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Health Risks Posed by Use of Di-2-Ethylhexyl Phthalate (DEHP) in PVC Medical Devices: A Critical Review

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Background *Polyvinyl chloride plastics (PVC), made flexible through the addition of di-2-ethylhexyl phthalate (DEHP), are used in the production of a wide array of medical devices. From the late 1960s, leaching of DEHP from PVC medical devices and ultimate tissue deposition have been documented.*
Methods *A critical review of DEHP exposure, metabolism, and toxicity data from human and animals studies was undertaken. A brief analysis of alternatives to DEHP-plasticized PVC for use in medical device manufacture was completed.*
Results *DEHP leaches in varying concentrations into solutions stored in PVC medical devices. Certain populations, including dialysis patients and hemophiliacs may have long-term exposures to clinically important doses of DEHP, while others, such as neonates and the developing fetus, may have exposures at critical points in development. In vivo and in vitro research links DEHP or its metabolites to a range of adverse effects in the liver, reproductive tract, kidneys, lungs, and heart. Developing animals are particularly susceptible to effects on the reproductive system. Some adverse effects in animal studies occur at levels of exposure experienced by patients in certain clinical settings. DEHP appears to pose a relatively low risk of hepatic cancer in humans. However, given lingering uncertainties about the relevance of the mechanism of action of carcinogenic effects in rodents for humans and interindividual variability, the possibility of DEHP-related carcinogenic responses in humans cannot be ruled out.*
Conclusions *The observed toxicity of DEHP and availability of alternatives to many DEHP-containing PVC medical devices presents a compelling argument for moving assertively, but carefully, to the substitution of other materials for PVC in medical devices. The substitution of other materials for PVC would have an added worker and community health benefit of reducing population exposures to DEHP, reducing the creation of dioxin from PVC production and disposal, and reducing risks from vinyl chloride monomer exposure.* Am. J. Ind. Med. 39:100–111, 2001. *© 2001 Wiley-Liss, Inc.*

KEY WORDS: di-ethylhexyl phthalate; polyvinyl chloride; medical device; peroxisome proliferation

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INTRODUCTION

Polyvinyl chloride plastics, also known as PVC or vinyl, are used in the production of a wide array of medical devices. More than 25% of all plastics used in medical applications are PVC [Huber et al., 1996]. Major medical uses of PVC include intravenous fluid bags and tubing, blood and plasma bags, enteral feeding and dialysis equipment, catheters, and gloves. PVC has specific properties that make it attractive in the health care setting, including flexibility, strength, suitability for steam sterilization, resistance to kinking, optical clarity, weldability, surface finish, and cost.

PVC is a relatively rigid and brittle polymer. Plasticizers are added to the PVC to facilitate processing and increase flexibility and toughness in the final product by internal modification of the polymer molecule. Other polymers are made more or less flexible through the rearrangement of polymer chains or the addition of other polymers to the mixture. While there are numerous plasticizers on the market, the largest group, accounting for about 70% of U.S. consumption of millions of pounds per year, are the phthalate esters [SRI, 1996]. Of 25 different phthalate esters, di-ethylhexyl phthalate (DEHP) is the one most commonly used in the production of medical devices.

In the late 1960s, leaching of DEHP from PVC medical devices into medical solutions and ultimate tissue deposition were documented [Jaeger and Rubin, 1970, 1972; Autian, 1972; Hillman et al., 1975; Petersen et al., 1975]. Despite two decades of research into patient exposures and DEHP toxicity, the human health risks posed by medical devices containing DEHP are uncertain and disputed.

We present here the results of a review of DEHP exposure, metabolism, and toxicity. We also provide an overview of the current understanding of peroxisome proliferation and other mechanisms by which DEHP may cause toxic effects in animals and humans. Finally, we present a brief analysis of available alternatives to DEHP-plasticized PVC for use in medical device manufacture. A more detailed analysis of DEHP exposure, metabolism, toxicity, and alternatives is contained in Tickner et al. [1999].

We conclude that, in some instances, humans are exposed to clinically important levels of DEHP through PVC medical devices. Evidence from in vitro and in vivo studies relevant for determining human health risks suggests that DEHP exposures resulting from medical care may lead to adverse health effects in certain groups of patients. We recommend that a precautionary approach be applied to minimize the risk to humans from exposure to DEHP through medical devices. Where alternative materials exist that are safer and meet existing performance requirements at reasonable costs, these materials should be substituted for DEHP-containing PVC medical devices. Where such materials do not exist, research and development efforts should be undertaken to ensure their availability in the future.

METHODS

An analysis of English language scientific reports of in vitro and in vivo DEHP exposure, metabolism, and toxicity for the period 1945–1999 was conducted using Medline, Toxline, the Government Printing Office Database, the Hazardous Substances Database, and the Environmental Health Information Service. We also obtained copies of government agency reports analyzing DEHP risks from Sweden, the World Health Organization, Denmark, and the United States. In some cases, researchers who had conducted primary research on DEHP were contacted to provide additional references and a better understanding of the main uncertainties and opinions regarding exposure, toxicity, and the relevance of animal studies to humans.

The final bibliographic database analyzed consisted of approximately 120 studies, including primary research on DEHP toxicity, exposure, and metabolism as well as literature reviews. The main criteria for inclusion in our analysis were: whether or not the reference addressed an important aspect of toxicity, exposure, or metabolism of DEHP; species differences in metabolism and toxicity; age-related toxicity; toxicity in multiple organ systems; and examination of key uncertainties. The final bibliography, although not exhaustive, was chosen to address the full spectrum of human and animal data, in vitro observations, varying exposure pathways, and controversies and uncertainties about risk. It is important to note that disagreements about DEHP health risks to humans have centered primarily on the relative importance of species differences in absorption, metabolism, and mechanisms of toxicity.

We attempted to identify the weight of evidence necessary to better understand human health risks resulting from DEHP exposure in medical care. While we have focused primarily on studies that demonstrate positive biological effects, we describe studies with negative results when they provide important information for understanding the overall weight of scientific evidence pointing to human risks.

Alternatives to DEHP-containing PVC medical devices were analyzed through technical literature searches, World Wide Web searches for manufacturing companies and interviews with manufacturers and suppliers of both PVC medical devices and those free of DEHP and PVC.

RESULTS

Exposure to DEHP

Human exposure to DEHP can occur through environmental sources in the community (food, air, water) and in

the medical setting. The average total daily individual ambient exposure to DEHP in the US has been estimated at 0.27 mg per day, but this figure does not include workplace air exposures, nor indoor air exposures from offgassing of building materials, which may result in substantially higher exposures [ATSDR, 1993; Oie et al., 1997; Jaakkola et al., 1999]. Daily DEHP exposures in the medical setting may exceed general population exposures by up to three orders of magnitude.

Medical Exposures

PVC medical devices, such as bags for the intravenous administration of fluids and blood, typically contain 30–40% DEHP by weight. Medical tubing may contain as much as 80% DEHP [DiGangi, 1999]. DEHP is not chemically bound to the PVC polymer and may leach when a medical device is heated or when the PVC comes into contact with blood, drugs, or IV fluids. Extraction occurs either by leaching or after an extracting material (blood, IV fluids) diffuses into the PVC matrix and dissolves the plasticizer, which is relatively lipophilic. [Nass, 1977; Rock et al., 1986; Lundberg and Nilsson, 1994]. Temperature, mechanical agitation, storage time, chemical nature of the medical device contents, and DEHP concentration in the device influence the degree of leaching, which can vary from a fraction to 10–15% of the available DEHP [Nass, 1977; Kevy and Jacobson, 1982; Lundberg and Nilsson, 1994; Latini and Avery, 1999].

DEHP has been measured in blood products (whole blood, plasma, platelet, and packed red cells) at 4–650 mg/L [Jaeger and Rubin, 1970; Gibson et al., 1976; Schneider et al., 1989; Chawl and Hinberg, 1991; Huber et al., 1996] drug-containing solutions (3.1–237 mg/L); and in sterile water, electrolyte, and sugar-based solutions (5 mg/L) [Pearson and Trissel, 1993; Baxter Healthcare, 1995; Mazzo et al., 1997; Trissel, 1998].

Since 1970, a series of studies have identified and measured DEHP or its metabolites in human tissue and serum of patients receiving dialysis, blood transfusions, artificial ventilation, and exchange transfusions [Jaeger and Rubin 1970; Hillman et al., 1975; Lewis et al., 1978; Kevy and Jacobson, 1982; Ganning et al., 1984; Roth et al., 1988; Sjoberg et al., 1985a, 1985b].

Particular concern has been raised in the pediatric setting because of DEHP exposures in newborns who receive among the highest doses of DEHP in the human population from blood transfusions, extracorporeal membrane oxygenation (ECMO) and respiratory therapy [Sjoberg et al., 1985a, 1985b; Roth et al., 1988; Schneider et al., 1989; Plonait et al., 1993]. DEHP can also cross the placenta [Singh, 1975; USCPSC, 1985; Tomita et al., 1986; KemI, 1998], exposing the fetus secondary to maternal exposures.

The range of human exposures to DEHP from PVC medical devices is summarized in Table I [as adapted from Huber et al., 1996]. Total DEHP exposure measured or estimated in these studies varies significantly. Differences in study design, conditions of use, DEHP content, and storage time, among others, may play a role in this variability.

Disposition and Metabolism of DEHP

In the intestine, DEHP is rapidly absorbed, primarily in the form of its monoester, mono ethyl hexyl phthalate (MEHP), which results from hydrolysis of the parent compound by gut lipases [Sjoberg 1985a; Pollack et al., 1985b]. The initial metabolism of DEHP to MEHP is qualitatively similar among mammalian species [Lake et al., 1977; Rhodes et al., 1986] though hydrolysis is more effective in rodents than in higher mammals and humans [KemI, 1998]. MEHP is thought to be responsible for much of the compound's toxicity [Lake et al., 1977; Foster, 1997; Li et al., 1998].

Table I. Human Exposure to DEHP Following Treatment with PVC Medical Devices

Treatment	Total exposure (mg) per patient	Time period	Mg/kg body weight	References
Hemodialysis	0.5–360	Dialysis session	0.01–7.2	Gibson et al. [1976]; Lewis et al. [1978]; Pollack et al. [1985b]; Schneider et al. [1989]
Blood transfusion in adults	14–600	Treatment	0.2–8.0	Jacobson et al. [1977]; Kevy and Jacobson [1982]
Extracorporeal oxygenation in infants		Treatment period	42.0–140.0	Schneider et al. [1989]
Cardiopulmonary bypass	2.3–168	Treatment day	0.03–2.4	Jaeger and Rubin [1972]; Barry et al. [1989]
Artificial ventilation in preterm infants	0.001–4.2	Hour		Roth et al. [1988]
Exchange transfusions in infants		Treatment	0.8–4.2	Sjoberg et al. [1985a,1985b]; Plonait et al. [1993]

Intestinal absorption occurs more readily in rodents than in primates, presumably because of higher concentrations of lipases [Rhodes et al., 1986]. Young rodents absorb DEHP/MEHP to a greater degree than adults [Gray and Gangolli, 1986]. Once absorbed, DEHP is widely distributed throughout the body, with fat, the lungs, absorptive organs (gastrointestinal tract), and excretory organs (liver, kidneys) being the major initial repositories. DEHP is also distributed to the heart, spleen, reproductive tract, muscles, and brain [Jaeger and Rubin, 1972; Kluwe, 1982; KemI, 1998]. Distribution of DEHP and its metabolites appears to be qualitatively similar across species [KemI, 1998].

DEHP is highly lipophilic and may bioaccumulate in some organisms with limited ability to metabolize the substance [IPCS, 1992]. Studies in higher mammals and humans indicate that DEHP has a urinary elimination half-life of 6–12 h [Peck and Albro, 1982; KemI, 1998], though some evidence indicates that the half-life might be much longer [Dirven et al., 1993]. In an analysis of human tissues at the autopsy of patients who had received blood transfusions, Jaeger and Rubin [1972] found that DEHP does accumulate in certain tissues, even though it may not be detectable in blood. Other studies have found no appreciable tissue accumulation [KemI, 1998]. Although DEHP may be quickly metabolized and excreted, some chronically ill patients, such as dialysis patients, will receive continuous doses of the substance.

The liver, kidney, lungs, pancreas, and plasma also contain enzymes that convert DEHP to MEHP. However, this conversion occurs more readily in the intestinal tract so that exposures to DEHP by ingestion may be more hazardous than intravenous exposure [Pollack et al., 1985a]. Nonetheless, MEHP has been measured in stored adult human serum as well as in the blood of neonates undergoing exchange transfusions and adults undergoing hemodialysis [Vessman and Rietz, 1978; Peck and Albro, 1982; Pollack et al., 1985b; Sjoberg et al., 1985a, 1985b]. Pollack et al. [1985b] found that time-averaged circulating concentrations of MEHP during dialysis were similar to those of DEHP. Albro et al. [1982] found that MEHP comprised 18.3% of total metabolites excreted in urine from two leukemia patients receiving platelets from DEHP-containing PVC medical devices, and 6.9% of the administered DEHP was excreted as MEHP [Peck and Albro, 1982].

MEHP and another primary metabolite of DEHP, 2-ethanohexanol (2-EH), are further converted in the liver into numerous secondary metabolites via pathways that differ across species. Rodents primarily metabolize MEHP by oxidation pathways, while primates largely glucuronidate MEHP prior to excretion. Many of the known secondary metabolites, which number at least 10, have not been studied for their toxicity. Secondary metabolites, measured in urine and feces, are qualitatively similar across species, although they are excreted in different quantities [Rhodes et al., 1986; KemI, 1998]. The ability to metabolize DEHP is age-related and may also depend on the underlying health status in ways that are not well understood [Gollamudi et al., 1983; Roth et al., 1988; Mettang et al., 1999]. For example, glucuronidation pathways are immature in human infants at birth. [Kawade and Onishi, 1981; Hartley et al., 1993; de Wildt et al., 1999].

DEHP Toxicity

DEHP produces a spectrum of toxic effects in developing and adult animals and in multiple organ systems including the liver, reproductive tract (testes, ovaries, secondary sex organs), the kidneys, lungs, and heart. The developing organism is much more susceptible to testicular toxicity than the adult. Testicular toxicity in the developing animal appears to be the critical health effect (the adverse effect appearing at the lowest exposure levels), although a No Observable Adverse Effects Level (NOAEL) is not firmly established.

A summary of studies providing evidence of DEHP organ toxicity is provided in Table II.

Testicular toxicity

The testicular toxicity of DEHP has been acknowledged since the 1940s [Shaffer et al., 1945; Autian, 1972]. The Sertoli cells are the likely target for male reproductive toxicity of DEHP and MEHP [Agarwal, 1986; Douglas, 1986]. Early studies in adult animals found that high levels of DEHP exposure (0.9–20 g/kg body weight per day) resulted in dose-dependent atrophy of the seminiferous tubules and testes, resulting in loss of spermatogenesis [Shaffer et al., 1945 as cited in Autian, 1972; Syracuse Research, 1982; Agarwal et al., 1986].

Studies in developing animals indicate that younger animals exhibit adverse testicular effects at substantially lower doses, with earlier on-set, and less reversibility than in adults [Foster, 1997; Arcadi et al., 1998]. An oral dose of 750 mg DEHP/kg per day from Day 14 of gestation to Day 3 of nursing resulted in a range of adverse effects in the developing male reproductive tract including testicular atrophy, epididymal abnormalities, and hypospadias [Gray et al., 1999]. This was the only dose-tested. Arcadi et al. [1998] found that the male offspring of female rats exposed to approximately 3.0–3.5 and 30–35 mg DEHP/kg per day in drinking water from Day 1 of pregnancy to Day 21 after delivery showed dose-dependent disorganization of the seminiferous tubules at both dose levels. This study is limited by imprecise measurement of drinking water intake, requiring estimates of DEHP exposure levels. Poon et al. [1997] found Sertoli cell vacuolation in ''young'' rats (exact age not specified) fed DEHP at 37.6 mg/kg per day for 13 weeks.

Table II. Observed Toxicity of DEHP to Different Organ Systems

Organ	Effect	Species	Dose	Duration	References
Testis	Tubular atrophy and degeneration	Rat, n = not reported	0.9 and 1.9 g/kg/day in diet	90 days	Shaffer et al. [1945]
	Disorganization of seminiferous tubule structure in male offspring	Rat, n = 36 dams, 7 offspring per dam	Approximately 3.0–3.5 mg/kg/day in water	Day 1 of gestation to Day 21 after delivery	Arcadi et al. [1998]
	Testicular and epididymal atrophy and testicular agenesis; hemorrhagic testes; hypospadias	Rat, n = 69	750 mg/kg/day in diet	Day 14 of gestation and to Day 3 of nursing	Gray et al. [1999]
Testicular cells in culture	Sertoli cell/gonocyte detachment	Rat (neonatal)	27 ug/L, concentration MEHP in culture medium	48 h	Li 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	3–12 days	Davis et al. [1994]
Lungs	Respiratory distress, pathological changes resembling hyaline membrane disease	Human neonate, n = 3	0.001–4.2 mg/h through artificial ventilation	12–30 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]
	Focal tubular degeneration; atrophy; cystic renal tubules	Mouse, n = 60 PPAR $\alpha \pm$	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 $\alpha \pm$	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 87.5–290.0 mg	1 year	Kevy and Jacobson [1982]
	Hepatocellular adenoma	Rat, n = 330	146.6 mg/kg/day in diet	104 weeks	Moore [1996]

N = total number of animals or individuals observed (controls and dosed), unless otherwise indicated; PPAR-$\alpha \pm$ indicates animals with and without the PPAR-α receptor were used and demonstrated positive toxicity.

A study in juvenile marmosets (12–15 weeks old at the beginning of exposure), exposed orally to DEHP (100–2500 mg/kg/day for 13 weeks) reported no change in testis/body weight ratio or blood levels of testosterone [Kurata et al., 1998]. The value of this study for estimating human health risks is limited by small numbers of animals in each dose group and the use of animals already in puberty at the beginning of the exposure period.

In an in vitro Sertoli cell/gonocyte co-culture system, Li et al. [1998] found that, unlike controls, MEHP concentrations as low as 0.1 μM (0.028 μg/ml) caused detachment of Sertoli cells from gonocytes. Moreover, this effect was noted at levels of MEHP exposure that caused no obvious cytotoxicity in Sertoli cells. Sertoli cell proliferation was also impaired in 0.1 μM MEHP. Others have shown that germ cell detachment from Sertoli cells is significantly greater in cultures from younger animals than in those from older animals when incubated with equal amounts of MEHP [Gray and Beamand, 1984] Since the Sertoli cell/gonocyte interaction is essential for normal spermatogenesis, these

observations raise important questions about identifying the critical endpoint that should serve as the earliest evidence of testicular toxicity.

The developing testis may be more susceptible to damage from DEHP exposure for several reasons. First, intestinal absorption of DEHP is greater in the immature animal than in the adult. Second, in species that rely on glucuronidation to clear MEHP, metabolism is likely to be delayed in young animals with immature conjugation pathways. Finally, in vitro studies of cultured Sertoli cells and germ cells suggest that younger cells may be inherently more sensitive to MEHP toxicity than older cells [Gray and Beamand, 1984]. In humans, Sertoli cells proliferate in early infancy and again in early puberty, when differentiation ultimately occurs [Cortes et al., 1987]. To the extent that immature, dividing Sertoli cells are more susceptible to MEHP exposure than fully differentiated cells, a period of enhanced human vulnerability may extend through early puberty.

Ovarian toxicity

Exposure of adult, regularly cycling female rats to 2 g/kg DEHP by gavage for 1–12 consecutive days resulted in prolonged estrous cycles, suppressed or delayed ovulation, and suppressed estradiol production [Davis et al., 1994]. Female mice fed 0.3% DEHP in diet experienced significant decreases in reproductive organ weights (though histological lesions were not observed) and infertility when mated with unexposed males [Lamb et al., 1987].

Developmental toxicity (teratogenesis)

A large number of animal studies, primarily in rodents, have examined the developmental toxicity of DEHP through dietary or gavage exposures. Most studies have examined DEHP fetotoxicity at single or multiple high doses (0.3–4 g/kg body weight per day), although lower doses (2.5 mg DEHP per day during days 7–13 of gestation, 50 mg/kg MEHP in a single dose) have resulted in effects in offspring [Syracuse Research, 1982; Tomita, et al., 1982, 1986; Ritter et al., 1987; Tyl et al., 1988; Peters et al., 1997]. At lower doses, increased fetal mortality and resorptions, malformed limbs, and somatic mutations in coat hair were observed. At higher doses fetotoxic and teratogenic effects included: a decrease in kidney and testes weights in offspring; spontaneous abortions; decreased implantation; heart malformations; eye defects; hydronephrosis; misplaced digits; malformed limbs, open neural tubes; exencephaly; and fetal death.

Tomita et al. [1982] found that single oral doses ranging from 1 to 5 ml/kg MEHP administered to pregnant mice resulted in dose- and time-dependent adverse outcomes in the fetus, including a marked decrease in litter size (number of live births) and malformations in live fetuses (gross and skeletal abnormalities including exencephaly, club foot and no tail). The authors estimated a non-fetolethal maximum dose of DEHP by single oral administration to be 64 mg/kg. Tomita et al. [1986] found that oral administration of 1 ml/kg MEHP to mice on Day 8 of gestation resulted in less than 32% live fetuses, all of which were deformed. Peters et al. [1997] found that pregnant mice fed 1,000 mg/kg DEHP on gestational (GD) days 8 and 9 had a significantly lower number of live pups on GD 18 compared to controls, with more than 40% of fetuses of treated animals exhibiting external abnormalities.

Nephrotoxicity

Mice fed high doses of DEHP (12,000 ppm dry weight in food) show renal toxicity after 4–8 weeks of feeding and moderate lesions after 24 weeks (including focal tubular degeneration and atrophy) [Ward et al., 1998]. Oral dosing of rats at approximately 2.15 mg DEHP/kg body weight/day three times per week over 1 year—designed to mirror chronic DEHP exposures from hemodialysis—resulted in significantly reduced kidney function and increased numbers of focal cysts when compared to controls [Crocker et al., 1988]. These doses are less than upper bound exposure levels for a patient (7.2 mg/kg, see Table I) undergoing three, 5-hour dialysis sessions per week.

Pulmonary toxicity

Intravenous administration of DEHP has been shown to cause respiratory distress, tracheal bleeding and inflammation, and subsequent death due to pulmonary edema in rats after large doses from 200 to 300 mg DEHP/kg body weight [Syracuse Research, 1982; Huber et al., 1996]. Roth et al. [1988] measured DEHP in the inspired air of five mechanically ventilated preterm infants and estimated exposures at 1 to 4,200 μg DEHP/h from respiratory tubing. After initial improvement due to the respiratory therapy, the three infants studied developed pathological changes in the lungs resembling those observed in hyaline membrane disease. One patient died of pneumothorax soon after being ventilated, and the other two recovered after PVC tubing was replaced with ethylene vinyl acetate tubing. This is the only published study of human inhalation exposures to DEHP from medical devices. Exposures were estimated from DEHP concentrations in the water traps of the respirators.

Cardiotoxicity

Rock et al. [1987] examined the acute cardiac effects of increasing doses of MEHP in five anesthetized rats injected via the femoral artery. They found a steady and significant decrease in heart rate beginning after a total dose of 20–

30 mg and a decline in blood pressure after a total dose of 40–50 mg MEHP, ending in cardiac arrest. DEHP cardiotoxicity has been confirmed by in vitro experiments involving isolated, perfused rat heart/lung preparations [Petersen et al., 1975; Labow et al., 1990].

Hepatotoxicity

Non-carcinogenic liver abnormalities—development of peroxisomes, cell membrane destabilization, effects on metabolic enzyme activity, reduction in liver function—have been observed in rodents, rhesus monkeys, and humans following DEHP exposure. In a small study (12 animals), rhesus monkeys receiving plasma transfusions from DEHP-containing PVC blood bags over a 6-month or 1 year period (yearly dose of 50–1,500 mg) had abnormalities in liver histology (hepatocyte degeneration and necrosis, binucleate cells) and function (as measured by sulfobromophthalein transport) that persisted up to 26 months after treatment [Jacobson et al., 1977; Kevy and Jacobson, 1982]. These effects were absent from control animals and those receiving transfusions using polyethylene-stored platelets. In an examination of liver biopsies from patients undergoing hemodialysis two to three times per week, Ganning et al. [1984, 1987] observed histological abnormalities (induction of peroxisomes) after 1 year of dialysis but not after one month. These patients had not received any drugs known to have peroxisome-proliferating effects. In a study of 29 infants with serum levels of 18–98 μg DEHP/ml following a 71–300-hour extracorporeal membrane oxygenation therapy session, Schneider et al. [1991] found that the degree of cholestasis was significantly correlated with DEHP exposure. Plonait et al. [1993] did not detect evidence of cholestasis in infants exposed to smaller amounts of DEHP.

Carcinogenicity

DEHP causes malignant hepatocellular tumors in rats and mice of both sexes [Kluwe, 1982; KemI, 1999], including a dose-dependent increase in hepatocellular adenomas in male mice at doses ranging from 98.5 to 1226 mg/kg per day, and an increased incidence of hepatocellular adenomas in rats at doses ranging from 146 to 789 mg/kg per day compared to controls [Moore 1996, 1997 as cited in KemI, 1999]. The U.S. Agency for Toxic Substances and Disease Registry has determined that DEHP ''may be reasonably anticipated to be a carcinogen'' based on animal data [ATSDR, 1993]. However, there is debate as to whether the mechanism by which DEHP causes liver cancer in animals is relevant to humans (see next section). Based on these mechanistic considerations, the International Agency for Research on Cancer recently reclassified DEHP to Class C (not classifiable as to carcinogenicity to humans) [IARC, 2000]. Some other authorities have removed DEHP from lists of human carcinogens [EU, 1990; IPCS, 1992].

Moore [1996, as cited in KemI, 1999] found an increased incidence of mononuclear cell leukemia (above that which is normally found at background levels in the strain of rat used) at a dose of 146.6 mg/kg per day for 104 weeks.

Mechanisms of Carcinogenesis and Other Effects

DEHP belongs to a class of chemicals called ''peroxisome proliferators.'' Peroxisomes are cellular organelles that contain enzymes with a variety of functions including oxidation of fatty acids and the biosynthesis of cholesterol [Reddy and Lalwani, 1983; Citron, 1995]. Animals that respond to this class of chemicals with peroxisome proliferation also tend to develop liver cancer after long-term exposure. One widely held opinion concludes that peroxisome proliferation is necessary for the carcinogenic response to this class of chemicals [Reddy and Lalwani, 1983; Reddy et al., 1986; Ward et al., 1998]. DEHP is considered only a weak peroxisome proliferator compared to some hypolipidemic drugs [Reddy et al., 1986].

Two theories have been proposed to explain the carcinogenic response: (1) the induction of peroxisome proliferation leading to oxidative stress and the generation of electrophilic free radicals; and (2) increased hepatocyte proliferation and suppression of hepatocellular apoptosis. While these two processes together may largely explain the mechanism of the carcinogenic response [Reddy and Lalwani, 1983; Doull et al., 1999], some research indicates that there may be other important factors such as indirect genotoxicity; effects on cell transformation and intercellular communication; and other non-peroxisomal parameters such as mitrochondrial effects and effects on enzyme activity [Cattley and Glover, 1993; Melnick and Cohen, 1996; Gonzalez et al., 1998; KemI, 1999]. For example, DEHP and diethylhexyl adipate, which result in similar levels of peroxisomal induction in rats do not lead to similar tumogenic responses [Melnick and Kohn, 1996]. Responses to peroxisome proliferators other than the hepatacarcinogenic response have not been widely examined in the literature.

Recent research has shown that a class of nuclear receptors, called the peroxisome proliferator-activated receptor (PPAR) plays a central role in mediating the carcinogenic effects of peroxisome proliferators. The PPAR receptor that is most studied and believed responsible for the hepatocarcinogenicity of DEHP is PPAR-α [Gonzalez et al., 1998]. Mice bred without this receptor (PPAR-α knockout mice) do not exhibit carcinogenic responses in the liver [Gonzalez et al., 1998; Ward et al., 1998]. Because humans have less than one-tenth the levels of PPAR-α expression in

the liver observed in mice [Gonzalez et al., 1998] and because many PPAR-binding sites in humans may be occupied by competing proteins, they may be less likely to develop liver cancer after exposure to peroxisome proliferators [Doull et al., 1999]. Indeed, hepatocarcinogenicity has not been observed in limited clinical trials involving the hypolipidemic drugs clofibrate and gemfibrozil, both of which are potent peroxisome proliferators in animal studies [KemI, 1999].

Reddy et al. [1984] argue that while there may be interspecies differences in the amounts of peroxisome proliferation, it is not a species-specific phenomenon. They report that administration of different doses of clofibrate over a 3–7 week period to cats, chickens, pigeons,and rhesus and cynomolgus monkeys resulted in peroxisome proliferation in all five species. Humans undergoing dialysis exhibit increased peroxisome development in liver tissue [Ganning et al., 1984, 1987].

Despite evidence that the mechanism of DEHP-induced carcinogensis in animals may not be applicable to humans, lingering uncertainties lead some researchers to conclude that the possibility of DEHP-related carcinogenic responses in humans cannot be ruled out [Citron, 1995; Melnick and Kohn, 1996]. One important uncertainty relates to interindividual variability in PPAR-α expression, peroxisome proliferation, and peroxisome proliferator-related impacts, which might be affected by age or health status.

With regard to non-carcinogenic effects of DEHP, recent studies in mice lacking the PPAR-α receptor show that the fetotoxicity, teratogenicity, testicular lesions, and kidney effects of DEHP occur at least partly independently of peroxisome proliferation [Peters et al., 1997; Ward, et al., 1998]. Thus studies of these effects in various animal species are likely to be directly relevant to humans. For example, the testicular toxicity of DEHP appears to be at least partially explained by interference with the binding of follicle-stimulating hormone to its receptor on Sertoli cells [Lloyd and Foster, 1988]. In an in vitro study, Maloney and Waxman [1999] found that MEHP activated both mouse and human PPAR-γ—highly expressed in various human tissues including adipose, testis, liver, and hematopoietic cells—which may play an important role in mediating extrahepatic toxicity of DEHP. However, the mechanisms of DEHP toxicity are likely to be multiple and variable, depending on the effect, organ, age, and species studied.

The Lifecycle Hazards of PVC

Given the human exposure to DEHP from medical uses and the potential for adverse health effects, it would be prudent to consider alternative non-DEHP-containing or non-PVC materials for medical applications. It is incumbent on medical and public health professionals to consider not only the potential direct impacts of products used in the medical setting but also the hazards they pose throughout their lifecycle. First, DEHP may pose risks to workers exposed during DEHP production, although this has not been well studied. A benefit of shifting to non-PVC medical devices would be to reduce dioxin produced during the PVC lifecycle, particularly its production and disposal through incineration [Evers et al., 1988; Green, 1992; Moller et al., 1995; Thorton et al., 1996].

Further, switching to non-PVC medical devices would reduce risks associated with the production and emission of the PVC building block vinyl chloride monomer (VCM). Since the early 1970s VCM has been recognized as an occupational carcinogen, causally related to angiosarcoma of the liver. More recent research has identified associations between workplace vinyl chloride exposure and hepatocellular carcinoma and brain cancer [Kielhorn et al., 2000]. While strict occupational exposure limits for VCM were instituted throughout the world in the mid-1970s, exposures may remain high in some countries [Kielhorn et al., 2000]. Community exposures also continue to occur through air emissions from production facilities.

A prudent and thoughtful course of action would be to identify materials that provide necessary performance characteristics, pollute less throughout their life cycles, and avoid exposing patients, workers, and communities unnecessarily to potentially hazardous chemicals (e.g., plasticizers, dioxin, and vinyl chloride monomer).

Alternative Materials

Alternatives to PVC are widely available or are in development for use in most medical devices, and many of those on the market are cost-competitive [Wagener et al., 1992; Czuba, 1998; Hakani et al., 1998; Lipsitt, 1998; Tickner et al., 1999]. Citrate plasticizers, a drop-in substitute for DEHP made from citric acid, have been available for years as plasticizers in medical devices. Several U.S. and European medical device manufacturers sell PVC-free IV bags, tubing, and platelet storage bags. Some alternatives command a substantial share of the United States market. For example, B. Braun/McGaw, which currently supplies about 18% of the IV bag market in the United States, uses a three-layer polymer laminate instead of PVC [Zawaideh, 1999, personnel communication]. In addition to existing polymers, new metallocene polyolefin polymers may soon compete with PVC in many applications. These are stronger (requires less material per unit of product), require less processing time, and use no plasticizers [Rothman, 1997; Wilson, 1997].

Large PVC medical device manufacturers and users are undertaking efforts to investigate and implement PVC-free alternatives as a result of potential DEHP/PVC health risks and superior material properties of alternatives. For example, Baxter International, the world's largest medical

device manufacturer, is ''committed to exploring and developing alternatives to PVC products and is developing and implementing proposed timetables for substituting its current containers for intravenous solutions (IV) with a container that does not contain PVC '' [Freudenheim, 1999]. United Health Services, the third largest hospital management company in the United States, has noted that it will seek to replace PVC medical supplies with cost-effective alternatives.

Only a few product lines have no economically and technically viable alternative to PVC. Red blood cell packaging is a notable example, where DEHP stabilizes red blood cells, extending their storage life. Efforts toward innovation in red blood cell storage and medical tubing will be needed, as PVC offers material advantages for these product uses. Where alternative materials do exist that meet existing performance requirements at reasonable costs, these materials should be considered as potential substitutes for DEHP-containing PVC medical devices. Any alternative material used in the medical setting should be carefully scrutinized for lifecycle and patient health risks with a goal of continuously reducing unfavorable impacts on human health and the environment.

CONCLUSIONS

Over the past 30 years, studies have demonstrated that DEHP can leach to varying degrees from medical devices into patients. Measures of human exposure to DEHP from medical devices vary widely, but leaching can result in clinically important DEHP exposures. Limited research has been conducted on the human health effects of DEHP, including virtually no epidemiological studies. Available toxicological testing in animals and in vitro tests, supported by limited human data, provide evidence linking DEHP and its metabolites to a wide range of adverse effects in the liver, reproductive tract, kidneys, lungs, fetus, and heart. Some of the effects observed in toxicity testing have occurred at levels of exposure experienced by patients in certain clinical settings.

Certain populations, including dialysis patients and hemophiliacs may have long-term exposures to relatively high doses of DEHP, while others, such as infants and the developing fetus, may have exposures at critical points in development. Moreover, developing organisms show evidence of increased tissue sensitivity to DEHP exposure. Immature detoxification pathways and tissue distribution of MEHP that differ from adults and add to their susceptibility. Due to the variable toxicity of DEHP in multiple organs, the variability in human exposure and susceptibility to effects, and uncertainties in extrapolating animal data to humans, quantitative estimates of human risks or of safe levels of exposure cannot be established with confidence at this time.

For the critical health effect, which appears to be testicular toxicity in the developing organism, both rodents and primates metabolize DEHP to its monoester, MEHP, which is the putative testicular toxicant. Humans may have a prolonged period of susceptibility to testicular toxicity because of periods of Sertoli cell proliferation both in infancy and again in puberty.

Epidemiological studies of DEHP-exposed humans are not available and, for some effects and susceptible populations, are unlikely ever to be conducted because of the virtual impossibility of assessing the long-term effects of early life exposures to this chemical with multiple-organ toxicity. For these reasons, lack of evidence of adverse health effects in humans should not be confused with evidence of safety. Sufficient toxicological data are readily available to cause concern about the advisability of exposing the fetus, neonate, infant, child, or chronically ill adult to DEHP, particularly when alternatives without substantial health-related disadvantages are available.

The current availability of some alternatives to DEHP-containing PVC medical devices presents a compelling argument for moving assertively, but carefully, to the substitution of other materials for PVC in medical devices. For those applications where no alternative currently exists, a dedicated research and development program, encouraged and supported by the FDA, should help identify safer substitutes.

Because of the limitations of current data, further research should also be undertaken to better understand and characterize life-course DEHP exposures and risks that these devices pose to humans, while efforts to minimize exposure are underway.

REFERENCES

Agarwal D, Eustis S, Lamb J, Reel J, Kluwe W. 1986. Effects of di(2-ethylhexyl) phthalate on the gonadal pathophysiology, sperm morphology, and reproductive performance of male rats. Environ Health Perspect 65:343–350.

Agency for Toxic Substances and Disease Registry (ATSDR). 1993. Toxicological profile for Di(2-ethylhexyl)phthalate (DEHP). TP92/05, April.

Albro P, Corbett J, Schroeder J, Jordan S, Matthews H. 1982. Pharmacokinetics, interactions with macromolecules and species differences in metabolism of DEHP. Environ Health Perspect 45:19–25.

Arcadi RA, Costa CE, Imperatore C, Marchese A, Rapisarda A, Salemi M, Trimarchi G, Costa G. 1998. Oral toxicity of DEHP during pregnancy and suckling in the Long–Evans rat. Food Chem Toxicol 36:963–970.

Autian J. 1972. Toxicity and health threats of phthalate esters:review of the literature. National Library of Medicine, Toxicology Information Response Center. Oak Ridge National Laboratory, Oak Ridge, TN. ORNL-TIRC-72-2.

Baxter Health Care Corporation. 1995. Dextrose and sodium chloride injection USP. Product insert Deerfield, IL: Revised in Nov., 1995.

Cattley R, Glover S. 1993. Elevated 8-hydroxydeoxyguanosine in hepatic DNA of rats following exposure to peroxisome proliferators:

relationship to carcinogenesis and nuclear localization. Carcinogenesis 14:2495–2499.

Chawl A, Hinberg I. 1991. Leaching of plasticizers from and surface characterization of PVC blood platelet bags. Biomater Artif Cells Immob Biotech 19:761–783.

Citron M. 1995. Perplexing peroxisome proliferators. Environ Health Perspect 103:232–235.

Cortes D, Muller J, Skakkebaek NE. 1987. Proliferation of Sertoli cells during development of the human testis assessed by stereological methods. Intl J Androl 10:589–596.

Crocker J, Safe S, Acott P. 1988. Effects of chronic phthalate exposure on the kidney. J Toxicol Environ Health 23:433–444.

Czuba L. 1998. PVC replacement in medical devices. Proceedings from Flexpo '98. Houston: Chemical Marketing Resources.

Davis B, Maronpot R, Heindel J. 1994. Di-(2-ethylhexyl) phthalate suppresses estradiol and ovulation in cycling rats. Toxicol Appl Pharmacol 128:216–223.

De Wildt S, Kearns G, Leeder J, van den Ankier J. 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.

Dirven H, van den Broek P, Arends A, Nordkamp H, de Lepper A, Henderson P, Jongeneelen F. 1993. Metabolites of the plasticizer di(2-ethylhexyl) phthalate in urine samples of workers in polyvinylchloride processing industries. Arch Occup Environ Health 64:549–554.

Douglas GR. 1986. Genetic toxicology of phthalate esters: mutagenic and other genotoxic effects. Environ Health Perspect 65:255–262.

Doull J, Casttley R, Elcombe C, Lack B, Swenberg J, Wilkinson C, Williams G, van Gemert M. 1999. A cancer risk assessment of di(2-ethylhexyl)phthalate: application of the new U.S. EPA risk assessment guidelines. Reg Toxicol Pharm 29:327–357.

European Commission. 1990. Commission Decision of 25 July 1990 on the Classification and Labeling of Di(2-ethylhexyl)Phthalate in Accordance with Article 23 of Council Directive 67/548/EEC. Official Journal of the European Communities No. L 222/49 (Aug. 17).

Evers E, Ree K, Olie K. 1988. Spatial variations and correlations in the distribution of PCDDs and PCDFs and related compounds in sediments from the river Rhine. Chemosphere 17:2271–2288.

Foster P. 1997. Assessing the effects of chemicals on male reproduction: lessons learned from di-*n*-butyl phthalate. CIIT Activities 17, No 9.

Freudenheim M. 1999. Maker of IV system to stop using a plastic. New York Times, 7 April.

Ganning A, Brunk U, Dallner G. 1984. Phthalate esters and their effect on the liver. Hepatology 4:541–547.

Ganning A, Brunk U, Edlund C, Elhammer A, Dallner G. 1987. Effects of prolonged administration of phthalate ester on the liver. Environ Health Perspect 73:251–258.

Gibson T, Briggs W, Boone B. 1976. Delivery of di-2-ethylhexyl phthalate to patients during hemodialysis. J Lab Clin Med 87:519–524.

Gollamudi R, Prasanna H, Rao R, Lawrence W, Autian J. 1983. Impaired metabolism of di(2-ethylhexyl) phthalate (DEHP) in old rat—an in vitro study. Toxicol Ind Health 12:623–632.

Gonzalez F, Peters M, Cattley R. 1998. Mechanism of action of the nongenotoxic peroxisome proliferators: role of the peroxisome proliferator-activated receptor-alpha. J Natl Cancer Inst 90(22):1702–1709.

Gray TJ, Beamand JA. 1984. Effect of some phthalate esters and other testicular toxins on primary cultures of testicular cells. Food Chem Toxicol 22:123–131.

Gray TJ, Gangolli SD. 1986. Aspects of the testicular toxicity of phthalate esters. Environ Health Perspect 65:229–235.

Gray E, Wolf C, Lambright C, Mann P, Price M, Cooper R, Ostby J. 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 sulphonate) during sexual differentiation produces diverse profiles of reproductive malformations in the rat. Toxicol Ind Health 14:94–118.

Green AE. 1992. The future of medical waste incineration. In: Green AE (ed.) Medical waste incineration and pollution prevention. New York; Van Nostrand Reinhold.

Hakani S, Sanjay M, McCarthy S. 1998. Flexible polyolefins as an alternative for PVC used in medical applications. Plastics Engineering Department, University of Massachusetts, Lowell.

Hartley R, Quinn M, Green M, Levene M. 1993. Morphine glucuronidation in premature neonates. Br J Clin Pharmacol 35:314–317.

Hillman L, Goodwin S, Sherman W. 1975. Identification and measurement of plasticizer in neonatal tissues after umbilical catheters and blood products. N Engl J Med 292(8):381–386.

Huber W, Grasl-Kraupp B, Schulte-Hermann R. 1996. Hepatocarcinogenic potential of DEHP in rodents and its implications on human risk. Crit Rev Toxicol 26:365–481.

International Agency for Research on Cancer (IARC). 2000. Di(2-ethylhexyl) phthalate. In: Monogr Eval Carcinog Risks Hum. Some Industrial Chemicals. Volume 77 (15–22 February), in preparation.

International Programme on Chemical Safety (IPCS). 1992. Environmental health criteria 131: diethylhexyl phthalate. Geneva: World Health Organization.

Jaakkola J, Oie L, Nafstad P, Botten G, Samuelsen S, Magnus P. 1999. Interior surface materials in the home and the development of bronchial obstruction in young children in Oslo, Norway. Am J Public Health 89:188–192.

Jacobson MS, Kevy SV, Gran RJ. 1977. Effects of a plasticizer leached from PVC on the subhuman primate: a consequence of chronic transfusion therapy. J Lab Clin Med 89:1066–1079.

Jaeger R, Rubin R. 1970. Plasticizers from PVC. Lancet 2: 778.

Jaeger RJ, Rubin RJ. 1972. Migration of a phthalate ester plasticizer from polyvinyl chloride blood bags into stored human blood and its localization in human tissues. N Engl J Med 287:1114–1118.

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

(KemI) Swedish National Chemicals Inspectorate. 1997. Additives in PVC, Marking of PVC. Report of a Government Commission. 1997, Stockholm, Report 4/97.

(KemI) Swedish National Chemicals Inspectorate. 1998. Risk assessment for bis(2-ethylhexyl) phthalate. Draft Document, Sept. EINECS-NO: 204–211-0. Stockholm.

(KemI) Swedish National Chemicals Inspectorate. 1999. Risk assessment for bis(2-ethylhexyl) phthalate. Update to Draft Document, February EINECS-NO:204–211-0. Stockholm.

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

Kielhorn J, Melber C, Wahnschaffe U, Aitio A, Mangelsdorf I. 2000. Vinyl chloride: still a cause for concern. Environ Health Perspect 108:579–588.

Kluwe W. 1982. Overview of phthalate ester pharmacokinetics in mammalian species. Environ Health Perspect 45:3–10.

Kurata Y, Kidachi F, Yokoyama M, Toyota N, Tsuchitani M, Katoh M. 1998. Subchronic toxicity of DEHP in common marmosets: lack of hepatic peroxisome proliferation, testicular atrophy, or pancreatic acinar cell hyperplasia. Toxicol Sci 42:49–56.

Lake B, Phillips J, Linell J, Gangolli S. 1977. The in vitro hydrolysis of some phthalate diesters by hepatic and intestinal preparations from various species. Tox App Pharm 29:239–248.

Labow R, Barry Y, Tocchi M, Keon W. 1990. The effect of mono(2-ethylhexyl)phthalate on an isolated perfused rat heart-lung preparation. Environ Health Perspect 89:189–193.

Lamb J, Chapin R, Teague J, Lawton A, Reel J. 1987. Reproductive effects of four phthalic acid esters in the mouse. Toxicol Appl Pharmacol 88:255–269.

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

Lewis L, Fletchner T, Kerkay J, Pearson K, Nakamoto S. 1978. Bis(2-ethylhexyl) phthalate concentrations in the serum of hemodialysis patients. Clin Chem 24(5):741–746.

Li L, Jester W, Orth J. 1998. Effects of relatively low levels of mono-(2-ethylhexyl) phthalate on cocultured sertoli cells and gonocytes from neonatal rats. Toxicol Appl Pharmacol 152:258–265.

Lipsitt B. 1998. Medical device films: performance properties of metallocene polyethylene films, EVA Films and flexible PVC films. From Flexpo '98 Proceedings. Houston: Chemical Marketing Resources.

Lloyd S, Foster P. 1988. Effect of mono(2-ethylhexyl) phthalate on follicle-stimulating hormone responsiveness of cultured rat sertoli cells. Toxicol Appl Pharmacol 95:484–489.

Lundburg G, Nilsson C. 1994. Phthalic acid esters used and plastic additives. Stockholm: Swedish National Chemical Inspectorate, Report No 12/94.

Maloney E, Waxman D. 1999. Trans-activation of PPAR-alpha and PPAR-gamma by structurally diverse environmental chemicals. Toxicol Appl Pharmacol 161:209–218.

Mazzo D, Nguyen-Huu J, Pagniez S, Denis P. 1997. Compatibility of docetaxel and paclitaxel in intravenous solutions with polyvinyl chloride infusion materials. Am J Health Syst Pharm 54:566–569.

Melnick RL, Kohn MC. 1996. Implications for risk assessment of suggested nongenotoxic mechanisms of chemical carcinogenesis. Environ Health Perspect, Supplement 104:123–135.

Mettang T, Alscher D, Pauli-Magnus C, Dunst R, Kuhlmann U, Rettenmeier A. 1999. Phthalic acid is the main metabolite of the plasticizer di(2-ethylhexyl) phthalate in peritoneal dialysis patients. Adv Perit Dial 15:229–233.

Moller S, Larsen J, Jelnes J, Faergemann J, Ottosen L, Knudsen F. 1995. Environmental aspects of PVC. Copenhagen: Danish Technology Institute, Environmental Technology, Danish Environmental Protection Agency, November.

Moore M. 1996. Oncogenicity study in rats with di-2-ethylhexyl phthalate including ancillary hepatocellular proliferation and biochemical analysis. Vienna, VA: Corning Hazleton, Inc., CHV-663–134. Conducted for Eastman Chemical Co.

Moore M. 1997. Oncogenicity study in mice with di-2-ethylhexyl phthalate including ancillary hepatocellular proliferation and biochemical analysis. Vienna, VA: Corning Hazleton, Inc., CHV-663–135. Conducted for Eastman Chemical Co.

Narotsky M, Weller E, Chinchilli V, Kavlock R. 1995. Nonadditive developmental toxicity in mixtures of trichloroethylene, di(2-ethylhexyl) phthalate and heptachlor in a $5 \times 5 \times 5$ design. Fundam Appl Toxicol 27:203–216.

Nass L. 1977. Encyclopedia of PVC. New York: M. Decker.

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

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

Peck C, Albro, P. 1982. Toxic potential of the plasticizer di(2-ethylhexyl) phthalate in the context of its disposition and metabolism in primates and man. Environ Health Perspect 48:11–17.

Peters JM, Taubeneck MW, Keen CL, Gonzalez FJ. 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 R, et al. 1975. Toxicology of plastic devices having contact with blood. Final Report. Contract NIH-NHLI-73-2098-B. Washington, DC: National Technical Information Service.

Plonait S, au H, Maier R, Wittfot W, Obladen M. 1993. Exposure of newborn infants to di-(2-ethylhexyl) phthalate and 2-ethylhexanoic acid following exchange transfusion with polyvinylchloride catheters. Transfusion 33:598–605.

Pollack G, Li R, Ermer J, Shen D. 1985a. Effects of route of administration and repetitive dosing on the disposition kinetics of di(2-ethylhexyl) phthalate and its mono-de-esterified metabolite in rats. Toxicol Appl Pharmacol 79:246–256.

Pollack G, Buchanan J, Slaughter R, Kohll R, Shen D. 1985b. Circulating concentrations of di(2-ethylhexyl) phthalate and its de-esterified phthalic acid products following plasticizer exposure in patients receiving hemodialysis. Toxicol Appl Pharmacol 79:257–267.

Poon R, Lecavaliert P, Mueller R, Valli V, Procter B, Chu I. 1997. Subchronic oral toxicity of di-n-octyl phthalate and DEHP in the rat. Food Chem Toxicol 35:225–239.

Reddy J, Lalwani N. 1983. Carcinogenesis by hepatic peroxisome proliferators: evaluation of the risk of hypolipidemic drugs and industrial plasticizers to humans. Crit Rev Toxicol 12:1–58.

Reddy J, Lalwani N, Qureshi S, Reddy M, Moehle C. 1984. Induction of hepatic peroxisome proliferation in nonrodent species, including primates. Am J Pathol, 114:71–83.

Reddy J, Reddy M, Usman M, Lalwani N, Rao M. 1986. Comparison of hepatic peroxisome proliferative effect and its implication for hepatocarcinogenicity of phthalate esters, di(2-ethylhexyl) phthalate, and di(2-ethylhexyl) adipate with a hypolipidemic drug. Environ Health Perspect 65:317–327.

Rhodes C, Orton T, Pratt I, Batten P, Bratt H, Jackson S, Elcombe C. 1986. Comparative pharmacokinetics and subacute toxicity of di(2-ethylhexyl) phthalate (DEHP in rats and marmosets: extrapolation of effects in rodents to man. Environ Health Perspect 65:299–308.

Ritter E, Scott W, Randall J, Ritter J. 1987. Teratogenicity of di(2-ethylhexyl) phthalate, 2-ethylhexanol, 2-ethylhexanoic acid, and valproic acid, and potentiation by caffeine. Teratology 35:41–46.

Rock G, Labow R, Franklin C, Burnett R, Tocchi M. 1987. Hypotension and cardiac arrest in rats after infusion of mono(2-ethylhexyl)phthalate (MEHP) a contaminant of stored blood. N Engl J Med 316:1218–1219.

Rock G, Labow R, Tocchi M. 1986. Distribution of di(2-ethylhexyl) phthalate and products in blood and blood components. Environ Health Perspect 65:309–316.

Roth B, Herkenrath P, Lehmann H, Ohlres H, Homig H, Benz-Bohm G, Kreuder J, Younossi-Hartenstein A. 1988. DEHP as plasticizer in PVC respiratory tubing systems: indications of hazardous effects on pulmonary function in mechanically ventilated, preterm infants. Eur J Pediatr 147:41–46.

Rothman D. 1997. Metallocene polyolefins, Chemical Week, May 21.

Schneider B, Cronin J, Van Marter L, Maller E, Truog R, Jacobson M, Kevy S. 1991. A prospective analysis of cholestasis in infants supported with extracorporeal membrane oxygenation. J Pediatr Gastroenterol Nutr 13:285–289.

Schneider B, Schena J, Truoug R, Jacobson M, Kevy S. 1989. Exposure to di(2-ethylhexyl) phthalate in infants receiving extracorporeal membrane oxygenation. N Engl J Med 320(23):1563 (letter).

Shaffer C, Carpenter C, Smyth H. 1945. Acute and subacute toxicity of di(2-ethylhexyl) phthalate with note upon its metabolism. J Indus Hygiene Toxicol 27: 130.

Singh AR, Lawrence WH, Autian J. 1975. Maternal–fetal transfer of 14C-di-2-ethylhexyl phthalate and 14C-diethyl phthalate in rats. J Pharm Sci 64(8):1347–1350.

Sjöberg P, Bondesson U, Sedin E, Gustaffson J. 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, Bondesson U, Sedin G, Gustafsson J. 1985b. Dispositions of di- and mono-(2-ethylhexyl) phthalate in newborn infants subjected to exchange transfusions. Eur J Clin Invest 15:430–436.

Stanford Research Associates (SRI) International. 1996. Plasticizers. Chemical Economics Handbook. Palo Alto, CA.

Syracuse Research Corporation. 1982. Information profiles on potential occupational hazards phthalates. Prepared for National Institutes for Occupational Safety and Health. Syracuse, NY.

Thornton J, McCally M, Oris P, Weinberg J. 1996. Dioxin prevention and medical waste incinerators. Public Health Rep 111(4):298–313.

Tickner J, Rossi M, Haiama N, Lappe M, Hunt P. 1999. The Use of di-2-ethylhexyl phthalate in PVC medical devices: exposure, toxicity, and alternatives. Lowell, MA: Lowell Center for Sustainable Production.

Tomita I, Nakamura Y, Yagi Y, Tutikawa K. 1982. Teratogenicity/fetotoxicity of DEHP in mice. Environ Health Perspect 41:71–75.

Tomita I, Nakamura Y, Yagi Y, Tutikawa K. 1986. Fetotoxic effects of mono-2-ethylhexyl phthalate (MEHP) in mice. Environ Health Perspect 65:249–254.

Trissel L. 1998. Handbook on injectable drugs. 10th edition. Washington, DC: American Society of Health Systems Pharmacists.

Tyl RW, Price CJ, Marr MC, Kimmel C. 1988. Developmental toxicity evaluation of dietary di(2-ethylhexyl) phthalate in Fischer 344 rats and CD-1 mice. Fundam Appl Toxicol 10:395–412.

United States Agency for Toxic Substances and Disease Registry (ATSDR). 1993. Toxicological profile for di(2-ethylhexyl)phthalate. Update. United States Department of Health and Human Services TP-92/05.

United States Consumer Product Safety Commission (US CPSC). 1985. Chronic hazard advisory panel on di(2-ethylhexyl)phthalate (DEHP). Report to the United States Consumer Product Safety Commission. Washington, DC.

Vessman J, Rietz G. 1978. Formation of mono(ethylhexyl) phthalate from di(ethylhexyl) phthalate in human plasma stored in PVC bags and it's presence in fractionated plasma proteins. Vox Sang 35:75–80.

Wagener KB, Batich C, Green A. 1992. Polymer substitutes for medical grade polyvinyl chloride (PVC). In: Green AE (editor), Medical waste incineration and pollution prevention. New York: Van Nostrand Reinhold, p.155–169.

Ward JM, Peters JM, Perella CM, Gonzalez FJ. 1998. Receptor and nonreceptor mediated organ-specific toxicity of DEHP in peroxisome proliferator-activated receptor alpha-null mice. Toxicol and Pathol 26:240–246.

Wilson R. 1997. The impact of metallocenes on PVC. Presented at the World Vinyl Forum, Akron, OH, September 9.