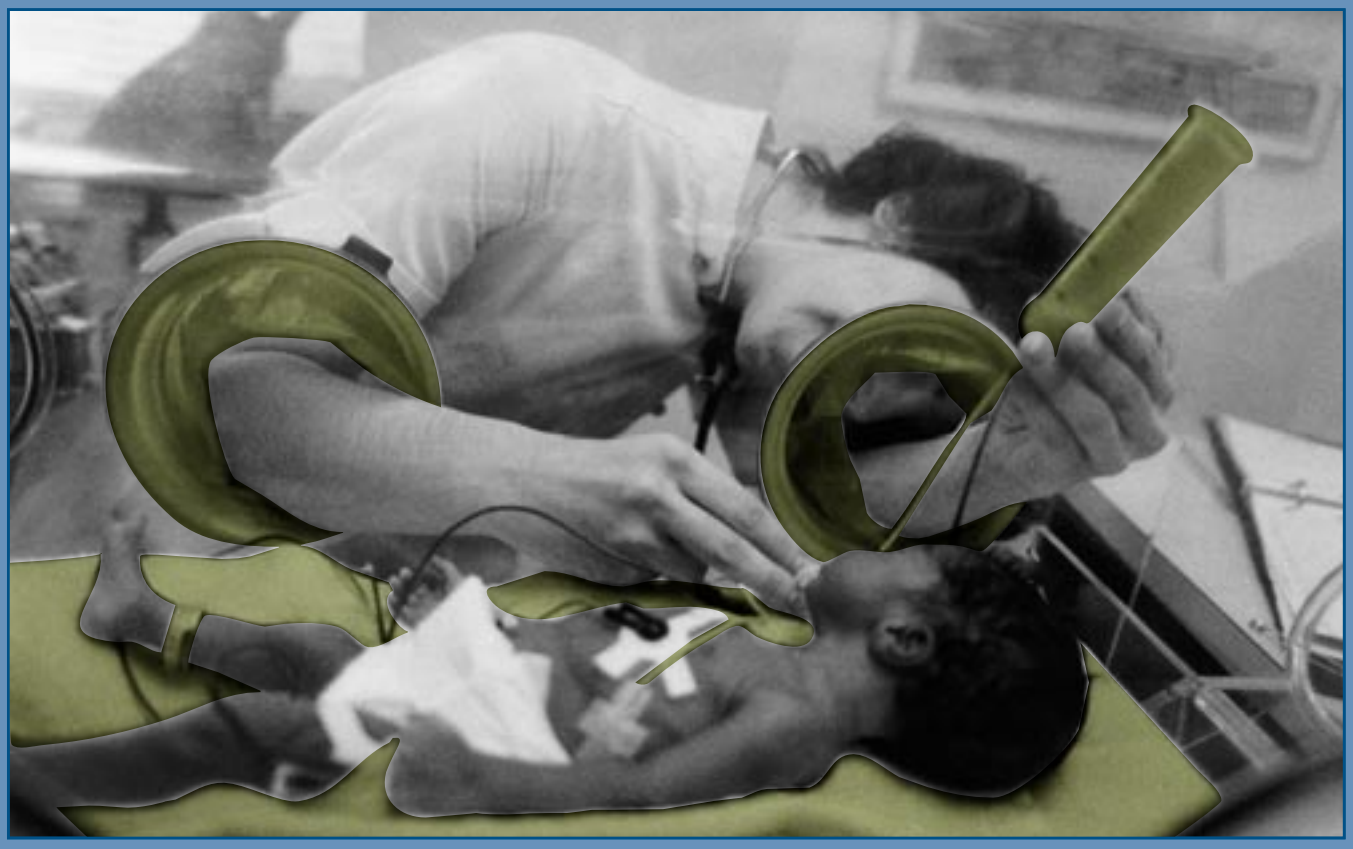
During critical stages of development, fetuses, preterm infants and other neonates are exposed to DEHP, a reproductive and development toxicant. Of particular concern are the multiple and relatively high exposures that can occur in Neonatal Intensive Care Units (NICUs). In the aggregate, these exposures are potentially at or in excess of levels known to cause adverse health effects in relevant animal studies.

Studies conducted for the governments of the United States, Canada, and the European Union have all concluded that exposures to DEHP are of concern to some patient populations and subsets of the general population. Especially vulnerable are healthy infants and toddlers, pregnant and lactating

women, and patients undergoing certain medical procedures. All of the government-led studies point to the need for action to reduce DEHP exposure in health care and other vulnerable populations. Most recently, the US Food and Drug Administration (FDA) recommended that health care providers consider using PVC-free materials or non-DEHP softened PVC for high risk procedures performed on male neonates, pregnant women who are carrying male fetuses, and peripubertal males.

Each of these government-led studies reached conclusions in sharp contrast to the study sponsored by the American Council on Science and Health (also referred to as the "Koop Study"), which found that "DEHP in medical devices is not harmful to even highly exposed people."

Fortunately, most of the exposures to DEHP in the NICU can be avoided by substituting already available PVC or DEHP-free alternative equipment. Since first publishing this report in 2000, the number of PVC and DEHP-free products on the market has expanded rapidly.



NEONATAL EXPOSURE TO DEHP AND OPPORTUNITIES FOR PREVENTION

Di-2-ethylhexyl phthalate (DEHP) is a reproductive and developmental toxicant, and the developing male reproductive tract is most sensitive to DEHP exposures. Because DEHP is used in many consumer products and is a ubiquitous environmental contaminant, humans are exposed to DEHP at some level on a daily basis throughout life, from conception to death. Exposure to DEHP from medical products adds substantially to that background level. Because of the sensitivity of the developing male reproductive tract, DEHP exposures in the fetus, infant, and prepubertal boy are of particular concern. The fetus and infant are also vulnerable because of immature metabolic detoxification pathways.

This report includes both a qualitative assessment of DEHP exposure to fetuses, newborns, and infants and a list of PVC and DEHP-free products available for preventing DEHP exposures in a NICU. The report begins with an introduction to the commerce of DEHP and its use in PVC (polyvinyl chloride) products. It then briefly reviews the toxicity of DEHP in different organ systems and identifies the potential sources of DEHP exposure for pregnant women, pre-term babies, neonates, and infants. Quantitative exposure data are included when available, although these data are quite limited. It also highlights the conclusions of government-initiated reviews of DEHP toxicity, all of which have concluded that, among other groups of patients, DEHP exposure is of concern to newborns. Finally, the report identifies PVC and DEHP-free medical products that NICUs can purchase to reduce DEHP exposures.

DEHP in Commerce

DEHP is one of a family of chemicals called phthalates. Manufacturers often use phthalates as softening agents (technically called "plasticizers") in the manufacture of PVC products. Plasticizers impart flexibility to inherently rigid plastics such as PVC. In 1998, US manufacturers consumed 255 million pounds of DEHP. Most DEHP, greater than 90%, is used as a plasticizer in the manufacture of PVC products including floorings, wall coverings, furniture, consumer goods such as luggage, and medical applications (Bizzari, et al., 2000). Manufacturers occasionally label PVC products, such as examination gloves, as "vinyl," short for polyvinyl chloride.

Medical device manufacturers use DEHP in flexible PVC products such as intravenous (IV) bags and tubing. It is "the preferred [phthalate] plasticizer in medical applications" because other phthalates have not been certified by the US Food and Drug Administration (FDA) for use in products such as intravenous (IV) bags (SRI, 1996). PVC is the most commonly used plastic in the manufacture of disposable medical products, accounting for 28% (or 200 million pounds) of all such products (Schlechter, 1996). Flexible PVC medical products, which typically contain 20-40% DEHP by weight (Rubin and Schiffer, 1976), can reach 80% by weight in applications where flexibility is critical, such as in tubing (DiGangi, 1999). Due to concerns with the toxicity of DEHP medical device manufacturers are increasingly turning to other plasticizers, including citrates, trimellitates, and adipates, to produce flexible PVC medical products.

The Toxicity of DEHP

DEHP causes abnormal sexual development in laboratory animals. In particular, the developing male reproductive tract is most sensitive to monoethylhexyl phthalate (MEHP), the toxic monoester metabolite of DEHP, and is far more sensitive than the reproductive tract of juvenile or adult male mammals (Moore, et al., 2001; Arcadi, et al., 1998;

Poon, et al., 1997; and Lamb et al., 1987). Within the developing male reproductive tract, the Sertoli cells are the most sensitive target tissue (NTP-CERHR, 2000; Li, 2000; and Poon, 1997), with other adverse effects including: undescended testes; abnormal sexual development; penile abnormalities; prostate agenesis; nipple retention; hypospadias; atrophy of the seminiferous tubes; changes in sperm production; and reductions in the weight of the testes, epididymis, prostate, seminal vesicle, and glans penis (Moore, et al., 2001; Gray, et al., 2000 and 1999; and Poon, et al., 1997). As Moore, et al. (2001), conclude, in utero and lactational "DEHP exposure can profoundly alter male reproductive system development (including sexual behavior) in rats."

Other reproductive and development effects in laboratory animals include: skeletal, cardiovascular, eye, and neural tube defects; intrauterine death and increased post-natal death; decreased intrauterine and postnatal growth; ovarian changes; and infertility in males and females (NTP-CERHR, 2000).

The lowest observed adverse effect level (LOAEL) from DEHP exposure varies across studies and depends upon the effects being observed. The lowest LOAEL reported was by Arcadi, et al. (1998), who observed testicular damage in the male offspring of female rats exposed to an estimated 3.0-3.5 milligrams per kilogram body weight per day (mg/kg bw/day) in drinking water. Testicular damage included the disorganization of the seminiferous tubule structure and the absence of spermatocytes. Poon, et al. (1997), reported testicular lesions and changes in liver enzymes at exposures of 38-42 mg DEHP/kg bw/day in young adult rats (4-6 weeks old at the start of the study). The expert panel of the National Toxicology Program, Center for the Evaluation of Risks to Human Reproduction (2000) concluded that the LOAEL is 38-144 mg/kg bw/day and the NOAEL (no observed adverse effect level) is approximately 3.7-14 mg/kg bw/day for reproductive effects in rodents by the oral route.

Other adverse effects of DEHP exposure in animal studies include suppressed or delayed ovulation, suppressed estradiol production, and polycystic ovaries (Davis, et al., 1994), reduced kidney function (Ward, et al., 1998), kidney atrophy (Crocker, et al., 1988), reduced liver function (Kevy and Jacobson, 1982), respiratory distress (Roth, et al., 1998), and decrease in heart rate and blood pressure (Rock, et al., 1987). For a summary of these studies see Table 1.

Species differences in toxicity and metabolism of DEHP have created considerable debate about the relevance of studies in rodents to human health. Research using genetically modified rodents has begun to answer some of the outstanding questions. For example, Peters, et al. (1997) found increased rates of fetal death and open neural tubes and reduced pup size in mice exposed to DEHP, despite their lack of the peroxisome proliferator activated receptor (PPAR)-alpha (which is thought to increase rodent susceptibility to cancer from DEHP exposure). Ward, et al., (1998) also found testicular and kidney damage in the same kind of genetically modified rodents. Human fetuses, pre-term babies, and other neonates may be more vulnerable to DEHP exposures because they lack mature metabolic (glucuronidation) pathways until three months of age, thereby prolonging their exposures when compared to adults (Kawade, et al., 1981; Hartley, et al., 1993; de Wildt, et al., 1999).

From Fetus to Toddler: Exposure to DEHP during a Critical Period of Development

Particularly troubling is the potential for exposing fetuses, premature infants (<35 weeks), and neonates to DEHP at critical points in their development. For pre-term babies requiring intensive care, the intensity of DEHP exposures differ markedly in comparison to the healthy full term newborn. Here we review the multiple sources of DEHP exposure from conception to an infant's first months at home.

Human exposure to DEHP begins at conception. Pregnant women, like the general population, are exposed to DEHP and similarly acting phthalates everyday. Flexible vinyl products made with DEHP are so pervasive that the plasticizer is a regular contaminant in food products, ambient air, and drinking water, which are all potential exposure sources for pregnant women (see Table 2). Overall, in the United States, the average adult exposure to DEHP from food, water, and outdoor air (excluding occupational and medical exposures, and off-gassing from building materials, such as vinyl flooring) is estimated at 0.0038-0.030 mg DEHP/kg bw/day, with the major source being food (Doull, et al., 1999). Fatty foods such as oils, milk, cheese, meat, and fish typically contain considerably higher DEHP residues than other foods (Doull, et al., 1999) because DEHP is lipophilic (it readily dissolves in fat). Pregnant women eat more fatty foods than other women according to the US Department of Agriculture's Continuing Survey of Food Intake by Individuals (1998).

Table 1. Toxicity of DEHP to Various Organ Systems

Organ	Effect	Species	Dose	Duration	Reference
Testes	Disorganization of seminiferous tubule structure in male offspring	Rat, n=36 dams, 7 offspring per dam	32-325 microl/l drinking water. LOAEL estimated at 3.0-3.5 mg/kg/day	Day 1 of gestation through postnatal day 21	Arcadi et al., 1998
	Sertoli cell vacuolation, atrophy of seminiferous tubules, loss of spermatogenesis	Rat, 10 per group, 8 groups, approx 4-6 wks old	0.4-375 mg/kg/day in diet, LOAEL 38 mg/kg	13 weeks	Poon et al., 1997
	Testicular and epididymal atrophy and testicular agenesis; hemorrhagic testes; hypospadias in male offspring	Rat, n=69	750 mg/kg/day in diet	Day 14 of gestation through postnatal day 3	Gray et al., 1999
Testicular cells in culture	Sertoli cell/gonocyte detachment	Rat (neonatal) in vitro	27 µg/l, concentration MEHP in culture medium	48 hours	Li et al., 1998
Ovaries	Suppressed or delayed ovulation, suppressed estradiol production, polycystic ovaries	Rat, n=6-9 per group, 8 groups	2 g/kg /day in food	3 to 12 days	Davis et al., 1994
Lungs	Respiratory distress, pathological changes resembling hyaline membrane disease	Human neonate, n=3	0.001-4.2 mg/hour through artificial ventilation	12 to 30 days	Roth et al., 1988
Heart	Decrease in heart rate and blood pressure	Rat, n=5	Threshold for effects: 20 mg MEHP (heart rate); 75 mg MEHP (blood pressure)	Short term - doses each minute	Rock et al., 1987
Kidneys	Reduction in creatinine clearance (measure of kidney function); cystic changes	Rat, n=65	2mg/kg, 3 times per week in diet	1 year	Crocker et al., 1988
	Focular tubual degeneration; atrophy; cystic renal tubules	Mouse, n=60 PPAR alpha +/-	12,000 ppm DEHP in food	4, 8, and 24 weeks	Ward et al., 1998
Fetus/Embryo	Fetal death, exencephaly, open neural tubes, reduced pup size	Mouse, n=89 litters examined PPAR alpha +/-	1000 mg/kg/day in diet on gestational days 8 and 9	2 days	Peters et al., 1997
Liver	Abnormalities in histology, reduction in liver function	Rhesus monkey (immature), n=12	Not directly measured - intravenous admin. of blood from PVC bags to mimic human exposure, estimated total dose 87.5-290.0mg	1 year	Kevy and Jacobson, 1982
	Hepatocellular adenoma	Rat, n=330	146.6 mg/kg/day in diet	104 weeks	Moore, 1996

N=total number of animals or individuals observed (controls and dosed), unless otherwise indicated; PPAR-alpha +/- indicates animals with and without the PPAR-alpha receptor were used and showed positive toxicity. Source: Tickner, et al., 1999.

Table 2. Potential Sources of DEHP Exposure During Pregnancy

Source	Daily Exposure per Body Weight(mg/kg/day)	Daily Exposure (mg/day)	Content	Source
Air, household dust	NR	NR	190-4,580 mg/kg of dust	Pfordt and Bruns-Weller, 1999
Air, in cars at 25°C	<0.001	<0.07	<10,000 ng/m^3	Huber, et al., 1996
Air, indoor room with PVC-flooring	0.014-0.086	1-6	50,000-300,000 ng/m^3	Huber, et al., 1996,
Air, outdoor urban	0.000006-0.000225	0.0005-0.016	22-790 ng/m^3	Huber, et al., 1996,
Drinking water	<0.001	<0.06	<30,000 ng/l	Huber, et al., 1996,
Food	0.0038-0.030	0.27 -2.0	NR	Doull, et al., 1999,
Special case: pregnant women on dialysis	0.01-7.2	0.004-3.1	NR	Huber, et al., 1996

NR = Not Reported

Excluded from estimates of average adult exposure, indoor vinyl products are a potentially large source of DEHP exposure. For example, the off-gassing of DEHP from vinyl flooring can result in respiratory exposures of 0.014-0.086 mg DEHP/kg bw/day (Huber, et al., 1996).[1] The highest exposure from vinyl flooring is almost three times greater than the highest estimate of total daily exposure (0.030 mg DEHP/kg bw/day). DEHP has also been found in household dust at 190-4580 mg/ kg dust (Pfordt and Bruns-Weller, 1999), reflecting the array of indoor products made with vinyl, including wall coverings, floorings, window shades, and furniture coverings.

Also excluded from estimates of average adult exposure is exposure to other phthalates with similar reproductive and developmental effects as DEHP: including di-(n-butyl) phthalate (DBP), butyl benzyl phthalate (BBP), and di-isononyl phthalate (DINP). When considered in the aggregate, the highest exposed women of reproductive age may be exposed to 0.13 mg of DEHP-equivalents/kg/day (DiGangi, et al., 2002).

Pregnant women undergoing medical treatment may be exposed to DEHP at substantially higher doses than the general population. In addition to episodic exposures that may occur during periods of acute illness, women on dialysis because of renal failure are exposed to 0.01-7.2 mg DEHP/kg bw per session (Huber, et al., 1996). According to one survey of 930 units, 2.4% of female hemodialysis patients of childbearing age became pregnant over a 4-year period (Okundaye, 1998).

DEHP can cross the placental barrier resulting in fetal exposures (Swedish National Chemicals Inspectorate, 2000; USCPSC, 1985). The National Toxicology Program-Center for the Evaluation of Risks to Human Reproduction expert panel report on DEHP estimated that in utero "exposures may be on the order of 3-30 μg/kg bw/day" (NTP-CERHR, 2000, p. 101). And, as noted above, fetal and newborn rodents were adversely effected by maternal DEHP exposures lower than those potentially received by women on hemodialysis.

For the 11% of all babies born premature in the US,[2] the chances of greater exposures to DEHP, relative to a healthy full term baby, rise dramatically. DEHP-plasticized PVC products are ubiquitous in neonatal intensive care units (NICUs). Blood bags, respiratory masks, oxygen tubing, intravenous (IV) bags and tubing, total parenteral nutrition tubing and bags, enteral feeding products, umbilical vessel catheters, mattress covers, examination gloves, patient identification bracelets, and floorings are among the many products that may be manufactured with DEHP-plasticized PVC in a NICU (see Table 3 for a complete list of products). The US FDA in its 2001 report on

Table 3. DEHP Plasticized Products in the NICU

Feeding-Related Products
Breast milk delivered by tube
Enteral feeding bags
Infant formula
Lipid extension tubes
Nasogastric tubes (short-term use: three days or less)
Tubing for breast pumps

Respiratory Therapy Products
Cannulas, nasal
Endotracheal and tracheostomy tubes
Humidifier, sterile water bag
Humidifier, tubing
Oxygen masks
Oxygen tubes
Resuscitators, oxygen reservoir bags
Suction tubing
Ventilator tubing

Extracorporeal Membrane Oxygenation (ECMO)
ECMO tubing

Intravenous (IV) Products
IV bags
IV tubing
Red blood cell bags
All other blood products, including platelets

Sources of Dermal Exposure
Examination gloves
Patient identification bracelets

Other Potential PVC Products
Drainage tubes and bags
Isolette porthole covers, flexible
Flooring
Mattress covers
Ostomy and neuro shunt bags
Plastic dividers for family privacy
Umbilical vessel catheters
Wall coverings

Sources: Sustainable Hospitals Project, 2000, "Alternative Products," see http://www.uml.edu/centers/LCSP/hospitals/ (Lowell: Sustainable Hospitals Project, UMass Lowell); and Tickner, et al., 1999, The Use of Di-2-Ethylhexyl Phthalate in PVC Medical Devices: Exposure, Toxicity, and Alternatives (Lowell: Lowell Center for Sustainable Production, UMass Lowell).

DEHP in medical devices concluded that these multiple DEHP exposures are of serious concern:

> "neonates in the NICU environment are exposed to DEHP from multiple devices. Based on the dose of DEHP received in such procedures as intravenous administration of sedatives, administration of TPN and replacement transfusion, all common procedures in the NICU, it is possible to estimate that a 4 kg infant could receive a DEHP dose on the order of 3 mg/kg/day for a period of weeks or months. … the dose of DEHP received by some infants from device-related sources [alone] could be 5-fold greater than the [FDA's] TI [tolerable intake level]" (p. 6).[3]

Not chemically bound to PVC, DEHP leaches or off-gasses from PVC products. The rate of DEHP leaching varies widely depending on a variety of factors, including storage and use temperatures, storage time, handling practices (whether agitated or not), contact with lipophilic solutions, and percent DEHP in a product. High lipid (fat) content products, such as blood, blood products, breast milk, and parenteral and enteral formulas, are of particular concern because DEHP is fat soluble. High lipid products more readily extract the plasticizer from vinyl bags and tubes (Pearson and Trissel, 1993).

Pre-term babies, especially low weight babies,[4] often require many medical treatments that use DEHP-plasticized PVC products. DEHP concentrations in blood and blood products are of particular concern for premature babies who receive regular blood transfusions. These children may receive one or more blood transfusions per week. The most commonly used blood products, packed red blood cells and fresh frozen plasma, are typically packaged in DEHP-plasticized bags and conveyed to the patient through DEHP-plasticized tubes. DEHP has been detected at levels as high as 174 mg per liter (mg/l) of packed red blood cells and 889 mg/l of plasma (see Table 4 for the range of DEHP concentrations in blood products).[5]

Total parenteral nutrition (TPN) and enteral nutrition are another set of potentially significant sources of DEHP exposure. Pre-term babies and infants that cannot breast or bottle-feed receive their nutrition either intravenously (TPN) or enterally (through tubes passed into the intestinal tract). Loff, et al. (2000) estimate that infants receiving TPN through DEHP-plasticized tubing can be exposed to 5 mg DEHP/kg/day.[6] This exposure includes DEHP contamination in the TPN formula itself: DEHP in lipid

Table 4. Accumulation of DEHP in Blood and Blood Products

Blood or Blood Product	Duration of Storage	Temperature(°C)	DEHP(mg/l)	MEHP(mg/l)
Whole blood	<3 weeks	NR	24-110	<5
Red cell concentrate	<3 weeks	NR	4-123	NR
Red cell concentrate	5 weeks	NR	174	6.3
Platelet concentrate	2-5 days	NR	180-650	<76
Plasma	1 week	4	<110	NR
Plasma	3 weeks	4	100-275	NR
Plasma	10 weeks	4	<890	NR
Platelet-rich plasma	3 days	22	181	31
Platelet-poor plasma	3 days	22	285	54
Platelet-poor plasma	1-2 weeks	20	<500	NR
Leukocyte-poor plasma	2 days	NR	25-32	NR

NR = Not Reported Source: Huber, et al., 1996.

emulsion 20% ranged from 0.75-4.05 μg/mL with a mean of 1.6 μg/mL. When combined with additional infusions of plasma stored in DEHP-plasticized PVC bags and medications the exposure doubles and reaches 10 mg DEHP/kg/day. This indicates how readily DEHP leaches from PVC into lipid solutions. The TPN is in contact with the tubing for only a short period, unlike red blood cells that can sit in DEHP-plasticized PVC bags for weeks.

While no studies have been published on DEHP exposure during enteral feeding, it is reasonable to expect similarly high exposure levels given the lipid content in enteral formula and the common use of DEHP-plasticized PVC tubing and bags. Enteral feeding for infants involves delivering formula or breast milk from a syringe, through an extension tube, to a nasogastric tube. The extension tubes may be, and the short-term (3 days or less) nasogastric tubes are, manufactured with DEHP-plasticized vinyl. Mothers may also express breast milk through DEHP-plasticized PVC tubes. An unpublished study of leaching from DEHP-plasticized nasogastric tubes at Stockholm University "showed that the section of the tube which had been inside the infant's stomach contained only half as much plasticiser as the rest of the tube" (which had 40% DEHP by weight to begin with) after only 24 hours of use (Landstingsförbundet, 2000, p. 4). The US FDA estimates neonate exposure at 0.14 mg/kg/day from enteral nutrition (US FDA, 2001, p. 11). The FDA concluded that: "Lipid in enteral nutrition solutions can leach out considerable doses of DEHP from PVC bags and tubing. As a result, these patients may be at increased risk of developing DEHP-mediated effects if PVC bags and tubing are used to deliver the enteral nutrition solutions" (US FDA, 2001, p. 6).

Less common treatments that involve potentially high DEHP exposures are blood exchange or replacement transfusions[7] and extracorporeal membrane oxygenation (ECMO).[8] The sources of DEHP exposure in blood exchange transfusions are the bags containing blood products and the tubes conveying the blood to the patient. Based on the volume of blood transfused and the mean concentration of DEHP in serum, researchers estimate that blood exchange transfusions result in DEHP exposures ranging from 0.5 to 22.6 mg DEHP/kg bw/treatment (Huber, et al., 1996; Plonait, et al., 1993; Sjöberg, et al., 1985a, 1985b; see Table 5).

In ECMO, the source of DEHP exposure is the tubing circuit. Schneider, et al. (1989), calculated that after 3 to 10 days of ECMO treatment an infant would be exposed to 42-140 mg DEHP/kg bw. Karle, et al. (1997), reported a lower level of exposure that ranged from non-detect to 34.9 mg DEHP/kg bw/treatment. The non-detect level resulted from the use of a DEHP-plasticized PVC circuit that was coated with heparin. In addition to the heparin coated tubing, Karle, et al., attributed the differences between their study and Schneider, et al., to the smaller surface area of the newer ECMO configurations and varying percentages of DEHP composition in each type of tubing.

The highest DEHP exposures from ECMO, TPN delivery, and blood exchange treatments resulted in exposures greater than the LOAEL observed by

Table 5. Potential Exposures to DEHP from Medical Procedures and Nutrition in a Neonatal Intensive Care Unit

Source of DEHP Exposure	Exposure (mg/kg body weight)	Unit	Total Exposure or Concentration in Product	Source
Artificial ventilation in preterm infants (PVC respiratory tubing; not polyethylene)	NR	hour (inhalation)	0.001-4.2 mg (estimated exposure)	Roth et al., 1988
Neonatal blood replacement transfusion; short-term, acute	0.3 (0.14-0.72)	treatment period	NR	Sjoberg, et al. 1985a
Neonatal blood replacement transfusion; double volume; short term, acute	1.8 (0.84-3.3)	treatment period	NR	Sjoberg, et al. 1985a
Platelet concentrates in newborns	1.9	treatment	NR	Huber et al., 1996
Enteral feeding	0.035	day	0.14 mg/kg(estimated exposure for 4 kg neonate)	US FDA, 2001
Extracorporeal membrane oxygenation (ECMO) in infants	42-140	treatment	NR	Schneider et al., 1989
ECMO in infants	4.7-34.9	treatment	NR	Karle et al, 1997
Congenital heart repair (neonates)		1-4 hours	0.3-4.7 µg/mL/hr(change in level in whole blood during procedure)	Barry et al., 1989
IV glucose solution	0.005 (maximum)	one liter of solution	NR	Roksvaag et al., 1990
Total parenteral nutritional formula (TPN)	NR	NR	3.1 µg/mL (concentration in TPN formula)	Mazur et al., 1989
TPN/IV Tubing	5	day	10 mg/2-kg baby/day	Loff et al., 2000
Multiple IV Sources: packed red blood cells, platelet rich plasma, fresh frozen plasma, and medications	5	day	10 mg/2-kg baby/day	Loff et al., 2000
Breast milk	0.0015-0.0165	day	0.01-0.11 mg/kg (concentration in breast milk)	Pfordt and Bruns-Weller, 1999
Infant formula	0.015	day	0.004-0.06 mg/kg wet weight	Petersen and Breindahl, 2000
Infant formula	0.0087-0.035	NR	0.33-0.98 mg/kg dry weight	MAFF, 1998

NR = Not Reported ND= Non-Detect

Arcadi, et al. (1998) and approach the low end of the LOAEL range (38-144 mg/kg bw/day) set by the NTP-CERHR Expert Panel (2000). The highest ECMO exposure (14 mg DEHP/kg bw/day), TPN exposure (10 mg DEHP/kg bw/day), and blood exchange transfusion exposure (22.6 mg DEHP/kg bw/treatment) are two to three orders of magnitude greater than average general population exposures (0.003 - 0.030 mg DEHP/kg bw/day), as is the highest.

In addition to blood infusions, NICU patients may receive medications, nourishment (such as total parenteral nutrition), and other fluids, such as dextrose or electrolyte solutions through infusion. An IV set-up includes a bag containing a solution and tubing that conveys the solution from the bag to the catheter inserted into the patient's vein. Approximately 80% of IV sets are manufactured with DEHP-plasticized PVC bags and tubes (Tickner, et al., 1999).

The leaching of DEHP into IV medications and products is well established. Trissel (1998), for example, has identified a range of drugs, including the cancer drug Taxol, that have been shown to increase DEHP leaching. DEHP leaching into standard IV products — such as glucose (sugar) solutions, or electrolyte (saline) solutions — is more likely when the bags have been agitated or warmed. DEHP concentrations have been found as high as 0.36 mg/l in glucose solutions and 0.16 mg/l in electrolyte solutions. An infusion of one liter of glucose solution could result in 0.005 mg DEHP/kg bw (Defoe, et al., 1990; Roksvaag, et al., 1990; Smistad, et al., 1989; Howard, et al., 1985).

Breast milk is another potential source of DEHP exposure for newborns. The Swedish National Chemicals Inspectorate (KemI) estimated the average daily intake of DEHP from nursing at 0.021 mg/kg/day for infants 0-3 months old and at 0.008 mg/kg/day for 3-12 month old children. This is from healthy mothers (KemI, 2000). For nursing mothers on hemodialysis, exposures to DEHP could be quite high. The US FDA (2001) estimated exposures "could be as much as 90 mg/kg/day" (p. 18).

DEHP has also been detected in infant formula (Loff et al., 2000; Petersen and Breindahl, 2000; MAFF, 1998; Sharman, et al., 1994). Studies from the United Kingdom estimated exposures to DEHP from infant formula (at birth) at 0.0087-0.035 mg DEHP/kg bw/day (MAFF, 1998).[9]

Respiratory therapy is quite common for pre-term babies because their lungs are frequently not fully developed. DEHP-plasticized PVC is commonly used in the following NICU respiratory products: respiratory masks, oxygen tubing, cannulas, suction catheters, endotracheal tubes, bags to contain sterile water for humidifiers, and humidifier tubing. It has also been used in ventilator tubing, although that is uncommon today. The US FDA (2001) estimates that "a patient undergoing respiratory therapy would receive a daily DEHP dose ranging from 28.4 to 94.6 µg, which is equivalent to a dose of 0.0004 to 0.001 mg/kg/day for a 70 kg adult" (p. 18).

Latini and Avery (1999) documented the leaching of DEHP from endotracheal tubes, finding a loss of 0.06-0.12 mg DEHP per mg of tube sample (6%-12%) after use.[10] They also noted that the material degraded, became less flexible, after a few hours of use. Other potential respiratory exposures to DEHP in the NICU include off-gassing from vinyl floorings, wallcoverings, mattress covers, drainage tubes and bags, and privacy dividers for mothers expressing breast milk.

No studies have measured 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. Individual studies of DEHP exposure from specific medical treatments, when viewed as a whole, reveal the potential for multiple exposures to DEHP through multiple pathways. The highest individual exposures — blood exchange and replacement transfusions, ECMO treatments, and TPN infusions — exceed the average daily adult exposure to DEHP by two to three orders of magnitude and approach the LOAEL for DEHP exposure in animal studies set by the expert panel of the National Toxicology Program, Center for the Evaluations of Risks to Human Reproduction (see Table 5). The FDA (2001) concluded that blood exchange transfusion, ECMO, and enteral nutrition pose the greatest threats to neonates because the individual procedure exposes the patient to DEHP levels greater than the FDA's estimated tolerable intake level.

A result of the use of flexible PVC products that contact human tissue, such as nasogastric tubes, endotracheal tubes, and umbilical vessel catheters is product degradation over time. They become brittle as the softening agent (DEHP or any other plasticizer) leaches out. Thus it should come as no surprise that staff at the Infant and Child Clinic at a Stockholm hospital "noticed that the discarded [nasogastric] tubes were brittle and hard, when removed after just 24 hours' use" (Landstingsförbundet, 2000, p. 4). Or that Latini and Avery (1999) "confirmed materials degradation in endotracheal tube after usage." Because flexible PVC products become brittle in the body and expose patients to DEHP (or any other plasticizer), medical device manufacturers do not market flexible PVC products for long-term use in the body (Brodhagen, 1991).

Exposure to DEHP continues when the neonate arrives at home. Many of the relevant exposures have been highlighted above, including DEHP exposure from breast milk and baby formula (see Table 5), as well as from house dust and off-gassing of indoor vinyl products (see Table 2).

House dust should be of special concern when babies begin to crawl. The natural inclination of babies to put hands and toys in their mouths, adds ingestion to inhalation as another exposure pathway to DEHP in the home. Baby food is another source of exposure,

with DEHP concentrations ranging from 0.01 to 0.63 mg DEHP/kg baby food (Petersen and Breindahl, 2000; Pfordt and Bruns-Weller, 1999).

Exposure Levels Are of Concern

In 1999 the American Council on Science and Health convened a panel of scientists to "evaluate the scientific evidence regarding potential health risks associated with DEHP."[11] The Panel came to the striking conclusion that "DEHP in medical devices is not harmful to even highly exposed people" (Koop and Juberg, 1999). The conclusion is striking for how dramatically it differs from the findings of government-initiated panels and bodies that examined the same evidence.

A year later, an expert panel of scientists appointed by the National Toxicology Program, Center for the Evaluation of Risks to Human Reproduction (NTP-CERHR, 2000),[12] concluded that three populations are at risk to DEHP exposure: critically ill infants, healthy infants and toddlers, and the offspring of pregnant or lactating women.

> **Critically ill infants:** "The available reproductive and developmental toxicity data and the limited but suggestive human exposure data indicate that exposures of intensively-treated infants/children can approach toxic doses in rodents, which causes the Panel serious concern that exposure may adversely affect male reproductive tract development" (p. 101).
>
> **Healthy infants and toddlers:** "If healthy human infant/toddler exposure is several-fold higher than adults, the Panel has concern that exposure may adversely affect male reproductive tract development" (p. 101).
>
> **Pregnancy and lactation:** "[T]he panel has concern that ambient oral DEHP exposures to pregnant or lactating women may adversely affect the development of their offspring" (p. 102).

Also in 2000, the Swedish National Chemicals Inspectorate in its final draft risk assessment on DEHP for the European Union concluded: "There is need for limiting the risks [of DEHP exposure] for human health" for all exposed populations, not just the especially vulnerable developing infants and toddlers. That includes workers, consumers (especially children and medical patients), and through ambient exposure, adults, children, babies, and infants.

Then in 2001 the US FDA concluded in its safety assessment of DEHP that exposures to patients during the following medical procedures may exceed the Agency's tolerable intake level for DEHP:

- all patients, including neonates, receiving enteral nutrition
- infants receiving total parenteral nutrition (TPN)
- infants undergoing exchange transfusions
- adults and infants undergoing extracorporeal membrane oxygenation (ECMO) therapy
- adults undergoing cardiopulmonary bypass
- nursing infants of mothers on hemodialysis

Based on its safety assessment of DEHP, the FDA issued a public health notification in 2002 that recommended:

> [For some medical procedures] PVC devices that do not contain DEHP be substituted or devices made of other materials (such as ethylene vinyl acetate (EVA), silicone, polyethylene, or polyurethane) can be used if available. … We [FDA] recommend considering such alternatives when these high risk procedures are to be performed on male neonates, pregnant women who are carrying male fetuses, and peripubertal males (US FDA, 2002).

Also in 2002, an Expert Advisory Panel appointed by Health Canada recommended a set of risk management options to reduce exposures to DEHP, including:

- labeling to indicate whether DEHP is present in medical products
- recommending that "total parenteral nutrition solutions be administered to newborns and infants only via products which do not contain DEHP."
- introducing as quickly as possible alternative measures "to protect those sub-populations at greatest risk, namely the fetus, newborns, infants and young children receiving transfusions, ECMO, cardio-pulmonary by-pass, exchange transfusion, hemodialysis, TPN and lipophilic drug formulations."

The conclusions of the US FDA, Health Canada Expert Panel, NTP-CERHR Expert Panel, and Swedish National Chemicals Inspectorate stand in contrast to the conclusion of the panel of the American Council on Science and Health that "DEHP in medical devices is not harmful to even highly exposed people".[13] In fact, the Health Canada expert panel explicitly disagreed with the ACSH panel: "Our conclusions therefore are contrary to the June 1999 review and consensus statement of the American Council on Science and Health, which states that 'DEHP, as used in medical devices, is not harmful to humans even under chronic or higher-than-average conditions of exposure.'"

Moreover in reaching their conclusions, the FDA, NTP and KEMI assumed that patients enter hospitals free of contamination with DEHP and other phthalates with similar toxicological effects. But we know that is not the case. Women of childbearing age, especially the most contaminated women, may carry the highest body burdens of phthalates that cause adverse reproductive and developmental effects in laboratory animals (Kohn, et al., 2000; DiGangi, et al., 2002).

The Transition to Safer Alternatives: DEHP-free Products

Most exposures to DEHP in the NICU can be avoided by replacing DEHP-plasticized PVC products with PVC and DEHP-free alternatives. Since the leaching and off-gassing of DEHP from PVC products are diffuse and uncontrollable sources of pollution, addressing the problem warrants a preventive approach — reducing pollution at the source (U.S. Congress, 1990). For DEHP in medical products, a preventive approach would eliminate the use of DEHP-containing products.

DEHP off-gassing and leaching can be prevented by replacing DEHP-plasticized PVC with PVC or DEHP-free products. Using a PVC-free product eliminates concerns over the potential for pharmacological doses of DEHP because the alternative polymers — ethylene vinyl acetate, polyethylene, polypropylene, polyurethane, and silicone — are inherently flexible and therefore, do not require a softening agent. For example, in a solvent extraction study of its medical grade polypropylene film, Basell Polyolefins identified <0.003% total phthalates (which are not DEHP)[14] by weight in its film (Phillips, 2001). This compares to the 20%-40% average DEHP content of medical film products.

Also, because the PVC-free polymers are inherently flexible, they pose less danger of becoming brittle when used in contact with human tissue. For example, because of the issues of material degradation and exposure to plasticizers, polyurethane and silicone are the polymers of choice for long-term nasogastric tubes.[15]

In addition, the non-chlorinated alternatives avoid the lifecycle hazards of PVC, including the use of the carcinogens ethylene dichloride and vinyl chloride monomer in manufacturing and the downstream formation of dioxin and hydrochloric acid during the burning of PVC in medical waste incinerators (Thornton, 2000; Wagner and Green, 1993; Wagner et al., 1992). In replacing PVC products with PVC-free products, the lifecycle hazards of alternatives must be considered to ensure environmental and safety concerns are minimized.

Using a DEHP-free PVC product prevents DEHP exposures, but still results in exposure to plasticizers and does not address the lifecycle hazards of PVC. The plasticizers available for use in medical products include citrates, trimellitates, and adipates. Another option for managing DEHP leaching is coating DEHP-containing products with a thin layer of another material to prevent or reduce leaching. While preferable to non-coated DEHP-plasticized vinyl, DEHP-coated products do not address off-gassing nor do they address the lifecycle hazards of vinyl.

Since first publishing this report in 2000, the number of PVC- and DEHP-free products on the market continues to grow. In 2000 Vital Signs, Inc. introduced a PVC-free oxygen mask. In 2002 Natvar introduced multi-layered flexible tubing manufactured from polyurethane. Bob Donohue, engineering manager for Natvar explained, "Many of our customers are looking to switch to non-PVC products to eliminate health and disposal concerns, but up to this point, there have been performance and processing issues associated with non-PVC alternatives. The goal in the industry has been to do away with PVC and plasticizers, but the right product just wasn't there." (Eastman Company, 2002)

And manufacturers of PVC-free medical grade plastics are experiencing increased demand. Chemical Week reported in April 2002 that Alloy Polymers recently expanded production of polypropylene because of "strong demand growth for compounding services in the personal care, food, and medical markets … The company particularly cites demand growth for medical devices" (Schmitt, 2002).

Table 6 lists PVC- or DEHP-free products that are on the market and available for use in NICUs today. For a given product line, if both PVC- and DEHP-free products are available, only the PVC-free product is listed because it eliminates the use of plasticizers that may leach. By purchasing PVC-free polymers or laminates (layers of plastics), NICUs will avoid the issue of which plasticizer is the safest to use. Inherently flexible, PVC-free medical grade plastics seldom use plasticizers.[16]

Table 6. DEHP-free Medical Products on the U.S. Market[1]

Product	Materials	Manufacturers
Bedding Products		
Disposable mattress/pillow covers	Polyethylene	Precision Dynamics Corp.
Catheters		
Catheters, central line and PICC lines	Polyurethane, silicone, or Teflon	Many
Epidural vessel catheters	Polyamide (nylon), polyethylene, or polyurethane	B. Braun, Vygon
Umbilical vessel catheters	Polyurethane or silicone	Many
Urinary catheters	Polyurethane or silicone	Many
Enteral Feeding Products		
Enteral feeding bags	3-layer laminate: nylon, ethylene vinyl acetate, and polyethylene	Corpak MedSystems
Nasogastric tubes	Polyurethane or silicone	Many
Gloves		
Examination gloves	Nitrile, polyurethane, or styrene butadiene	Many
Intravenous (IV) Products		
IV bags	3-layer laminate: polyolefin copolymer, polyester, and elastomer	B. Braun
IV tubing	Polyethylene, polyurethane, or silicone	Biometrix; Degania Silicone; Natvar; Tygon (Saint Gobain Plastics)
Total parenteral nutrition bags	Ethylene vinyl acetate or polyurethane	Baxter Healthcare; Biometrix; Vygon
Platelet and fresh frozen plasma bags	Polyolefins	Baxter Healthcare
Red blood cell and whole blood containers	DEHP-free PVC bag plasticized with citric acid ester (butryl-trihexyl citrate)	Baxter Healthcare
Patient ID Bracelets		
ID bracelets	Tyvek®	Precision Dynamics Corp. Wristband & Medical Special Products
Respiratory Therapy Products		
Anesthesia masks	Silicone	Laerdal
Endotracheal tubes	Polyurethane or rubber	Portex (Smiths Medical); Rusch, Inc.
Oxygen and aerosol masks	Polyester or silicone	DHD HealthcareVital Signs

1. The author does not endorse any of these products and has not tested them for safety or efficacy. Listing here is based solely on information provided by the manufacturer. Products that contain latex and chlorine are excluded from this table: latex products because of concerns over latex allergies and chlorine containing products because of concerns over lifecycle hazards. Exceptions are made for the few PVC products for which few or no PVC-free products are available. In those cases DEHP-free products are listed.

Sources: Sustainable Hospitals Project, 2001, "Alternative Products," see http://sustainablehospitals.org/ (Lowell: Sustainable Hospitals Project, UMass Lowell); Tickner, Joel, et al, 1999, The Use of Di-2-Ethylhexyl Phthalate in PVC Medical Devices: Exposure, Toxicity, and Alternatives (Lowell: Lowell Center for Sustainable Production, UMass Lowell); and interviews with company representatives.

For nearly every device manufactured with PVC, a PVC-free product is currently on the market. A notable exception is for packaging red blood cells. In the case of red blood cells, PVC offers a unique, although accidental, advantage: the slow but steady leaching of DEHP acts as an unintentional, unregulated preservative of red blood cells.[17] Baxter International, a leading producer of DEHP-softened PVC red blood cell bags, also markets a non-DEHP-softened red blood cell bag, which uses butyryl-trihexyl citrate as a plasticizer (Anonymous, 1992). Both bags preserve red blood cells for the same length of time.

The alternative plasticizers to DEHP in medical products — citrates, trimellitates, and adipates — may leach from PVC, although at different rates, depending on the product, the fluid or gas contained in or passed through it, and the conditions of use. Citrates are generally recognized as less hazardous than DEHP, as indicated by their use as a food additive. Much less is known about the safety/hazards of the trimellitates (Christensson et al., 1991; and Quinn et al., 1986).

Alternative polymers are typically more expensive, on a per pound basis, than PVC. However, in applications where downgauging (making a similar product with less material) is possible, such as IV and enteral feeding bags, manufacturers often produce direct substitutes that are cost-competitive (Leaversuch, 1999).

Certainly hospitals are, and will continue to be, cost-conscious in their purchasing decisions. However, the incremental, additional costs for safer alternatives may well be justified both because of the potential for adverse health effects and the extremely small fraction of total cost of care for a pre-term baby represented by PVC-free products.[18] While NICUs may shoulder an initial increase in product prices for some alternative products, these price increases are likely to be short-lived. First, for a number of product lines, especially solution-containing bags, cost-competitive bags are already on the market. Second, in a competitive market, suppliers are likely to reduce prices to retain or gain market share. Third, as the demand for alternative products increases, economies of scale will drive initial prices down (Wagner et al., 1992). For example, Kaiser Permanente, which purchases 43 million gloves per year, received a cost-competitive bid for its purchase of nitrile gloves.

Conclusion

During critical stages of development, fetuses, pre-term babies, neonates, infants, and toddlers are consistently exposed to the reproductive and developmental toxicant, DEHP. Of particular concern are the multiple and relatively high levels of DEHP exposure that can occur in NICUs. In the aggregate, these exposures are potentially at or in excess of levels known to cause adverse health effects in relevant animal studies. Virtually no data are available on developmental impacts of DEHP exposure in humans or other primates.

Since DEHP releases from PVC products are not easily controlled, prevention should be the primary management option: use PVC- and DEHP-free products. For nearly all of the medical applications of concern, PVC-free and DEHP-free products are on the market. For relatively minor, short-term cost increases, NICUs could replace nearly all DEHP-plasticized vinyl products with PVC-free or DEHP-free products. Market forces will likely drive the costs of alternative products down rather quickly. While precise cumulative DEHP exposure data in a NICU are not available, the US FDA concluded that even some single source exposures are sufficiently high enough to be of significant concern, particularly for delayed adverse impacts on reproductive tract development. Given the availability of safer alternatives, the prudent course of action is for NICUs to purchase PVC-free products.

ENDNOTES

1. Huber, et al., did not report on DEHP exposure from vinyl floorings in mg DEHP/kg bw/day (see Table 2).
2. In 1996, there were 3,891,494 births in the U.S.; 423,107 of which were pre-term (NCSH, 1998).
3. The TI level is the dose of DEHP that is not expected to result in adverse effects after exposure to DEHP.
4. A "low weight baby" is 2,500 grams or less at birth. Seven percent of all babies were low weight in 1996 (NCSH, 1998).
5. In some blood products, varying amounts of DEHP are converted to the metabolite, mono-ethylhexyl phthalate (MEHP), by enzymes present in the blood (Cole, 1981; Rock 1978). This metabolic transformation may be reduced when storage time and temperature are reduced.
6. The TPN bag was non-PVC, therefore it was a non-DEHP containing bag.
7. In a blood exchange transfusion all of the blood of a newborn is replaced with new blood.
8. During ECMO a patient's blood is circuited outside of the body through PVC tubing. ECMO has become standard treatment for severe neonatal respiratory failure. At the University of Michigan Medical Center, of the 6,000 newborn infants treated for severe respiratory failure in the neonatal intensive care units, eight percent (460 patients) were treated with ECMO (Shanley, et al., 1994).
9. Estimated exposures to DEHP from infant formula decline with age, with an exposure range of 0.0061-0.023 mg DEHP/kg bw/day at six months (MAFF, 1996).
10. An endotracheal tube delivers oxygen to the trachea: it is inserted through the nose or mouth, through the larynx, into the trachea.
11. And another phthalate not used in medical devices, DINP.
12. The National Toxicology Program is part of the U.S. Department of Health and Human Services.
13. For insights into how the American Council on Science and Health reached its conclusion, see Schettler, 2000.
14. The phthalates are used as processing aids in the manufacture of the film.
15. For example, see Landstingsförbundet (2000) and the University of Massachusetts Lowell, Sustainable Hospitals Project (www.sustainablehospitals.org).
16. It is true there are other contaminants that may leach out, but that is true of PVC as well.
17. The U.S. Food and Drug Administration does not regulate DEHP as an additive.
18. For example, the first eight weeks of care for a 25 week pre-term baby resulted in hospital bills exceeding $500,000 (Funderburg, 2000).

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