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

Mark Rossi

HEALTH CARE WITHOUT HARM

# TABLE OF CONTENTS

# ACKNOWLEDGEMENTS

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

PHOTOGRAPHS

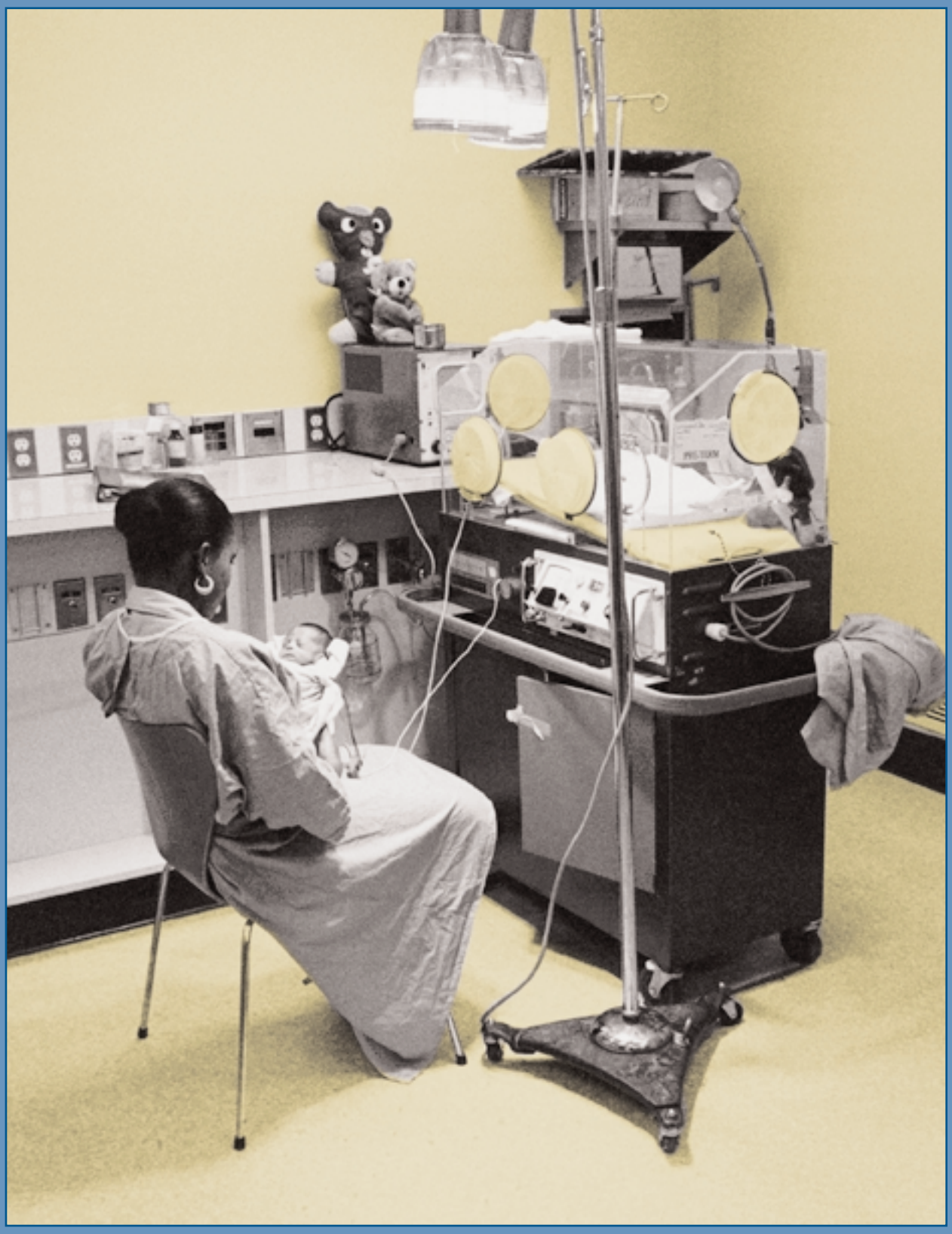
The yellow coloring in the photographs represents potential sources of DEHP plasticized PVC in a neonatal intensive care unit.

# 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* succinctly compiles the multiple exposures pre-term 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 pre-term 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 commercially or technically available. 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 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. Preterm babies, especially low-weight babies, may require many of the medical treatments that use DEHP-plasticized vinyl 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-ethylhexyl phthalate) is part of a family of chemicals called phthalates (pronounced "THA' lates"). These chemicals are used to make polyvinyl chloride (PVC or vinyl) 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 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 while the child is still in the mother's womb as DEHP crosses 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.

## The Health Risks of DEHP

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.

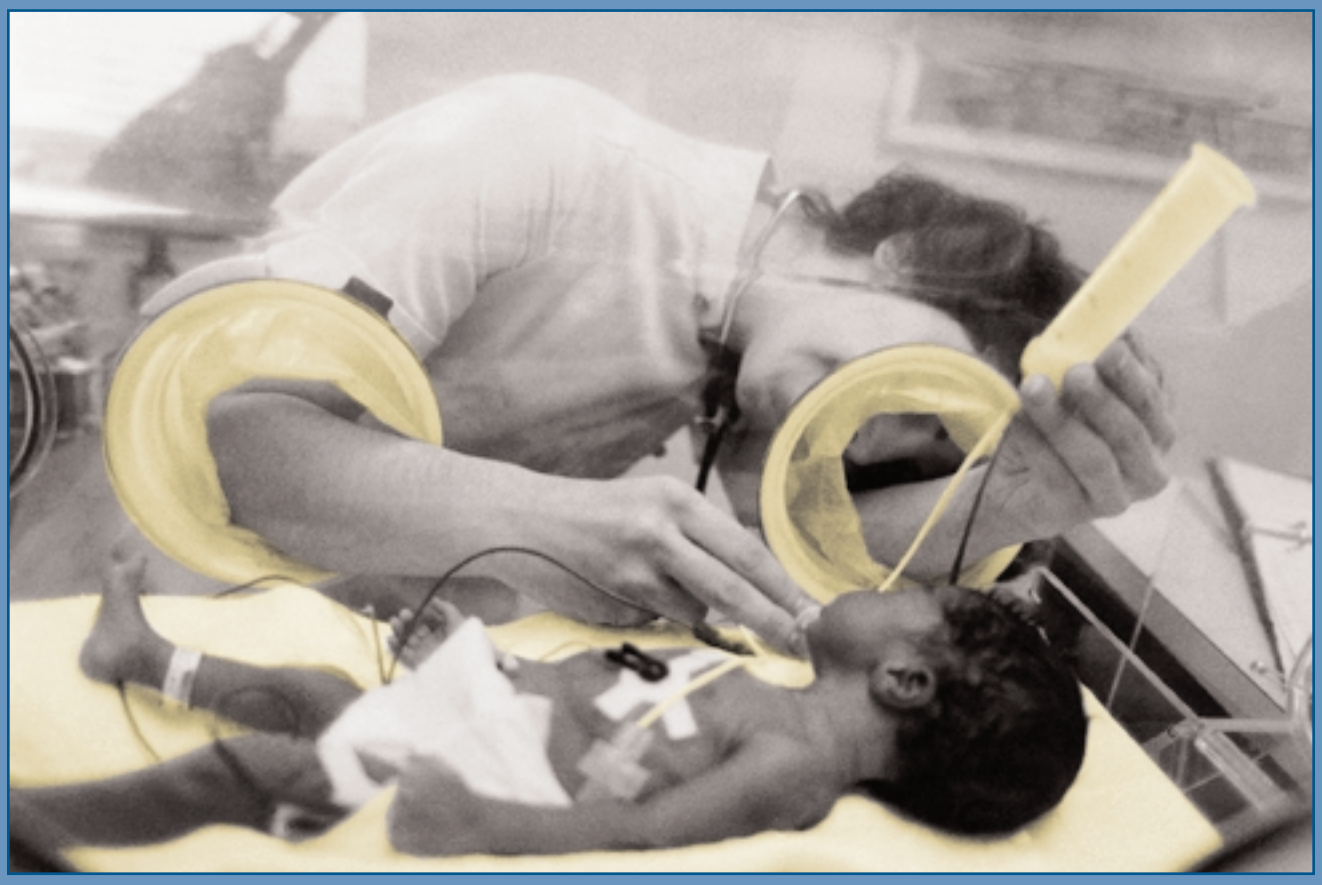
While no studies have looked directly at the effects of DEHP on the developing human reproductive system, animal studies that are relevant for predicting human risk suggest likely toxic effects in humans. Thus, it is of particular concern that human exposures are the highest for very small and underdeveloped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

## Exposures Continue at Home

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.

## A step toward reduction of exposure: DEHP- and PVC-free Neonatal Intensive Care Units

During critical stages of development, fetuses, pre-term 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. Fortunately, most of the exposures to DEHP in the NICU can be avoided by substituting already available PVC- or DEHP-free alternative equipment.



# NEONATAL EXPOSURE TO DEHP AND OPPORTUNITIES FOR PREVENTION

Human exposure to di-2-ethylhexyl phthalate (DEHP) occurs throughout life. Of particular concern are DEHP exposures to fetuses, 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 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 (also called vinyl) 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- 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. The primary use of phthalates is to serve as a plasticizer in the manufacture of vinyl products. Plasticizers impart flexibility to rigid plastics such as PVC. In 1994, U.S. manufacturers used 240 million pounds of DEHP. Most DEHP, greater than 90% in 1994, is used in the manufacture of vinyl products including floorings, wall coverings, furniture, consumer goods such as luggage, and medical applications (SRI, 1996).

DEHP is "the preferred [phthalate] plasticizer in medical applications" because other phthalates have not been certified by the U.S. Food and Drug Administration for use in products such as intravenous (IV) bags (SRI, 1996). Vinyl is the most commonly used plastic in the manufacture of disposable medical products. It accounted for 28% (or 200 million pounds) of all such products in 1996 (Schlechter, 1996). Flexible vinyl 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 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).

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 Conception through the Neonatal Period: Human Exposure to DEHP during a Critical Time 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 everyday. Flexible vinyl 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, page 8). 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 U.S. Department of Agriculture's Continuing Survey of Food Intake by Individuals, 1998.

Indoor vinyl 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 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

## 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 25oC | <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

(Pfordt and Bruns-Weller, 1999), reflecting the array of indoor products made with vinyl, 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[2], 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 KemI, 1998; USCPSC, 1985). No studies were found on human fetus exposure levels. Yet, 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 U.S.[3], the chances of greater exposures to DEHP, relative to a healthy full term baby, rise dramatically. DEHP plasticized vinyl 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 vinyl in a NICU (see Table 3 for a complete list of products).

DEHP leaches or off-gasses from vinyl 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 vinyl 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: 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).

Pre-term babies, especially low weight babies[4], often require many medical treatments that use DEHP plasticized vinyl 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 liter (mg/l) of packed red blood cells and 889 mg/l of plasma (see Table 4 on page 10 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 on page 10).

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

## 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) | | 1-4 hours | 0.3-4.7 ug/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 ug/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

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.

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/day) 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. 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. 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).

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 (3 days or less) nasogastric tubes are, manufactured with DEHP plasticized vinyl. 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) (Tickner, et al., 1999). 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 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 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 pre-term 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 after use. This translates into a 1.3 gram DEHP loss per use for a typical pediatric endotracheal tube.[14] 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. 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 vinyl 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).

## DEHP- and PVC-free Alternatives for the NICU

Most exposures to DEHP in the NICU can be avoided by replacing DEHP plasticized vinyl products with PVC- or DEHP-free alternatives. Since DEHP off-gassing and leaching from vinyl 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 (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 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, polyethylene, polypropylene, polyurethane, and silicone – rarely have added DEHP. In addition, PVC-free products avoid the lifecycle hazards of vinyl, including the use of a known carcinogen to manufacture vinyl (vinyl chloride monomer) and the downstream formation of dioxin when vinyl is burned in a medical waste incinerator (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 minimized.

## Table 6. Alternatives to DEHP Plasticized Medical Products

| Product | Availability of Alternatives: PVC-Free Products | Availability of Alternatives: DEHP-Free or Coated DEHP Products |
|---|---|---|
| *Extracorporeal Membrane Oxygenation (ECMO)* | | |
| ECMO tubing | Technically available. Similar product: -- venous and arterial cannulas for ECMO circuits made from PUR. | Commercially available heparin coated DEHP product. |
| *Feeding-Related Products* | | |
| Enteral feeding bags | Commercially available. Product: -- a nylon, EVA, PE laminate. | |
| Lipid extension tubes | Technically available. Similar products:-- gastrostomy feeding tubes made from PUR or silicone; and-- see "nasogastric tubes" below. | Commercially available DEHP-free product. |
| Nasogastric tubes (short-term use) | Technically available. Similar product: -- infant, indwell nasogastric feeding tubes made from PUR or silicone. | |
| Tubing for breast pumps | Technically available. Similar product: -- see "lipid extension tubes" above. | Commercially available DEHP-free product. |
| *Intravenous (IV) Products* | | |
| IV bags | Commercially available. Products: -- multilayer laminate bags made with PP/PE copolymer; polyester; and elastomer laminate; and -- TPN bags made from EVA. | |
| IV tubing | Technically available. Similar product:-- umbilical vessel catheters made from PUR. | Commercially available DEHP-free and polyethylene-coated DEHP products. |
| Red blood cell bags | None available. | Commercially available DEHP-free blood bag plasticized with citrates. |
| Platelet and plasma bags | Commercially available. Product: -- platelet and plasma bags made from polyolefins. | |
| *Respiratory Therapy Products* | | |
| Cannulas, nasal | Technically available. Similar product:- endotracheal tubes made from silicone. | |
| Endotracheal tubes | Commercially available. Products:-- disposable tubes made from silicone; and -- reusable tubes made from red rubber. | |
| Humidifier, sterile water bag | Commercially available. Products:-- see "IV bags" above. | |
| Humidifier, tubing | Technically available. Similar product:-- see "ventilator tubing" below. | |
| Oxygen masks | Technically available. Similar product:-- aerosol masks made from silicone for use in specialty medical treatments; and -- anesthesia masks made from PE. | |
| Oxygen tubes | Technically available. Similar products:-- see "ventilator tubing" below. | |
| Suction tubing | Technically available. Similar products:-- see "endotracheal tubes" above. | |
| Ventilator tubing | Commercially available. Products:-- disposable tubing made from PE or EVA; and -- reusable tubing made from black rubber or polyester elastomer. | |

"Commercially available:" direct substitute products are on the market."Technically available:" similar PVC-free products are on the market, but they are designed to meet more exacting product performance requirements.. Blank cell: no research done to identify alternative. Abbreviations: EVA = ethylene vinyl acetate; PE = polyethylene; PUR = polyurethane; and TPN = total parenteral nutrition.

Using a DEHP-free PVC product prevents DEHP exposures but does not address the lifecycle hazards of vinyl. 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 European Union's ban on the use of the phthalates in the manufacture of toy products for young children (Toloken, 2000) other phthalates seem to be a questionable alternative.

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.

Table 6 summarizes the PVC- and DEHP-free and coated DEHP alternatives for many of the vinyl products used in a NICU. Available products are divided into two categories: commercially available and technically available. "Commercially available" means a product is on the market and sold as a direct substitute for the uncoated, DEHP plasticized PVC product. For example, PVC-free IV bags are commercially available and economically competitive with the uncoated, DEHP plasticized PVC IV bags (Tickner, et al., 1999). "Technically available" means a similar PVC-free product is on the market, but it is designed to meet more exacting product performance requirements than the target PVC product; therefore it costs more than the target PVC product. For example, "indwell nasogastric tubes" made from polyurethane and silicone are currently used for enteral feeding when the tube will be in place for three days or more. However, the polyurethane and silicone indwell tubes are not price-competitive with the "short term nasogastric tubes" made from PVC (Tickner, et al., 1999).

For every PVC-product listed in Table 6, a commercially or technically PVC-free alternative is available, with the exception of blood bags. While technically available alternatives can compete with PVC on material performance, many are not economically competitive. Alternative polymers are typically more expensive, on a per pound basis, than PVC. In applications where downgauging (making a similar product with less material) is possible, such as IV bags, manufacturers often produce direct substitutes that are cost-competitive.

No PVC-free alternative has been developed for red blood cell bags. A comparable DEHP-free red blood cell bag that uses citrates rather than DEHP as the plasticizer is on the market, but it is more expensive than the DEHP plasticized red blood cell bag (Tickner, et al., 1999).

While hospitals must be cost-conscious, 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 costs of care for a pre-term baby represented by these alternative products.[15] 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 market share. Third, as the demand for alternative products increases, economies of scale will drive initial prices down.

## Conclusion

During critical stages of development, fetuses, 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 vinyl 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 commercially or technically available. 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, 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. For example, DEHP exposure from routine intravenous (IV) treatments (see below for more detail on DEHP exposure from IV treatment).

3. In 1996, there were 3,891,494 births in the U.S.; 423,107 of which were pre-term (NCSH, 1998).

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. 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 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).

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 testicualr 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. Source for the 1.3 gram DEHP loss estimate is Dr. Irwin Hinberg of Health Canada in a posting to the Phthalate Esters Discussion Group.

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).

# BIBLIOGRAPHY


Arcadi RA, Costa CE, Imperatore C, et al. 1998. Oral toxicity of DEHP during pregnancy and suckling in the Long-Evans rat. Food and Chemical Toxicology, 36: 963-970.

Barry YA, Labow RS, Keon, WJ, et al. 1989. Perioperative exposure to plasticizers in patients undergoing cardiopulmonary bypass. J Thorac Cardiovas Surg, 97: 900-905.

Cole RS, Tocchi M, Wye E, et al. 1981. Contamination of commercial blood products by di-2-ethylhexyl phthalate and mono-2-ethylhexyl phthalate. Vox Sang, 40:317-322(1981).

Crocker J, Safe S, and Acott P. 1988. Effects of chronic phthalate exposure on the kidney. Journal of Toxicology and Environmental Health, 23:433-444.

Davis BJ, et al. 1994. Di-(2-ethylhexyl) phthalate suppresses estradiol and ovulation in cycling rats. Toxicol Appl Pharmacol, 128: 216-223.

Defoe D, Holcombe G, Hammermeiser D, et al. 1990. Solubility and toxicity of eight phthalate esters to four aquatic organisms. Environ Toxicol Chem, 9: 623-636.

de Wildt SN, et al. 1999. Glucuronidation in humans: pharmacogenetic and developmental aspects. Clin Pharmacokinet, 36: 439-452.

DiGangi J. 1999. Phthalates in Vinyl Medical Products. Washington DC: Greenpeace USA.

Doull J, Cattley R, Elcombe C, et al. 1999. A cancer risk assessment of di(2-ethylhexyl)phthalate: application of the new U.S. EPA risk assessment guidelines. Regulatory Toxicology and Pharmacology, 29: 327-357.

Funderburg L. 2000. Saving Jason. Life, May: 48-62.

Gray E, et. al. 1999. Administration of potentially antiandrogenic pesticides (procymidone, linuron, iprodione, chlozolinate, p,p'-DDE, and ketoconazole) and toxic substances (dibutyl- and diethylhexyl phthalate, PCB 169, and ethane dimethane suphonate) during sexual differentiation produces diverse profiles of reproductive malformations in the rat. Toxicology and Industrial Health, 15: 94-118.

Hartley R, et. al. 1993. Morphine glucuronidation in premature neonates. Br J Clin Pharmacol, 35: 314-317.

Howard P, Banerjee S, and Robillard K. Measurements of water solubilities, octanol/water partition coefficients and vapor pressure of commercial phthalate esters. Environ Toxicol Chem, 1985; 4: 653-661.

Huber WW, Grasl-Kraupp B, and Schulte-Hermann R. 1996. Hepatocarcinogenic potential of DEHP in rodents and its implications on human risk. Critical Reviews in Toxicology, 26: 365-481.

Karle VA, Short BL, Martin GR et al. 1997. Extracorporeal membrane oxygenation exposes infants to the plasticizer, DEHP. Critical Care Medicine, 25: 696-703.

Kawade O. 1981. Prenatal and post-developmental UDP-glucuronyltransferases in the human liver. Biochem J, 196: 257-273.

Kevy S and Jacobson M. 1982. Hepatic effects of a phthalate ester plasticizer leached from poly(vinyl chloride) blood bags following transfusion. Environmental Health Perspectives, 45: 57-64.

Latini G and Avery G. 1999. Materials degradation in endotracheal tubes: a potential contributor to bronchopulmonary disease (letter). Acta Paeditr, 88: 1174-1175.

MAFF. 1996. Food surveillance information sheet - Phthalates in infant formulae. Joint Food Safety and Standards Group: MAFF - UK.

Mazur HI, Stennett DJ, and Egging PK. 1989. Extraction of diethylhexylphthalate from total nutrient solution-containing polyvinyl chloride bags. J Parenter Enter Nutr, 13: 59-62.

NCHS. National Center for Health Statistics. 1998. Health, United States, 1998. Hyattsville, MD: Public Health Service.

Oie L, Hersoug L, and Madsen J. 1997. Residential exposure to plasticizers and its possible role in the pathogenesis of asthma. Environmental Health Perspectives, 105: 964-971.

Okundaye I, Abrinko P, and Hou S. 1998. Registry of pregnancy in dialysis patients. American Journal of Kidney Disease, 31(5):766-773.

Pearson S and Trissel L. 1993. Leaching of diethylhexyl phthalate from polyvinyl chloride containers by selected drugs and formulation components. American Journal of Hosp Pharm, 50: 1405-1409.

Peters JM, Taubeneck MW, Keen CL, et al. 1997. DEHP induces a functional zinc deficiency during pregnancy and teratogenesis that is independent of peroxisome proliferator-activated receptor-alpha. Teratology, 56: 311-316.

Petersen J, and Breindahl T. 2000. Plasticizers in total diet samples, baby food, and infant formulae. Food Additives and Contaminants, 17(2): 133-141.

Pfordt J. and Bruns-Weller E. 1999. Die Phthalsäureester als eine Gruppe von Umwelt-chemikalien mit endokrinen Potential. Niedarsächsisches Ministerium fhr Ernährung, Landwirschaft und Forsten, Germany.

Plonait SL, et al. 1993. Exposure of newborn infants to di-(2-ethylhexyl) phthalate and 2-ethylhexanoic acid following exchange transfusion with polyvinylchloride catheters. Transfusion, 33: 598-605.

Poon R, Lecavaliert P, Mueller R, et al. 1997. Subchronic oral toxicity of di-n-ocytl phthalate and DEHP in the rat. Food Chemistry and Toxicology, 35: 225-239.

Rock G, et. al. 1987. Hypotension and cardiac arrest in rats after infusion of mono(2-ethylhexyl)phthalate (MEHP) a contaminant of stored blood. The New England Journal of Medicine, 316: 1218-1219.

Roksvaag PO, Smistad G, and Waaler T. 1990. The covariation of chemical contamination, particulate matter and turbidity in soft polyvinyl chloride infusion fluid bags. Acta Pharm Nord, 2: 327-332.

Roth B, Herkenrath P, Lehmann HJ, et al. 1988. DEHP as plasticizer in PVC respiratory tubing systems: indications of hazardous effects on pulmonary function in mechanically ventilated, preterm infants. European Journal of Pediatrics, 147: 41-46.

Rubin RJ and Schiffer CA. 1976. Fate in humans of the plasticizer, di-2-ethylhexyl phthalate, arising from transfusion of platelets stored in vinyl plastic bags. Transfusion, 16(4): 330-335.

Schlecter M. 1996. Plastics for Medical Devices: What's Ahead. Norwalk, CT: Business Communications Company, Inc.

Shanley C, Hirschl R, Schumacher R, et al. 1994. Extracorporeal Life Support for Neonatal Respiratory Failure. Annals of Surgery, 220(3): 269-280.

Sharman M, Read WA, Castle L, et al. 1994. Levels of di-(2-ethyhexyl) phthalate and total phthalate esters in milk, cream, butter, and cheese. Food Addit Contam, 11: 375-385..

Shneider B, et al. 1989. Exposure to di(2-ethylhexyl) phthalate in infants receiving extracorporeal membrane oxygenation. New England Journal of Medicine, 320(23): 1563 (letter).

Sjöberg P, et al. 1985a. Exposure of newborn infants to plasticizers: Plasma levels of di-(2-ethylhexyl) phthalate and mono-(2-ethylhexyl) phthalate during exchange transfusion. Transfusion, 25(5): 424-428.

Sjöberg P, et al.1985b. Dispositions of di- and mono- (2-ethylhexyl) phthalate in newborn infants subjected to exchange transfusions. European J Clin Investigation, 15: 430-436.

Smistad G, Waaler T, and Roksvaag PO. 1989. Migration of plastic additives from soft polyvinyl chloride bags into normal saline and glucose infusions. Acta Pharm Nord, 1: 287-290.

SRI. Stanford Research Associates International. 1996. Plasticizers. Chemical Economics Handbook.

Swedish KemI. National Chemicals Inspectorate. 1998. Risk Assessment for bis(2-ethylhexyl) phthalate, Preliminary Draft Document, September, EINECS-NO: 204-211-0.

Thornton J, McCally M, Orris P, et al. 1996. Hospitals and plastics. Public Health Reports, 11: 298-313.

Tickner J, Hunt P, Rossi M, et al. The use of di-2-ethylhexyl phthalate in PVC medical devices: exposure, toxicity, and alternatives. Lowell, MA: University of Massachusetts Lowell, Lowell Center for Sustainable Production.

Toloken S. 2000. European parliament expands phthalate ban. Plastic News, July 6.

Trissel L. 1998. Handbook on Injectable Drugs. American Society of Health Systems Pharmacists. 10th Edition.

USCPSC. US Consumer Product Safety Commission (CPSC). 1985. Chronic Hazard Advisory Panel on Di(2-ethylhexyl)Phthalate (DEHP). Report to the U.S. Consumer Product Safety Commission. Washington, DC.

U.S. Congress. 1990. Pollution Prevention Act of 1990.

United States Department of Agriculture, Food Surveys Research Group. 1998. 1994-96, 1998 Continuing Survey of Food Intakes by Individuals (CFSII) Data Release. NTIS Accession Number PB2000-500027.

Wagner J and Green A. 1993. Correlation of chlorinated organic compound emissions from incineration with chlorinated organic input. Chemosphere, 26: 2039-2054.

Ward JM, Peters JM, Perella CM, et al. 1998. Receptor and nonreceptor mediated organ-specific toxicity of DEHP in peroxisome proliferator-activated receptor alpha-null mice. Toxicology and Pathology, 26: 240-246.


P.O. Box 6806

Falls Church, VA 22040

T: 703.237.2249

F: 703.237.8389

Email: NOHARM@IATP.ORG

www.noharm.org