Executive Summary

The Health Care Without Harm Campaign has commissioned the Lowell Center for Sustainable Production to examine two aspects of human exposure to di-ethylhexyl phthalate (DEHP): the health risks associated with this exposure; and alternatives to its use. DEHP is a phthalate ester widely used as a plasticizer to make polyvinyl chloride (PVC or vinyl) medical products soft and flexible. PVC is used in a range of medical devices from intravenous (IV) fluid containers and blood bags to medical tubing.

This review was conducted by examining the published literature on laboratory studies in animals, *in-vitro* studies in human or animal cell lines, and evidence in humans, when available. Variability and uncertainties regarding exposure and toxicity were carefully considered as was the relevance of studies in experimental animals to the possibility of risk in humans, as this has been an especially contentious issue for DEHP.

Exposure to DEHP

Human exposure to DEHP can occur in the ambient environment and in the medical setting. DEHP exposures occurring in the medical setting are of particular concern because the amount of exposure can be substantial and because those exposed, such as premature infants and other neonates or adults with life-threatening illnesses, may be particularly vulnerable to the effect of toxic chemicals.

Medically-related exposure

PVC medical devices, such as IV bags and blood bags, typically contain 30-40% DEHP by weight; other devices, such as medical tubing, may contain as much as 80% DEHP by weight. Because DEHP is not chemically bound to the polymer in a PVC medical device, it can be released when the device is heated or it can leach out when the device comes into contact with certain media, such as blood, drugs, saline, or water. The major factors determining the degree to which DEHP leaches from medical devices are temperature, amount of DEHP in the device, agitation of the device while in contact with medical solutions, storage time of the device while in contact with medical solutions, and the type of medium being stored in or moving through the medical device. In practice the amount of leaching varies widely; an example is endotracheal tubing, from which 6-12% of the DEHP was found to leach.

Two types of studies have been conducted in order to quantify human exposure to DEHP in the medical setting. The first type measures the amount of DEHP that leaches from common medical devices, such as PVC blood bags, IV bags, and tubing, into the physiologic medium that each device contains, such as blood or saline solution. The second type measures the amount of DEHP or metabolites found in the blood, urine, or tissues of patients treated with PVC medical devices.

Several studies found that DEHP leached from PVC blood bags, IV bags and tubing into blood, blood products, and medical solutions. DEHP has been measured in blood products (whole blood, plasma,

platelet, and red cell concentrates) in concentrations ranging from 4 to 650 mg/liter. DEHP has been measured in concentrations ranging from 3.1 to 237 mg/liter in solutions containing drugs and solvents and 5 mg/liter in sterile water and salt and sugar-based solutions. In at least some situations, the DEHP that is leached into drugs can interfere with their delivery or their effects on humans. As a result of DEHP leaching PVC medical devices, several pharmaceutical manufacturers provide warning labels advising against the use of DEHP-plasticized PVC for administration of specific products.

As early as 1970, studies identified and measured DEHP and its metabolites in human tissue and serum. These studies identified human exposure to DEHP in patients receiving dialysis, blood transfusions, artificial ventilation, and exchange transfusions. Particular concern has been raised by researchers in the pediatric setting who have documented DEHP exposures among premature and ill newborns receiving blood transfusions, extracorporeal membrane oxygenation therapy (ECMO), or respiratory therapy. These infants, whose limited development and generally immature metabolic pathways may place them at greater risk of toxic insults, receive among the highest doses of DEHP from medical devices. In addition, because DEHP can cross the placental barrier, researchers have proposed that the developing fetus can be exposed when the mother undergoes certain medical treatments, although the amounts received have not been well quantified.

A few limited studies in humans have found adverse health effects such as respiratory distress, cholestasis, and histological abnormalities of the liver in the same subjects having documented exposure to DEHP. In these studies, the researchers proposed that the observed health effects were related to the DEHP exposure.

The range of human exposures to DEHP from PVC medical devices identified in the literature are as follows:

Human exposure to DEHP following treatment with PVC medical devices

Treatment	Total exposure (mg)	Exposure Rate	
		mg/kg body weight	Time period
Hemodialysis	0.5-360	0.01-7.2	Dialysis session
Blood transfusion in adults	14-600	0.2-8.0	Treatment
Extracorporeal oxygenation in infants		42.0-140.0	Treatment period
Cardiopulmonary bypass	2.3-168	0.03-2.4	Treatment day
Artificial ventilation in preterm infants		0.001-4.2	Hour
Exchange transfusions in infants		0.8-4.2	Treatment

Total DEHP exposure measured or estimated in these studies varies significantly, although the exact reasons for the variability are unclear. Differences in study design and conditions, DEHP content in devices, and blood storage time, among others, may play a role in this variability.

Ambient environmental exposure

Human exposure to DEHP also occurs in the general environment through inhalation of DEHP in air from the off-gassing from PVC products such as flooring, drinking water contaminated with DEHP (from various sources, including runoff and fallout of factory emissions), and through the ingestion of food containing DEHP that has either leached into it from packaging or from exposures to livestock, poultry,

and dairy cattle. The average total daily ambient exposure to DEHP in the U.S. has been estimated at 0.27 mg per day, with exposure through food contributing 0.25 mg per day, exposure through water contributing 0.02 mg per day, and exposure through air contributing 0.4 µg per day (though this does not include workplace air exposures, nor indoor air exposures from off-gassing of building materials, which may result in substantially higher exposures).

Because DEHP is widely dispersed in the environment, ambient environmental exposures need to be considered in addition to exposure from PVC medical devices when assessing the risk of DEHP to human health.

Metabolism and toxicity of DEHP

When DEHP enters the human body, the compound is metabolized into various substances that are more readily excreted. Unfortunately, the most important of these metabolites, mono-ethylhexyl phthalate (MEHP) is thought to be responsible for much of DEHP's toxicity. The enzymes that break down DEHP into MEHP are found mainly in the intestines but also occur in the liver, kidney, lungs, pancreas, and plasma. Because conversion of DEHP to MEHP occurs primarily in the intestinal tract, exposures to DEHP by ingestion may be more hazardous than by intravenous exposure, which largely bypasses the intestinal tract. However, MEHP has been measured in stored adult human serum as well as in the blood sera of neonates undergoing exchange transfusions and adults undergoing hemodialysis. MEHP is not the only metabolite of DEHP and many of the known secondary metabolites have not been studied for their toxicity. The initial metabolism of DEHP is qualitatively similar among mammalian species, so that animal studies are likely to be useful in understanding the consequences of human exposure. The ability to metabolize DEHP is age-related and may also depend on underlying health status in ways that are not well-understood. It is generally accepted that the toxicity of DEHP via one route of exposure should be considered relevant to exposure by other routes, in the absence of evidence to the contrary.

DEHP produces a spectrum of toxic effects in laboratory animals (including rodents and primates) in multiple organ systems including the liver, reproductive tract (testes, ovaries, secondary sex organs), the kidneys, lungs, and heart. It is also toxic to the developing fetus. The studies documenting these effects range from large studies involving hundreds of animals, to smaller ones with few animals, as well as cell culture studies, and case reports in humans. While most of these effects have been observed in laboratory animals at high doses (the standard procedure by which experimental studies are made sufficiently powerful to detect small effects), in some cases these doses were close to those that might be experienced by individuals undergoing medical treatment. For some adverse effects, such as testicular toxicity, the developing organism (fetus and neonate) appears to be much more sensitive (greater toxicity and irreversibility of effect) than the adult. It is unclear whether a threshold (a level of exposure below which no adverse effect will occur) for adverse effects exists. A summary of key studies suggesting adverse effects of DEHP exposure is provided in the table on the next page.

DEHP belongs to a class of chemicals called "peroxisome proliferators." Peroxisomes are cell membrane organelles that contain enzymes responsible for oxidation of fatty acids, the biosynthesis of cholesterol, and other biochemical pathways. It is generally thought that peroxisome proliferation is associated with liver cancer in animals, although the causal mechanisms by which this happens are not currently known. Peroxisome proliferation occurs to a much lesser degree in humans than in rodents and for this reason some researchers have questioned the relevance of animal studies of DEHP to humans.

Observed toxicity of DEHP to different organ systems

Organ	Effect	Species	Dose	Duration	Reference
Testis	Tubular atrophy and degeneration	Rat	0.9 and 1.9 g/kg/day in diet	90 days	Shaffer, et. al., 1945
	Histological damage to the testes in offspring	Rat	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 agenesis; hemorrhagic testes; hypospadias	Rat	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 hours	Li, et. al., 1999
Ovaries	Suppressed or delayed ovulation, suppressed estradiol production, polycystic ovaries	Rat	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	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	Total cumulative arterial dose: 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	2mg/kg, 3 times per week in diet	1 year	Crocker, et. al., 1988
Fetus/ Embryo	Fetal death, exencephaly, open neural tubes, reduced pup size	Mouse	1000 mg/kg/day in diet	2 days	Peters, et. al., 1997
Liver	Abnormalities in histology, reduction in liver function	Rhesus monkey (immature)	Not directly measured – intravenous admin. Of blood from PVC bags to mimic human exposure, estimated total dose 87.5-290.0mg	1 year	Kevy and Jacobson, 1982
	Hepatocellular adenoma	Rat	146.6 mg/kg/day in diet	104 weeks	Moore, 1996

There is still considerable uncertainty as to the exact mechanisms by which DEHP may cause various different adverse effects in diverse organs of laboratory animals. The mechanisms of toxicity are likely to be multiple and variable, depending on the health endpoint, the organ, and species studied. Recent studies in mice exposed to DEHP show fetal toxicity, teratogenicity, testicular lesions, and kidney cysts, though not liver lesions, in laboratory animals bred without the receptor necessary for mediating the enzymatic activity of peroxisomes (PPAR alpha, a receptor also present in humans). That is, mice that have been bred to lack one of the receptors necessary for the peroxisome development, in response to exposure to a peroxisome proliferator, still exhibit toxic effects of DEHP. These studies strongly support the conclusion that much of the non-hepatic toxicity of DEHP is at least partly independent of peroxisome proliferation.

As regards toxic effects that are mediated exclusively through peroxisome proliferation, our understanding of their relevance to humans turns on the extent of knowledge concerning the prevalence of this phenomenon in humans. There may, for example, be considerable inter-individual variability in the phenomenon of peroxisome proliferation from exposure to a chemical such as DEHP. As a result, it is prudent to assume that at least some fraction of the population may be as effective at peroxisome proliferation as the laboratory animals in which most DEHP toxicity studies have been done. Moreover, it is still not clear that peroxisome proliferation is absolutely necessary for malignant transformation. It remains plausable that another mechanism, such as genotoxicity, may also contribute to cancer risks. For these reasons the carcinogenic activity of DEHP in animal experiments may well be relevant to humans. This same conclusion was recently reached by the California Office of Environmental Health Hazard Assessment with regards to DEHP carcinogenicity. They stated, ”at this point...OEHHA does not find this new body of evidence [on perixosome proliferation] points toward a determination that human exposure to any level of DEHP is without carcinogenic risk. Rather, the literature presents data that leave open the possibility of human sensitivity to DEHP’s carcinogenic effects.“

There is a general lack of adequate human toxicity or epidemiologic studies to determine whether DEHP exposure is associated with adverse outcomes in humans, despite the compound’s high volume production, documented human exposure, and documented adverse effects in animals. The lack of epidemiologic studies is at least partly explained by: (1) the difficulty in following high risk groups, such as premature infants, because of long latent periods between exposures and possible effects; (2) the impacts of DEHP exposure may be subtle (such as a partial loss in sperm production); (3) the considerable variability in human exposure levels and the difficulty in measuring human exposure adequately; and (4) the ubiquity of phthalate exposure in the environment, which means that humans are exposed to DEHP through many different routes, making it difficult to distinguish exposed and unexposed groups.

Alternative materials

Given the human exposure to DEHP from medical uses and the potential for adverse health effects, it would be prudent to investigate alternative materials for use in medical environments. When considering potential alternative materials, other health and environmental concerns of PVC should also be borne in mind. These concerns include: potential health hazards posed by other extractable plasticizers (which PVC will always require), as well as the hazards posed by PVC production and disposal, such as the creation of toxic dioxins and related toxic chemicals (a brief review of the hazards posed by dioxin from PVC production and incineration is included in an appendix to this report). 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 unnecessarily to potentially hazardous chemicals.

A review of the literature, coupled with supplier interviews, suggests that PVC alternatives are widely available for use in most medical devices and can be cost-competitive. Several U.S. and European medical device manufacturers already have developed government approved PVC-free alternatives for IV bags, tubing, and platelet storage, some of which command a substantial share of their product market. The development of new metallocene polyolefin polymers in the coming years will likely lead to the creation of additional alternative products. Efforts towards 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.

Conclusions

On the basis of a review of more than one hundred published studies, reports, and analyses, the following conclusions have been reached:

1. Humans are exposed to substantial levels of DEHP through medical devices. Certain populations such as hemophiliacs, kidney dialysis patients, and high risk newborns are particularly heavily exposed.

2. The nearly complete absence of rigorous studies of exposed human populations means that conclusions about DEHP risks must necessarily be based on laboratory animal studies.

3. Studies of laboratory animals, supported by very limited human data, suggest that a wide range of toxic effects occur in exposed mammals. Inadequate evidence exists to conclude that the toxic mechanisms found in laboratory animals do not occur in humans.

4. Considerable uncertainty about many aspects of the potential health hazards of DEHP remains. Quantitative estimates of risk to humans at various stages of life or health, or of safe levels of exposure, cannot be established with confidence at this time.

5. Materials exist which do not contain DEHP or other similar plasticizers, and which are currently being used in medical devices. These materials have the potential to be safer alternatives to DEHP-containing medical devices.