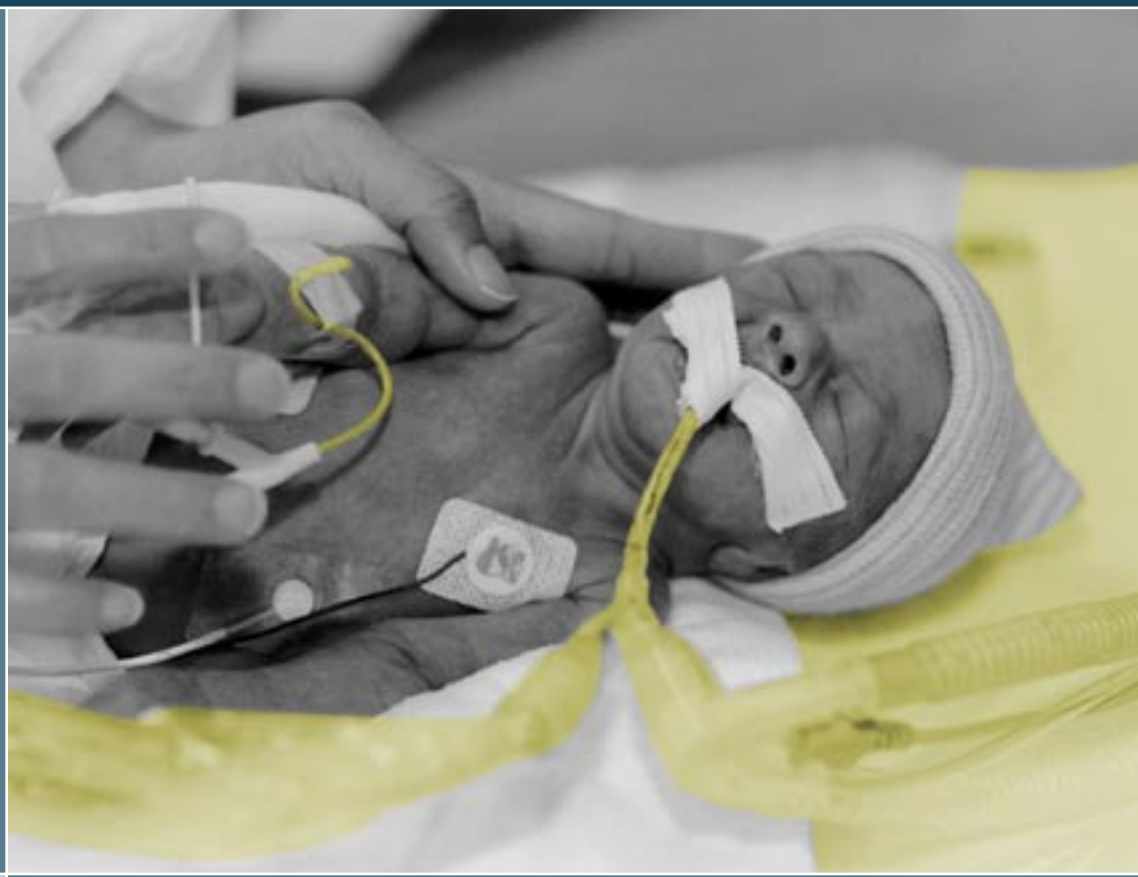
Neonatal Exposure to DEHP (di-2-ethylhexyl phthalate) and Opportunities for Prevention in Europe



Mark Rossi and Manfred Muehlberger

HEALTH CARE WITHOUT HARM

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PHOTOGRAPHS

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

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

AUTHORS:

Mark Rossi
and
Manfred Muehlberger

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HEALTH CARE WITHOUT HARM

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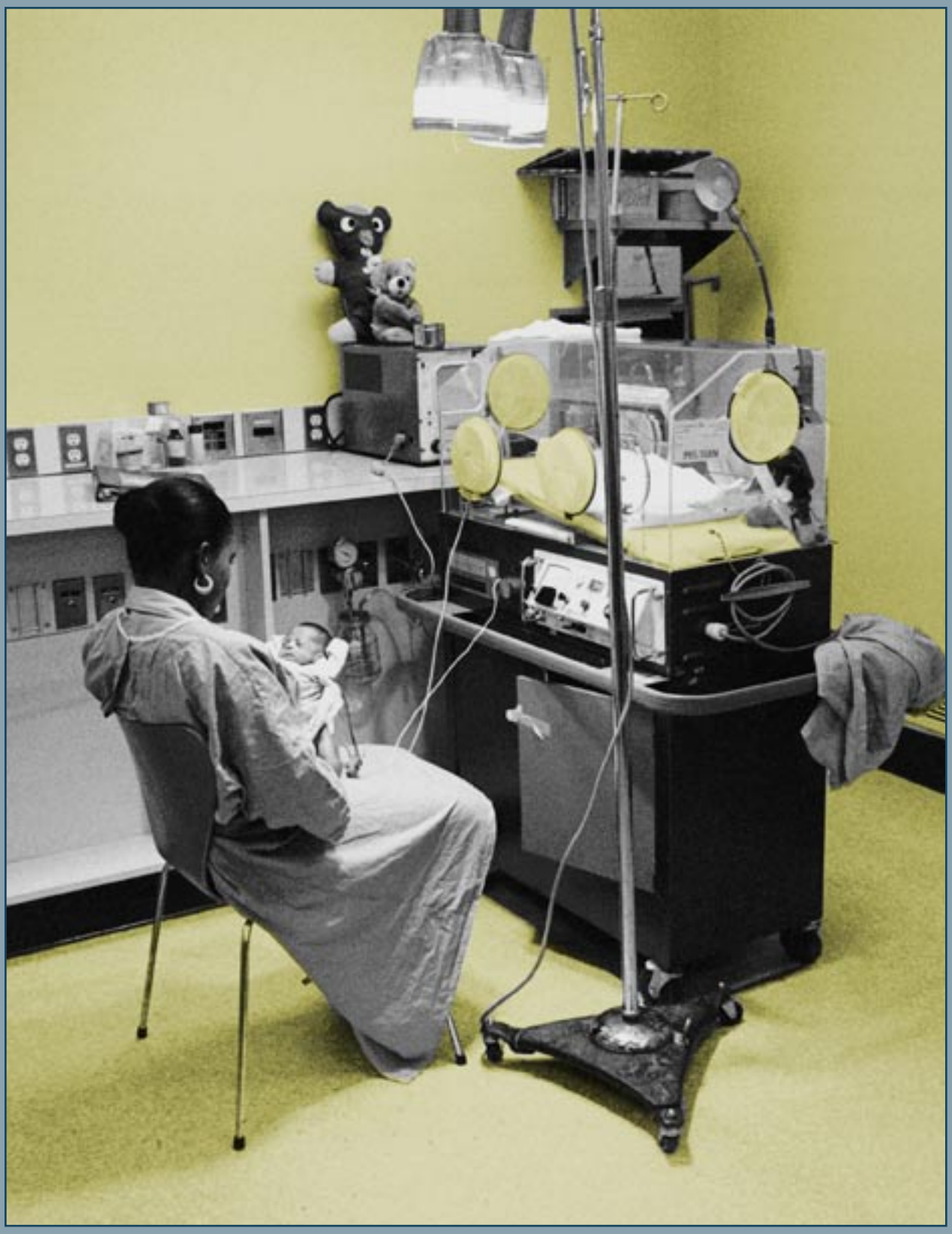
PREFACE

Last year Health Care Without Harm published an extensive review on the health risks and alternatives to di-2-ethylhexyl phthalate (DEHP) by the Lowell Center for Sustainable Production. In this new report, the focus is the hospital patient most vulnerable to the effects of DEHP - the infant born prematurely and receiving care in a neonatal intensive care unit (NICU). *Neonatal Exposure to DEHP and Opportunities for Prevention in Europe* succinctly compiles the multiple exposures preterm infants may receive in a NICU.

While peer reviewed studies have documented potentially high DEHP exposures from medical treatments involving polyvinyl chloride (PVC) plasticized with DEHP, none have measured the cumulative exposures a preterm infant receives in a NICU. This serious shortcoming in peer reviewed studies, however, should not be an excuse for inaction. Alternative products that do not leach DEHP are available on the market. Given the availability of alternatives, the evidence of harm and the examples of multiple exposures during a critical period in human development, health care professionals should act upon the credo, "First Do No Harm." Health care providers can protect neonates and other patients from exposure to DEHP by insisting on PVC-free products.

Charlotte Brody, RN
Health Care Without Harm



EXECUTIVE SUMMARY

Human exposure to DEHP (di-2-ethylhexyl phthalate) 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). The result, pre-term babies may receive multiple and relatively high exposures to DEHP.

DEHP is part of a family of chemicals called phthalates. 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 exposed to DEHP in air, water, and food as a result of DEHP leaching and off-gassing from products and emissions from industrial facilities. Human exposure to DEHP begins with the foetus in the mother's womb when DEHP crosses the placenta.

DEHP is 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.

The Health Risks of DEHP

DEHP is a reproductive and developmental toxicant. Animal studies have shown DEHP to be particularly harmful to the developing foetus. 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. Exposures in neonatal intensive care units (NICUs) are potentially at or in excess of levels known to cause adverse health effects in relevant animal studies.

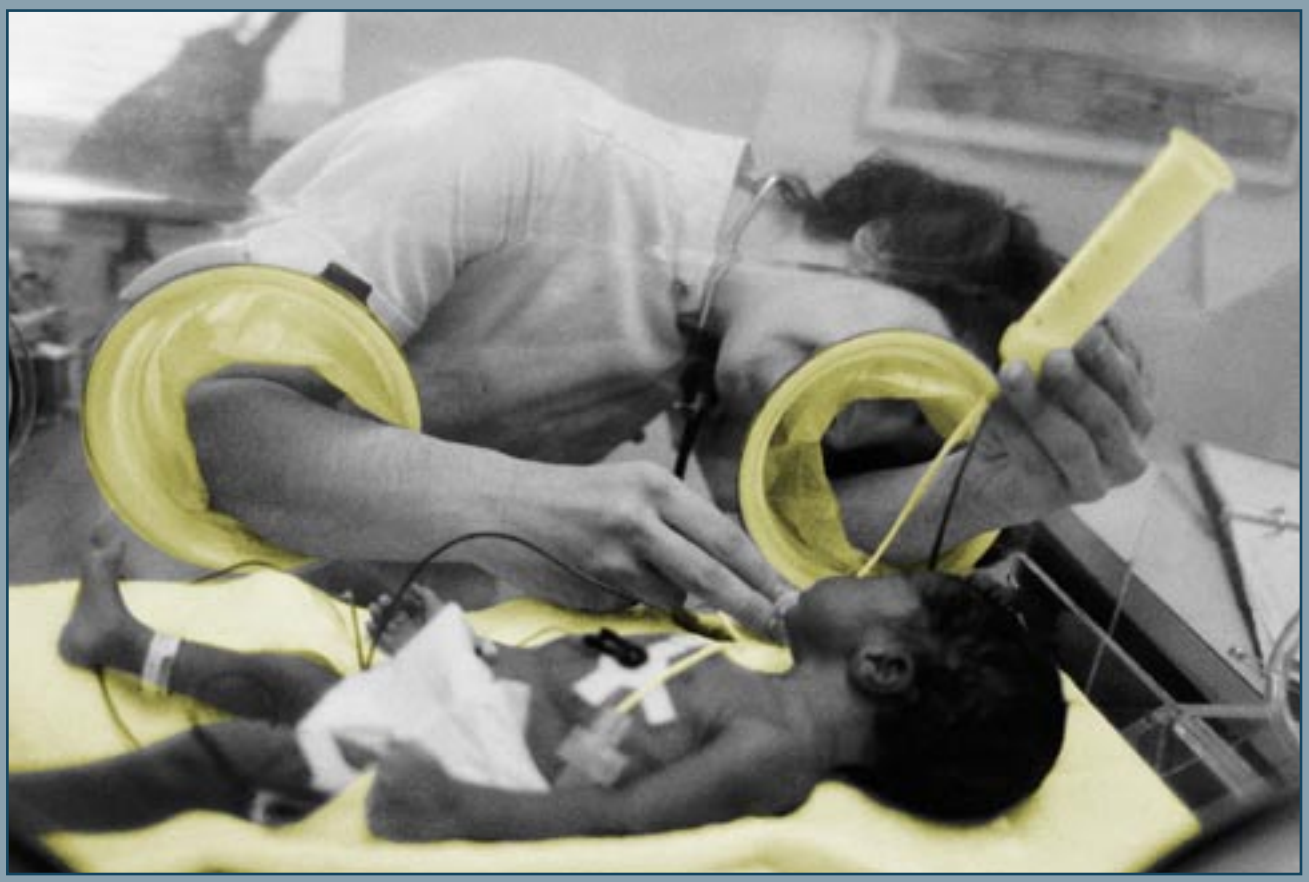
While no studies have looked directly at the effects of DEHP on the developing human reproductive system, animal studies that are relevant for predicting human risk suggest likely toxic effects in humans. Thus, it is of particular concern that human exposures are the highest for very small and underdeveloped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

In the United States, an Expert Panel on Phthalate Esters appointed by the National Toxicology Program's Center for the Evaluation of Risks to Human Reproduction recently concluded that DEHP exposures are of concern for pre-term babies, children, and pregnant women. In their summary statement, the expert panel expressed "serious concern" for the possibility of adverse effects on the developing reproductive tract of male infants exposed to high levels of DEHP from medical procedures such as those used in NICUs. The Panel also expressed "concern" that, if infants and toddlers are exposed to levels of DEHP substantially higher than adults, adverse effects might occur in the developing male reproductive tract. Finally, they expressed "concern" that the exposure of pregnant women to ambient levels of DEHP might adversely effect their offspring.

PVC-free Alternatives for the NICU

Fortunately, most exposures to DEHP in the NICU are unnecessary and preventable because PVC-free alternatives are on the market. For relatively minor, short-term cost increases, NICUs could replace nearly all DEHP plasticized PVC products with PVC-free or DEHP-free products. Given the availability of safer alternatives, the prudent course of action is for NICUs to purchase PVC-free products.



NEONATAL EXPOSURE TO DEHP AND OPPORTUNITIES FOR PREVENTION IN EUROPE

Human exposure to di-2-ethylhexyl phthalate (DEHP) occurs throughout life. Of particular concern are DEHP exposures to foetuses, pre-term babies, and infants because they occur when the human reproductive system is developing and metabolic pathways of detoxification are immature. A reproductive and developmental toxicant, DEHP has been shown to damage the male and female reproductive systems in newborn animals.

For infants requiring intensive care, DEHP exposures can occur at three orders of magnitude greater than average adult exposures and at or above levels causing reproductive effects in animals. Intensive care for infants can result in multiple exposures to DEHP through multiple pathways: intravenously, orally, and by inhalation. The cumulative exposures to DEHP for an infant receiving multiple medical treatments in a neonatal intensive care unit (NICU) have not been quantified. DEHP exposure from medical care products can be prevented by switching to commercially available products manufactured without DEHP or polyvinyl chloride (PVC).

This report includes both a qualitative assessment of DEHP exposure to foetuses, newborns, and infants and a list of PVC-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 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 exposure data are quite limited. Finally, the report identifies PVC-free medical products that NICUs can purchase to reduce DEHP exposures.

DEHP in Commerce

DEHP is one of a family of chemicals called phthalates. The primary use of phthalates is to serve as a plasticizer in the manufacture of PVC products. Plasticizers impart flexibility to rigid plastics such as PVC. In 1994, Western European manufacturers used 420 million kilograms of DEHP. Most DEHP, greater than 90% in 1994, is used in the manufacture of PVC products including floorings, wall coverings, furniture, consumer goods such as luggage, and medical applications (SRI, 1996).

DEHP is the only phthalate plasticizer the *European Pharmacopoeia* recognises for medical use in PVC (Lichtman, 2000). PVC is used widely in disposable medical products because it is cheap, flexible, and clear. A recent study by Frost & Sullivan estimates that PVC products accounted for 56% of all unit shipments of disposable medical products in Europe in 1998 (Lichtman, 2000). Flexible PVC medical products typically contain 30-40% DEHP by weight (Rubin and Schiffer, 1976). However, DEHP content by weight can reach 80% in applications where flexibility is critical, such as in tubing (DiGangi, 1999).

The Toxicity of DEHP

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 (mg/kg bw/day) daily in drinking water. Testicular damage included the disorganisation 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).

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 foetal 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 foetuses, 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 Foetus to Toddler: Human Exposure to DEHP during a Critical Period of Development

Particularly troubling is the potential for exposing foetuses, 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 everyday. Flexible PVC products made with DEHP are so pervasive 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 PVC flooring) is estimated at 0.0038-0.030 mg DEHP/kg bw/day, with the major source being food (Doull, et al., 1999). Because pregnant women usually eat more fatty foods than other women, their exposure to DEHP may be greater than the average adult.[1] 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).

Indoor PVC products are a potentially large source of DEHP exposure and have been excluded from estimates of average adult exposure. For example, the off-gassing of DEHP from PVC flooring can result in respiratory exposures of 0.014-0.086 mg DEHP/kg bw/day (Huber, et al., 1996).[2] The highest exposure from PVC 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 PVC,

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
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

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

including wall coverings, floorings, window shades, and furniture coverings.

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,[3] women on dialysis 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 foetal exposures (Swedish KemI, 1998; USCPSC, 1985). No studies were found on human foetus exposure levels. Yet, as noted above, foetal and newborn rodents were adversely effected by maternal DEHP exposures lower than those potentially received by women on hemodialysis.

For babies born premature, 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 bags, enteral feeding products, 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).

DEHP leaches or off-gasses from PVC products because it is not bound to PVC. 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 PVC bags and tubes (Pearson and Trissel, 1993).

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)
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
Platelet and fresh frozen plasma bags

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); 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); and Greenpeace, 1995.

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 (red cell concentrate) and 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 litre (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]

Less common treatments that involve potentially high DEHP exposures are blood exchange (or replacement) transfusions[6] and extracorporeal membrane oxygenation (ECMO).[7] 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. Shneider, 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 Shneider, et al., to the smaller surface area of the newer ECMO configurations and varying percentages of DEHP composition in each type of tubing.

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.

Table 5. Potential Exposures to DEHP in a NICU

Source of DEHP Exposure	Exposure (mg/kg body weight)	Unit	Total Exposure or Concentration in Product	Source
Artificial ventilation in preterm infants	NR	hour	0.001-4.2 mg (total exposure)	Huber, et al., 1996
Blood replacement transfusion in newborns	0.5-4.2	treatment-period	NR	Huber, et al., 1996
Blood replacement transfusion in newborns	1.2-22.6	treatment period	NR	Huber, et al., 1996
Blood replacement transfusion in newborns	0.8-3.3	treatment period	NR	Sjöberg, et al., 1985b
Platelet concentrates in newborns	1.9	treatment-period	NR	Huber, et al., 1996
Extracorporeal oxygenation in infants	42-140	treatment-period	NR	Huber, et al., 1996
Extracorporeal oxygenation in infants	ND-34.9	treatment period	NR	Karle, et al., 1997
Congenital heart repair (neonates)	NR	1-4 hours	0.3-4.7 mg/mL/hr (+change in blood)	Barry, et al., 1989
IV glucose solution	0.005 (maximum)	one liter of solution	NR	Roksvaag, et al., 1990
Total parenteral nutrition (TPN)	NR	NR	3.1 mg/mL (concentration in TPN)	Mazur, et al., 1989
Breast milk	0.002-0.02 (estimated by author)	NR	0.01-0.11 mg/kg (concentration in breast milk)	Pfordt and Bruns-Weller, 1999
Infant formula	NR	NR	0.004-0.06 mg/kg (concentration in formula)	Petersen and Breindahl, 2000
Infant formula	0.0087-0.035	NR	NR	MAFF, 1996
Infant formula powder	NR	NR	0.2-0.4 mg/kg (concentration in formula)	Sharman, et al., 1994

NR = Not Reported ND= Non-Detect

The highest DEHP exposures from ECMO and blood exchange treatments resulted in exposures greater than the LOAEL observed by Arcadi, et al. (1998) and near or above the LOAEL observed by Poon, et al. (1997). The highest ECMO exposure (140 mg DEHP/kg bw/treatment) is over three orders of magnitude greater than average general population exposures (0.003 - 0.03 mg DEHP/kg bw/day), as is the highest blood exchange transfusion exposure (22.6 mg DEHP/kg bw/treatment).[8]

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.

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. 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 litre 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).

Pre-term babies and infants that cannot breast or bottle feed receive their nutrition either intravenously (called total parenteral nutrition, TPN) or enterally (through tubes passed into the intestinal tract). Mazur, et al. (1989), found DEHP in TPN formulations containing lipids (but not in formulations without lipids).[9] The highest concentration Mazur, et al., detected was 3.1 micrograms DEHP/ml of TPN.

Enteral feeding for pre-term babies 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 nasogastric tubes are, manufactured with DEHP plasticized PVC. Mothers may also express breast milk through DEHP plasticized PVC tubes. No studies have been found on the leaching of DEHP into enteral formula from extension tubes, nasogastric tubes, or DEHP plasticized enteral feeding bags (which contain formula for delivery to children who are fed greater volumes of formula). Since enteral formulas contain lipids, leaching is likely.

Little is known about population-wide concentrations of DEHP in breast milk. In a study from Lower Saxony, Germany, a range of 0.01-0.11 mg DEHP/kg breast milk was reported in samples from five women (Pfordt and Bruns-Weller, 1999).[10] At these concentrations, an infant ingesting 150 ml of breast milk/kg bw/day would consume about 0.002-0.02 mg DEHP/kg bw/day.

DEHP has also been detected in infant formula (Petersen and Breindahl, 2000; MAFF, 1996; Sharman, et al., 1994). Studies from the United Kingdom have estimated exposures to DEHP from infant formula (at birth) at 0.0087-0.035 mg DEHP/kg bw/day (MAFF, 1996).[11]

Respiratory therapy is quite common for preterm 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 is also used, although less commonly, in ventilator tubing.

A study by Roth, et al. (1988; as quoted in Huber, et al., 1996), identified the potential for exposures of 0.001-4.2 mg DEHP/hour of treatment from artificial ventilation of preterm infants. Since most ventilator tubing is now manufactured from polyethylene, DEHP exposures from ventilators is probably much less today. DEHP exposures from ventilators

are likely to continue due to the use of DEHP plasticized PVC in the humidifier system.[12] Humidifiers draw sterile water from a DEHP plasticized bag, through a DEHP plasticized tube, and add it to ventilator oxygen.

Latini and Avery (1999) have documented the leaching of DEHP from endotracheal tubes.[13] They found a loss of 0.06-0.12 mg DEHP per mg of tube sample (6%-12%) after use. Other potential respiratory exposures to DEHP in the NICU include off-gassing from PVC floorings, wallcoverings, mattress covers, drainage tubes and bags, and privacy dividers for mothers expressing breast milk. As noted above, the off-gassing of DEHP can result in respiratory exposures as high as 0.86 mg DEHP/kg bw/day.

The cumulative DEHP exposures for a patient in a NICU have not been quantified. 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 exposures from blood replacement transfusions, ECMO treatments, and infant formula all exceed the average daily adult exposure to DEHP, and in some cases even exceed the LOAEL for DEHP exposure in animal studies (see Table 5).

DEHP exposures continue 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 PVC products (see Table 2).

House dust should be of especial 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).

In the United States, an Expert Panel on Phthalate Esters appointed by the National Toxicology Program's Center for the Evaluation of Risks to Human Reproduction recently concluded that DEHP exposures are of particular concern for pre-term babies, pregnant women and children.[14] In their summary statement, the expert panel expressed "serious concern" for the possibility of adverse effects on the developing reproductive tract of male infants exposed to high levels of DEHP from medical procedures such as those used in NICUs. They also expressed "concern" that the exposure of pregnant and lactating women to ambient levels of DEHP, largely from dietary sources, might adversely affect their offspring. When DEHP exposures from the use of PVC medical devices are added to general dietary exposures during pregnancy, the risk of adverse effects obviously increases. The Panel also expressed "concern" that, if infants and toddlers are exposed to levels of DEHP substantially higher than adults, adverse effects might occur in the developing male reproductive tract.

PVC-free Alternatives for the NICU

Most exposures to DEHP in the NICU are unnecessary and preventable because alternative products are widely available. Since DEHP off-gassing and leaching from PVC products are diffuse and uncontrollable sources of pollution, a preventive approach is warranted for addressing the problem of DEHP exposures. A preventive approach entails reducing pollution at the source. 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 PVC products with PVC-free products or replacing DEHP with an alternative plasticizer.

Using a PVC-free product practically ensures that it is DEHP-free because the alternative polymers — ethylene vinyl acetate, polyolefins (polyethylene and polypropylene), polyurethane, and silicone — rarely have added DEHP. In addition, substitute products avoid the lifecycle hazards of PVC, including the use of carcinogens to manufacture PVC

Table 6. PVC-free Medical Products on the Market in Europe

PRODUCT	PVC-FREE PRODUCTS
Body Fluids Collection	
Bladder Catheter	**Materials:** polyurethane or silicone **Manufacturers include:** Astra, B. Braun, Rüsch, Tyco
Collection Bags or Bottles	**Materials:** polypropylene bags or reusable polyolefin bottles **Manufacturers include:** B. Braun, Benesch, Dahlhausen, Odelga, Sterimed
Dialysis Products	
Peritoneal Dialysis Sets	**Materials:** polyolefins or silicone **Manufacturers include:** Fresenius, Gambro, Meise GmbH, Tyco Healthcare
Enteral Feeding Products	
Enteral Feeding Bags	**Material:** ethylene vinyl acetate **Manufacturer:** Nutricia Pfrimmer
Nasogastric Tubes (short-term use)	**Material:** polyurethane **Manufacturer:** Tyco Healthcare
Gloves	
Examination Gloves	**Materials:** polyethylene or polyethylene copolymer **Manufacturers include:** B. Braun, Odelga
Intravenous (IV) Products	
IV Bags	**Materials:** ethylene vinyl acetate, polyolefin laminates, or polypropylene/styrene ethylene butadiene styrene laminate **Manufacturers include:** Baxter, B Braun, Fresenius, Haemotronic S.p.A., Nutricia Pfrimmer, Pharmacia, Sengewald Verpackungen GmbH
IV Tubing	**Materials:** ethylene vinyl acetate, ethylene vinyl acetate copolymers, or polyolefins **Manufacturers include:** B. Braun, Clinico, Maersk Medical a/s, Nutricia Pfrimmer
Parenteral Nutrition Bags	**Materials:** polyolefin laminates **Manufacturers include:** B. Braun, Pharmacia
Platelet and Fresh Frozen Plasma Bags	**Materials:** polyolefins **Manufacturer:** Baxter **Comments:** on the market in the United States at similar cost
Red Blood Cell and Whole Blood Containers	**Material:** DEHP-free PVC bag plasticized with citrates **Manufacturer:** Baxter **Comments:** on the market in the United States, 5%-10% higher cost
Umbilical Vessel Catheters	**Material:** polyurethane **Manufacturers:** many
Respiratory Therapy Products	
Endotracheal Tubes	**Materials:** rubber or silicone **Manufacturers include:** Rüsch, SIMS
Humidifier, Sterile Water Bag	**Material:** polypropylene **Manufacturer:** Tyco Healthcare
Humidifier, Tubing	**Material:** silicone **Manufacturers include:** Dräger GesmbH, Tyco Healthcare
Oxygen masks	**Materials:** rubber or silicone **Manufacturers include:** Rüsch, SIMS

Disclaimer: The listing of products in this table does not constitute an endorsement of the products by the authors or Health Care Without Harm. Products should be tested and evaluated before purchasing to ensure they meet required performance specifications.

Sources: Lichtman, 2000; Tickner, et al., 1999; Greenpeace, 1995; and interviews with company representatives.

(ethylene dichloride and vinyl chloride monomer) and the downstream formation of hydrochloric acid and dioxin when PVC is burned in a medical waste incinerator (European Commission, 2000; Thornton, et al., 1996; Wagner and Green, 1993). In replacing PVC products with PVC-free products, the lifecycle hazards of alternatives must also be considered to ensure environmental and safety concerns are minimised.

Using a DEHP-free PVC product prevents DEHP exposures but does not address the lifecycle hazards of PVC. The primary alternative plasticizers for use in medical products are citrates and trimellitates. Other potential plasticizers include phosphates, benzoates, and aliphatic dibasic esters. There are also other phthalate plasticizers with different toxicological profiles than DEHP. However, given the recent adoption of a resolution by the European Parliament's Environment Committee to prohibit the use of all phthalates in toys, other phthalates seem to be a questionable alternative (European Parliament, 2000). As noted above, DEHP is the only phthalate plasticizer the *European Pharmacopoeia* recognises for medical use in PVC.

Table 6 identifies the many PVC-free medical products currently available on the market in Europe. While alternative polymers are typically more expensive than PVC on a per pound basis, their costs are declining, especially for the polyolefins. In applications where downgauging (making a similar product with less material) is possible, such as enteral feeding and IV bags, manufacturers often produce direct substitutes that are cost-competitive with PVC bags (Lichtman, 2000).

A significant development is the product and polymer innovation now occurring in the market as hospitals request PVC-free products. Examples abound. Maersk Medical a/s of Denmark has introduced PVC-free medical grade tubing manufactured from polyolefins. Sengewald Verpackungen GmbH & Co. of Germany won a WorldStar 99 packaging award from the World Packaging Organization for its PVC-free medical fluid bag manufactured from polypropylene. And two Italian firms, Haemotronic S.p.A. and S.I.F.R.A. EST S.p.A. are marketing PVC-free medical fluid bags from polyolefins (Lichtman, 2000).

As a result of the innovation and hospital demand, the market share for PVC medical products is declining. In 1995, PVC accounted for 58% of unit shipments of disposable medical products in Europe. By 1998, PVC's market share had declined to 56%, and is forecasted to decline further, to 48% by 2005 (Lichtman, 2000).

The one product area where no PVC-free plastic alternative is on the market, at least yet, is for red blood cell and whole blood bags. However, Baxter Healthcare sells a comparable DEHP-free red blood cell/whole blood bag in the United States. The DEHP-free red blood cell bag uses citrates rather than DEHP as the plasticizer. It costs 5-10% more than the DEHP-plasticized bag (Tickner, et al., 1999).

While hospitals must be cost-conscious, the incremental, additional costs for PVC-free products may well be justified by the potential for adverse health effects and the extremely small fraction of total costs these products represent for pre-term baby care.[15] NICUs may shoulder an initial increase in product prices for PVC-free products. However, these price increases are likely to be short-lived. First, for a number of product lines, especially solution-containing bags, prices of PVC-free bags are declining. Second, in a competitive market, suppliers are likely to reduce prices to retain market share. Third, as the demand for alternative products increases, economies of scale will drive initial prices down.

Conclusion

During critical stages of development, foetuses, pre-term babies, and neonates are consistently exposed to DEHP, a reproductive and developmental toxicant. 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-free products. For most medical applications of concern, PVC- or DEHP-free products are available on the market. For relatively minor, short-term cost increases, NICUs could replace nearly all DEHP plasticized PVC 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, 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. See the United States Department of Agriculture's Continuing Survey of Food Intake by Individuals, 1998.

2. Huber, et al., did not report on DEHP exposure from household dust in mg DEHP/kg bw/day (see Table 2).

3. For example, DEHP exposure from routine intravenous (IV) treatments (see below for more detail on DEHP exposure from IV treatment).

4. A "low weight baby" is 2,500 grams or less at birth (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. In a blood transfusion all of the blood of a newborn is replaced with new blood.

7. During ECMO a patient's blood is circuited outside of the body through PVC tubing. ECMO is used to treat severe neonatal respiratory failure.

8. However, the LOAEL's were observed after oral exposure to DEHP while the ECMO and exchange transfusion exposures were intravenous, not oral. Plasma concentrations of MEHP, the testicular toxicant, are expected to be higher after oral exposure to DEHP than after intravenous exposure because of more complete metabolic conversion in the intestine. Nevertheless, Sjöberg, et al. (1985a) measured MEHP levels in children after exchange transfusions and estimated exposures to MEHP at 0.2-0.7 mg/kg/transfusion.

9. No data were found on the frequency with which TPN formulations are packaged in DEHP plasticized bags.

10. How the women were selected is unknown.

11. 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).

12. Humidifiers add moisture to ventilator oxygen.

13. An endotracheal tube delivers oxygen to the trachea: it is inserted through the nose or mouth, through the larynx, into the trachea.

14. See the Center for the Evaluation of Risks to Human Reproduction webpage: http://cerhr.niehes.nih.gov/.

15. 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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CNIID
Centre national d'information
indépendante sur les déchets
51 rue du Fbg St-Antoine
75011 Paris, France

T: +31 1 55 78 28 64
F: +33 1 55 78 28 61

Email: pierre@cniid.org
or noharm@iatp.org

Webpage: www.noharm.org