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# Executive Summary

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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/<br>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 plausible 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 peroxisome 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.

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# Introduction

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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 human health risks associated with this exposure; and alternatives to its use. DEHP belongs to a class of chemicals called the phthalate esters and is 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.

The report consists of the following sections:

1. An overview of the production of DEHP and its use in PVC medical devices, including the function and migration of DEHP.
2. A review of human exposure to DEHP. This review summarizes what is known about environmental exposures to DEHP from air, contaminated food, and water as well as exposures from PVC medical devices. The migration of DEHP into blood and other fluids contained in medical devices is reviewed, as are the levels of DEHP reaching the human body.
3. A review of the toxicity of DEHP to different organ systems. Following an overview of DEHP uptake and metabolism, animal and *in-vitro* studies, and human case reports are reviewed, summarizing the reported health effects of DEHP on the reproductive tract, the kidney, the heart, the lungs, and the liver. The relevance to humans of proposed mechanisms by which DEHP causes toxic effects in animals is also discussed.
4. A description of risk management options for reducing the human health risks associated with DEHP exposure. These options range from continued study on DEHP health risks, without any action at this time, to the substitution of DEHP-containing PVC in medical devices.
5. An analysis of alternatives to PVC in the medical bags and tubing markets. In this section, a market analysis of alternative products that could replace PVC, thus eliminating DEHP exposure to patients, is provided. This analysis is divided by IV bags; blood bags and other storage products; and medical tubing. Alternative resins that could be used to produce medical products are also examined.



# Use of Polyvinyl Chloride Plastics and DEHP in Medical Devices

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Polyvinyl chloride plastics, (PVC or vinyl), are used in the production of a wide array of medical devices, from intravenous (IV) bags to catheters. Their use has grown considerably over the past 30 years, to the point where PVC represents more than 25% of all plastics used in medical devices (Huber, et al., 1996). PVC intravenous bags, introduced in the early 1970s, and tubing represent the largest PVC uses in medical devices (see page 13, below, for further elaboration on PVC use in medical devices). Other major uses of PVC in medical devices and the health care industry include: blood bags, plasma collection bags, dialysis bags, catheters, and gloves. PVC use has grown because of its specific material properties which are important in the health care setting. These include: flexibility, strength, suitability for steam sterilization, resistance to kinking, optical clarity, weldability, surface finish, and cost. Its use has been predominant in the production of certain types of flexible products because of its ease of processing using a wide variety of techniques.

The specific characteristics of vinyl medical devices are achieved through the addition of a wide variety of additives. PVC is a unique polymer because of its need for and ability to accept large quantities of additives to achieve specific qualities. It is a relatively rigid and brittle polymer; flexibility is achieved through the addition of chemical plasticizers.<sup>1</sup> Plasticizers are organic compounds added to the PVC to facilitate processing and increase flexibility and toughness in the final product by internal modification of the polymer molecule. PVC consumes approximately 90% of the plasticizers produced globally. Other polymers can be made more or less flexible through the rearrangement of polymer chains or the addition of additional polymers to the mixture instead of adding plasticizers. While there are numerous plasticizers on the market, the largest group of plasticizers, accounting for around 70% of U.S. consumption, are the phthalate esters. The phthalate esters are produced through the reaction of phthalic acid with a specific alcohol to form one of several specific di-esters.

While there are some 25 different phthalate esters, only a few account for the vast majority of global production. Di-ethylhexyl phthalate (also known as DEHP), a colorless, slightly lipophilic, and generally odorless liquid, is the most important phthalate in the production of medical devices and is the international standard PVC plasticizer. It accounts for some 18% of total phthalate production in the United States, down from more than 30% in the mid-1970s. Five producers (Exxon, Eastman Chemical, Aristech, BASF, and Monsanto) account for more than 90% of U.S. phthalate production. Eastman Chemical and Aristech are the largest U.S. producers of DEHP.

The overall growth rate for consumption of DEHP has decreased since the late 1980s. This can be explained in part by a number of restrictions based on concerns that DEHP acts as an animal carcinogen (NTP, 1982) and is labelled as a possible human carcinogen by the International Agency for Research on Cancer (IARC, 1987). These concerns have caused some manufacturers, including some in the toy industry, to switch to other phthalates.<sup>2</sup> Total U.S. production of phthalate esters in 1994 was 1.4 billion pounds of which DEHP accounted for some 260 million pounds (SRI, 1996). The annual growth rate for all

phthalates in the U.S. was projected to be 2.1% from 1994-1999, while the annual growth rate for DEHP was projected to be 1.0% for the same period .

DEHP is primarily used as a plasticizer for PVC; non-plasticizer uses, such as dielectric fluids in electrical capacitors, insecticides for orchards, and as an inert component in pesticide formulations, represent a small fraction of total consumption. Major uses of DEHP for PVC include such products as flooring, wall coverings, medical applications, as well as furniture and consumer applications including baggage and footwear. While DEHP use is decreasing in many sectors, medical applications actually represent a growing market for DEHP, with a growth rate higher than that of the U.S. Gross Domestic Product (SRI, 1996).

### *DEHP function and migration*

DEHP has high compatibility with PVC resins. Depending on the flexibility needed in a PVC product, the formulation may contain more than 50% di-ethylhexyl phthalate (CP Hall, 1986). A recent study found that some medical devices contain between 29% and 81% DEHP by weight (DiGangi, 1999).<sup>3</sup> DEHP is not chemically bound to the polymer, but is dispersed in the matrix of the polymer chains to decrease the interaction forces of adjacent chains, lower the glass transition temperature of the polymer, and produce chain and material mobility. The plasticizer moving around in the polymer matrix imparts flexibility and other features such as surface characteristics, burning characteristics, resistance to flexing, and tensile strength. These characteristics are established by modifying the amount of the plasticizer and sometimes the type of plasticizer as well.

Because DEHP is not chemically bound to the polymer, the plasticizer can leach out during normal use. This extraction occurs either by the DEHP directly leaching out of the PVC product or when an extracting material (blood, IV fluids) diffuses into the PVC matrix, dissolves the plasticizer, and the two diffuse out together (Nass, 1977, Lundberg and Nilsson, 1994, Rock, et al., 1986). Leaching of DEHP from any given PVC product is dependent on many factors and is highly variable. Some of these factors include: concentration of the phthalate in the PVC matrix (greater concentration leads to more leaching), vapor pressure of the plasticizer (greater vapor pressure leads to more leaching), surrounding temperature (greater temperature leads to more leaching), size of the sub-chains, presence of secondary plasticizers to reduce leaching, the degree of "curing" of the plasticizer and polymer, the type of surrounding media, application of pressure or agitation, and storage or use time (Nass, 1977, Nilsson and Lundberg, 1994, Ganning, 1984, Kevy and Jacobson, 1982). Thus, DEHP leaching could vary widely by manufacturer or even batch of materials. The most important factors in DEHP leaching from medical devices are likely temperature, concentration of phthalate, agitation, storage time, and surrounding media.

According to the Encyclopedia of PVC (Nass, 1977), phthalate migration from a PVC product containing 40% DEHP by weight is expected as follows: volatility loss (4.5% of total DEHP); loss in water (0.01%); and solvent loss (44%). DEHP loss has been reported as approximately 15% in 1% soapy water, 19% in cottonseed oil, and 0.98% in a high humidity environment (CP Hall, 1996). These results are corroborated by Latini and Avery (1999), who found a 6%-12% DEHP loss from endotracheal tubes used to provide nasal Continuous Positive Airway Pressure (CPAP) to premature newborns. These researchers found that plasticizer loss increased over time and that the tubing changed in color and flexibility after only a few hours of use. The changes in flexibility and color are consistent with a loss of plasticizer from the PVC tubing.

# Human Exposure to DEHP

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Research indicates that the most important routes of human exposure to DEHP are through products, and not through direct manufacturing facility emissions (KemI, 1997). Since DEHP is not chemically bound to PVC products, it can leach into air, water, and soil during use and disposal. Humans can be exposed through inhalation of DEHP in air, ingestion of DEHP in water, and through contaminated food. They can also receive exposure through medical devices. Thus, humans are exposed to DEHP through multiple sources and routes: ingestion, inhalation, and intravenously. Since DEHP is widely dispersed in the environment, direct human exposure from medical devices should not be considered in isolation. Assessment of human health risk from DEHP should consider additive and cumulative exposures to DEHP, in addition to other physical conditions or chemical exposures which may interact with DEHP.

## General population DEHP body burdens

Humans undergoing long term medical treatment may receive doses of DEHP that are or near doses that cause adverse effects in laboratory animals or cultured cells. Environmental exposures add to these direct medical device exposures. Humans may also receive large doses of DEHP at critical junctures in development. There is great uncertainty and variability as to the exact dose that any specific patient will receive and the relevance of that dose to possible adverse health effects.

The Agency for Toxic Substances and Disease Registry (ATSDR) reports that DEHP was detected in 31% of 46 composite human adipose tissue specimens analyzed for the National Human Adipose Tissue Survey at levels up to 850 ppb (ATSDR, 1993). Twenty-five different phthalates were detected in six cord blood samples taken from newborns in the UK in varying quantities (Howard, 1995), meaning that phthalates may be passed from mother to fetus across the placental barrier. The ubiquitous nature of DEHP and other phthalates means that humans receive exposures starting inside the womb, through a variety of sources, some greater than others. These exposures persist throughout the human lifespan. Thus identifying a population that has not been exposed to DEHP or does not carry a DEHP body burden may be difficult.

The human exposure to DEHP caused by its ubiquitous nature in products and the environment has led the National Center for Environmental Health (NCEH) at the U.S. Centers for Disease Control to embark on a multi-year national survey of phthalate metabolites in the U.S. population (Brock, personal communication, 1999). Due to their concerns regarding human exposure to DEHP, other phthalates, and the potential for adverse health impacts as a result of this exposure, NCEH researchers will spend several years examining exposure and trying to link these exposures to targeted outcomes and populations. Of concern to NCEH researchers are reproductive and other developmental impacts on children. The researchers have found that analysis of human exposure to phthalates is complicated by the variability in measurements and the ubiquity of the phthalates in the environment.

## Environmental exposures to DEHP

DEHP has been considered a priority environmental pollutant by governments in North America and Europe (Wams, 1987) due to its ubiquity in the environment. Phthalates in general are considered to be among the most universal of all environmental pollutants. Phthalates have been found throughout the globe, from the air above the open ocean, to the ocean floor, to the Andes Mountains in Bolivia. DEHP has been found globally in air, precipitation, water, sediment, biota, food, animals, and the human body (Toppari, et al., 1996).

DEHP enters the environment throughout its entire life cycle: during its production, use, and disposal. According to the U.S. Toxics Release Inventory, more than 500,000 pounds of DEHP were released to the environment from manufacturing facilities in 1997 (U.S. EPA, 1999). Swedish studies have found that some 17 million pounds of phthalates are released to the environment in Western Europe each year. Indoor and outdoor use of PVC products account for the greatest percentage of phthalates released to the environment, primarily to air, but some to water (KemI, 1997). Estimates of the amount of DEHP released by products in use range from 0.1% per year when in direct contact with air to 1% per year when in direct contact with water (Peakall, 1975 as cited in Wams, 1987). Berndtsson (1982, as cited in Department of the Environment, 1991) found that 0.35% of annual phthalate consumption would be released to the atmosphere from articles in use, with a further 0.15% entering aquatic systems. While these percentages appear small, Leah (1977, as cited in Department of the Environment, 1971) noted that despite uncertainty in estimating the overall environmental burden of phthalates, given the large quantities of phthalates used in PVC products, the environmental contamination could be considerable.

Once emitted to the air, only small portions of DEHP are photo-oxidized, meaning that the substance can be transported long distances over air currents. The majority of DEHP is deposited either in soil or water. In the latter case, DEHP is readily adsorbed to organic particles on the water's surface because of its lipophilic properties. Suspended in water (under aerobic conditions), the half-life of DEHP (the time for half of the DEHP to degrade) is around 2-5 weeks (Department of Environment, 1991). DEHP's half-life in sediments has been estimated to be over 100 years due to its very low degradation in water (Wolfe, 1980, as cited in Department of Environment, 1991). Thus, although DEHP has been demonstrated to be easily biodegraded in laboratory experiments, the fact that most of the chemical deposited in water is 'captured' by particulate matter makes DEHP unavailable for biodegradation (Baughman, 1980).

### *Exposure through air*

Exposure to DEHP via inhalation of ambient air is generally considered a minor source of human exposure, except in certain indoor settings. DEHP is a viscous liquid at room temperature, and its low vapor pressure ( $6.2 \times 10^{-8}$  mmHg at 25 °C) makes it slow to vaporize. However, indoor inhalation exposure may be significant in two settings: (1) in industries in which PVC is formulated or where PVC products are manufactured; and (2) in residential and office environments where there has been extensive use of PVC products, especially construction materials. These higher indoor levels may be a result of slow vaporization of phthalates from PVC products such as floorings, wall coverings, shower curtains, and furniture. The National Institute for Occupational Safety and Health (NIOSH) estimated that 340,000 workers were potentially exposed to DEHP in industrial settings in the early 1980s (ATSDR, 1993). Workplace air levels of DEHP have been measured ranging from 0.02 to 4.1 mg/m<sup>3</sup> at facilities using or manufacturing the compounds. The U.S. Agency for Toxic Substances and Disease Registry (ATSDR) estimated that U.S. average airborne human exposure to DEHP from PVC products is approximately 0.4 µg/day (as cited in Oie, et al., 1997).

The ATSDR report only considered exposure to DEHP through vapor, which could underestimate overall exposure. Oie et al. (1997), demonstrated that the residential exposure to DEHP through the amount adsorbed onto airborne suspended particulate matter may be one to three fold higher than the estimated daily vapor phase exposure in the general population (Oie, et al., 1997). Several commentators have noted the difficulty in quantifying indoor air exposure to DEHP. Wams (1987) and Oie, et al. (1997) note that small children are at risk of being more heavily exposed to DEHP through indoor air because they spend most of their time indoors, their rooms are smaller, and per unit body weight they have a respiration rate twice that of adults.

### *Exposure through food*

Ingestion of contaminated food is the primary route of DEHP exposure in humans. DEHP has been found in foodstuffs such as meat, fish, and milk and its derivatives (Wams, 1987). Sources of food contamination by DEHP include: direct environmental contamination (e.g. fish ingesting contaminated water); manufacturing the food product (e.g. use of PVC milk tubing); and leaching from food contact with PVC packaging (Wams, 1987). According to Wams (1987), Dutch residents are exposed to 0.5 to 0.8 mg DEHP per day, and the Japanese population is exposed to 2.0 mg DEHP each day by food contamination. ATSDR estimates that the average American ingests some 0.25 mg of DEHP each day through food (ATSDR, 1993). It has been estimated by the International Programme on Chemical Safety (1992) that the average intake of DEHP via food contamination is about 0.3 mg per person per day and the maximum daily intake is 2 mg per person.

In the case of small children, ingestion of DEHP may also occur through chewing or sucking on PVC products, especially toys. While the U.S. toy industry has eliminated its use of DEHP in toys, the plasticizer is still found in some toys produced and sold in other countries (Stringer, et al., 1997).

### *Exposure through water*

Humans can be exposed to DEHP through drinking water. DEHP levels of 0.04-30 parts per billion have been found in the drinking water of some U.S. cities. This corresponds to an average daily intake of DEHP from water of 0.02 mg. Drinking water from wells near landfills, production facilities, or waste sites could result in higher than average exposures (ATSDR, 1993).

## **Exposure through medical devices**

In addition to human exposure to DEHP through food, indoor air, and water, certain sub-populations are at higher risk of being exposed to DEHP and its metabolites through PVC medical devices. PVC medical devices containing DEHP as a plasticizer are used extensively in modern health care facilities in examination gloves, blood bags, intravenous bags, tubing, artificial heart valves, and catheters. DEHP has been found to leach from intravenous bags, blood bags, tubing (endotracheal and transfusion) and catheters into the solutions and blood products transported by these devices. This greater exposure source is particularly relevant for individuals who are ill, and therefore potentially less able to cope with any toxicant exposure.<sup>4</sup>

### *Leaching from blood bags into blood products*

A 1972 survey of DEHP toxicity outlined the evolution of concerns regarding DEHP leaching into medical products (Autian, 1972). The authors noted that as early as 1960, Meyler Willebrands, and Durrer reported that certain types of PVC tubing used in rat heart experiments would release additives affecting the

heart. The authors were unclear whether this effect was caused by the phthalate plasticizer, or organotin stabilizers, or both. Braun and Kummell in 1963 (as cited in Autian, 1972) reported that PVC blood storage containers released phthalate esters as well as other additives to extracting water. In 1967, Guess, Jacob, and Autian (as cited in Autian, 1972) published results on chemical contamination of a number of U.S.-produced blood bags containing anticoagulant solution. All of the anticoagulant solutions stored up to one year in these bags contained concentrations of phthalates.

Numerous other investigators have noted that PVC devices can release DEHP into blood and solutions, with the quantity of plasticizer extracted greater for solutions with a higher lipid (fat) content (Autian, 1972). Jaeger and Rubin (1970) found that blood and its anticoagulant solution may contain 6 mg of DEHP per 100 ml after being stored in PVC blood bags for 21 days at 4 degrees Celsius. A 1972 study by the same authors (Jaeger and Rubin) found that DEHP was extracted from PVC blood bags by human blood at the rate of 2.5 mg/liter per day at 4 degrees Celsius. Wams (1987) showed that DEHP migrates rapidly from the PVC into the blood, resulting in a concentration of 5-10 mg/100ml in blood which has been stored for several weeks. Additional researchers such as Trimble et al. (1966), Guess and Haberman (1968), and Marcel and Noel (1970) found leaching of DEHP from blood bags into blood products. For example Marcel and Noel found leaching of DEHP from PVC blood bags into human blood plasma at a level of 11.5 mg/100 ml of plasma after 21 days of storage.

While Autian (1972) noted that newer PVC containers may be less prone to leaching due to improved production processes, more recent studies indicate that DEHP migration occurs with even newer PVC medical devices (Chawl and Hinberg, 1991, ATSDR, 1993). In a 1996 survey of DEHP health risks, Huber et al. reported that duration of storage, lipophilicity of the surfaces of the storage container, the extent to which the container is filled, and temperature all affect the speed of DEHP migration from blood bags (Huber, et al., 1996). They found that whereas a blood preparation stored in DEHP for 72 hours at 4 degrees Celsius had a DEHP concentration of 100 mg/l, the concentration reached 300 mg/l at 22 degrees Celsius. DEHP migration decreased significantly at -20 degrees Celsius. The uptake of DEHP into the blood bag did not appear to occur in a linear manner, but showed a faster initial phase. These authors provided an overview of the ranges of DEHP migration from PVC medical devices into blood and blood products (Table 1). They also examined levels of mono-ethylhexyl phthalate (MEHP), a primary metabolite of DEHP thought to be responsible for much of the chemical's toxic effects (see Chapter 3 for further discussion).

**Table 1: Migration of DEHP from PVC medical products into blood and blood products**

| Material              | 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               | 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       |             |

Source: Huber, et al., 1996

NR = Not reported

### *Leaching from medical tubing*

Jaeger and Ruben (1970) found that up to 1.5 mg of DEHP was extracted from hemodialysis tubing during 8 hours circulating in human blood. Easterling, et al. (1974, as cited in Gibson, et al., 1976) found that up to 13mg of DEHP can be extracted from medical grade polyvinyl chloride tubing by 500 to 700 ml of fresh human blood over a six hour period. Schneider, et al. (1989), found DEHP to leach from tubing used in Extra Corporeal Membrane Oxygenation Therapy (ECMO) at a rate of 3.5 µg/ml per hour after 48 hours and 4.1µg/ml per hour after 84 hours. Latini and Avery (1999) found that DEHP leached from endotracheal tubing and that plasticizer loss increased with increasing intubation time. These results are consistent with studies on PVC milk tubing which have found DEHP leaching into cow milk samples (Castle, et al., 1990).

### *Leaching from intravenous bags into solutions*

Certain drugs may cause DEHP to leach from PVC intravenous (IV) bags into solutions. Pearson and Trissel (1993) found that DEHP was leached from PVC IV bags into numerous drugs and drug components (solvents and surfactants). The researchers tested numerous drug and solvent solutions for DEHP content after storage in PVC intravenous bags for 4, 8, and 24 hours. Leaching into drugs such as Dioxinor cyclosporine or the solvent Polysorbate 80 ranged from 3.1 to 237.7 µg/ml after a 24 hour period. Detectable leaching began in as little as one hour and increased over the 24 hour test period. Shaking did not appear to increase leaching but increasing the concentration of the surfactant or solvent did. On the other hand, some studies, such as Smistad, et al. (1989) have demonstrated that agitation of PVC bags containing common solutions significantly increases migration of DEHP into the solutions. Pearson and Trissel concluded that “drugs that leach DEHP should be prepared in non-PVC containers and administered through non-PVC tubing.”

In his *Handbook on Injectable Drugs*, Trissel (1998) identified a wide range of drugs that have been shown to increase the leaching of DEHP from IV bags (Table 2). These results have been repeated by other researchers (Mazzo, et al., 1997). Trissel noted that “the presence of surface-active agents or large amounts of organic co-solvents in the formulation may enhance leaching of the plasticizer (Trissel, 1998).” The leaching of DEHP into the fluids contained in PVC enteral feeding bags has apparently not been studied. The nutrient fluids used in these bags have a high lipid content, which would likely increase the leaching of DEHP. People using these feeding bags often use them for prolonged periods, thus potentially increasing their DEHP exposure.

Taxol (used to treat AIDS-related Kaposi’s sarcoma, ovarian, and breast cancer) is an example of a drug that fits these characteristics. Taxol’s instructions for preparation for intravenous administration include this paragraph (Bristol Myers Squibb Co, 1998):

Data collected for the presence of the extractable plasticizer DEHP [di-(2-ethylhexyl) phthalate] show that levels increase with time and concentration when dilutions are prepared in PVC containers. Consequently, the use of plasticized PVC containers and administration sets is not recommended.

A similar warning exists for the cancer medication Taxotere (Docetaxel). Manufacturers of both medications recommend that the solutions be prepared and stored in glass or polyolefin bottles and administered with non-PVC or polyethylene-lined administration sets.

**Table 2: Some drugs that have been shown to increase the leaching of DEHP from PVC plastic into solution**

|                    |   |
|--------------------|---|
| Chemotherapeutic:  | Etoposide (VePesid), Paclitaxel (Taxol), Teniposide (Vumon) |
| Antianxiety:       | Chlordiazepoxide HCL (Librium)                              |
| Antifungal:        | Micronazole (Monistat IV)                                   |
| Immunosuppressive: | Cyclosporine (Sandimmune) and Tacrolimus (Prograf)          |
| Nutritional:       | Fat Emulsions and Vitamin A                                 |

Source: Trissel, 1998

DEHP that has leached into medical solutions may interact with those solutions, affecting delivery of the appropriate amount of therapeutic drugs and thus altering their effects on humans. These interactions may have important implications for patients and have received little research attention. Petersen, et al. (1975) found that DEHP may compete for the same binding protein sites as the drug dicumarol, significantly increasing the coagulation time of mouse blood. This occurred following intraperitoneal administration of DEHP, when combined with the intravenous administration of dicumarol. The researchers noted that “caution should be exercised in patients on anticoagulant therapy if they are exposed to DEHP.” Petersen et al. (1975) also demonstrated that DEHP increases hexobarbital (a barbiturate) sleep time in rats by increasing the retention time for hexobarbital (due to DEHP’s lipophilic characteristics). Mahomed, et al. (1998) found that the concentration of the drug diazepam (Valium) fell to around 80% in glass and to 50% in a PVC container after four hours and to an even lower concentration in the PVC container after eight hours. While not implicating DEHP leaching directly, the authors concluded that “the present study is reported so as to alert clinicians of this effect and to promote efforts to utilize non-PVC bags and the shortest possible infusion sets.”

The leaching of DEHP from PVC IV bags is not limited to some pharmaceutical agents and solvents. Leaching may also occur into sterile water or any salt or sugar-based solution contained in PVC plastic. The information sheets for Abbott Laboratories PVC IV bags as well as Baxter Healthcare Corporation’s Viaflex plastic containers both include language that describes the bags as being made of “specially formulated polyvinyl chloride that can leach out small amounts of the plastic’s chemical components.” These advisories have not changed during 30 years, as shown by a 1972 Travenol Laboratories (now Baxter) label for Viaflex Plastic Containers (Autian, 1972). On that label DEHP was estimated to leach up to 5 parts per million (5 µg/ml). In a 1995 study, Baxter Healthcare noted that DEHP can reach concentrations of 5 ppm in intravenous fluids, confirming the earlier reports (Baxter Healthcare).

A 1994 article in the *Journal of Intravenous Nursing* found that hospital staff may not be aware of leaching of DEHP from IV products and may not routinely read package literature that directs the use of non-PVC products (Noah and Godin, 1994). This may result in certain lipid-based products, such as alimentary fat emulsions, being administered inappropriately in PVC bags to chronically ill patients (including pregnant patients who receive parenteral nutrition) for extended periods of time. The authors concluded that “although PVC plastic has a valuable role in the provision of medical care because of its low cost and flexibility, it is nevertheless evident that many infusates leach DEHP from PVC in sizable amounts with toxic results and caution is advised. ... Cost-containment, versatility and convenience are important aspects of modern health care, but not at the expense of safe, risk-free therapy.”

### ***Leaching from medical devices into human serum and tissues***

A number of studies have demonstrated that DEHP leached from medical devices into blood products and medications is delivered to and stored by animals and humans. It has been measured in the blood of patients undergoing cardiac bypass, those receiving platelet transfusions, hemodialysis patients and infants receiving whole blood transfusions, mechanical ventilation, or umbilical catheterization. According to Huber, et al. (1996) and other researchers, human exposure to DEHP through medical treatments can be substantial.

DEHP and its metabolites have been identified and measured in human tissue and serum in studies dating back to 1970. Studies have identified human exposure to DEHP in patients receiving dialysis, blood transfusions, artificial ventilation, and exchange transfusions. Premature infants receiving medical care may be exposed to DEHP during critical periods of development. Total DEHP exposure measured or estimated in these studies varies significantly, even among patients undergoing the same treatment, although the exact reasons for this variability are unclear. Differences in study design and conditions, dialysis protocol, or DEHP content in devices, may play a role in this variability. A recent study (Faouzi, 1999) found that a large percentage of the DEHP leached from tubing during dialysis may not be retained by the human body. This finding adds another layer of uncertainty to the exact DEHP doses to which some chronically ill patients might be exposed. Some studies indicate that multiple exposures to DEHP may result in a cumulative body burden of the chemical. A cumulative body burden might have implications in terms of DEHP toxicity in humans and would complicate efforts to understand doses at which adverse effects might occur in humans. A summary of results from various DEHP leaching studies is presented in Table 3.

Jaeger and Rubin (1970) raised concerns about DEHP leaching from blood bags into humans when they detected DEHP in the tissues of patients who had received transfusions of stored blood. The researchers examined tissues from the autopsies of 13 patients who had died after receiving blood transfusions (6 of them after cardiopulmonary-bypasses) using PVC blood bags. The researchers detected DEHP in lung tissues in 7 of 12 patients at concentrations of 13.4 to 91.5 mg/kg, and detected DEHP in liver, spleen and abdominal fat. Based on their research, they calculated that a whole body exchange transfusion, as occurs with cardiopulmonary bypass surgery, in a 70 kg male with 21 day old blood would result in the intravenous administration of approximately 300 mg of DEHP.

In a study on immature rhesus monkeys, Kevy and Jacobson (1982) transfused animals with platelet rich or platelet poor plasma contained in PVC blood bags either once or twice weekly over six months or one year. Transfusions were undertaken in a manner identical to that used in clinical treatment. They found that the amount of DEHP the animals received ranged from 56 to 1500 mg over a one year period. No DEHP was infused to animals receiving transfusions from polyethylene blood bags. In a small secondary experiment, the researchers tested DEHP plasma concentrations in humans undergoing intensive plasma exchange. These patients received from 3.3 to 11.6 mg of DEHP during a single two plasma volume plasma exchange. It was estimated that the patients could receive from 87.5 to 290 mg per year of DEHP from this process.

Lewis, et al. (1978) found that the mean post-dialysis DEHP concentration in patients undergoing hemodialysis was 751 µg/liter of serum (range: 250 to 1,946 µg/liter). They estimated (after a 1 hour in-vitro perfusion) that 3.23 mg of DEHP was extracted into the blood from tubing and a total of 6.10 mg from the tubing plus the artificial kidney. The DEHP level rose in all patients during the dialysis period, peaking up to three hours after dialysis. Post-dialysis blood concentrations of DEHP decreased significantly in the 5 hours following dialysis. According to the authors, the 750 µg/l dose of DEHP would result in an annual dose of at least 250 mg in the case of a patient dialyzed twice per week. Many factors, including hematocrit, platelet counts, lipid concentrations, and hepatic function, may influence the actual concentrations of DEHP found in the serum. The researchers noted that as renal excretion is a major

pathway for excreting DEHP and its metabolites, much of this 250 mg, in addition to the DEHP absorbed during the dialysis, may accumulate in patients who lack kidney function.

Other researchers have found varying results in investigations of DEHP exposure from dialysis. In a review on the phthalate esters and their effects on the liver, Ganning, et al. (1984) found that depending on conditions, the amount of DEHP transferred to a patient during one dialysis session could range from 100 to 300 mg. They concluded that “independent of possible toxic effects of phthalates, such a high concentration in medical practice is not desirable.” Kevy and Jacobson (1982) found that total DEHP delivered to three patients during a single dialysis session ranged from 32 to 90 mg. These authors found that because the rate of leaching of DEHP from PVC is dependent on temperature and lipid content of the media, dialysis patients who characteristically have elevated serum lipids would be at an increased risk compared to chronically transfused patients.

Gibson, et al. (1976) studied nine patients who had been on dialysis for periods ranging from 1 to 156 weeks at the following times: prior to dialysis, at several points during dialysis and immediately following dialysis. In five of the nine patients, no measurable DEHP was detected in the predialysis venous blood samples. The estimated total amount of DEHP delivered to each patient during hemodialysis ranged from 1.5 mg (after 15 minutes) to 150 mg (after 5 hours). The authors assumed that their exposure probably came from dialysis tubing.

In a study of eleven maintenance hemodialysis patients, Pollack, et al. (1985a) found that the average patient would receive approximately 105 mg of DEHP per session. This would result in a range of 3.7 to 56 g of DEHP over the course of a year, assuming a three times per week treatment schedule. Time averaged circulating concentrations of the primary metabolite MEHP during dialysis (roughly equivalent to the systemic arterial concentration) ranged from 0.9 to 2.83  $\mu\text{g}/\text{ml}$ , similar to those found for DEHP (0.34 to 3.67  $\mu\text{g}/\text{ml}$ ). Levels of DEHP and MEHP in serum did not appear to depend on the length of time of the dialysis treatments. The researchers noted that their results “indicated substantial exposure to DEHP during hemodialysis and that the de-esterified products [metabolites] of DEHP are present in significant concentrations in the systemic circulation.”

Faouzi, et al., 1999 studied the migration of DEHP from dialyzers in 21 patients undergoing maintenance hemodialysis for chronic renal failure. The researchers found that during treatment of renal failure using DEHP-plasticized PVC tubing, the plasma levels of DEHP in the patients increased with time. An average of 75.2 mg of DEHP was extracted from the dialyzer during a single dialysis session. However, the total amount of DEHP retained by the patient during the dialysis session ranged from 3.6 to 59.6 mg, meaning that a substantial percentage of the DEHP was likely removed by the dialyzer. The rate of DEHP extraction was moderately correlated with the serum lipid content. The researchers concluded that “patients on hemodialysis are always regularly exposed to considerable amounts of DEHP.... DEHP leached during the dialysis session could be easily avoided by careful selection of hemodialysis tubing.”

DEHP exposures to premature and ill newborns occur through blood transfusions, extracorporeal membrane oxygenation therapy (ECMO)<sup>5</sup>, or respiratory therapy. For example, Lundburg and Nilsson (1994) found that newborn infants can be exposed to more than 4 mg per kg of DEHP per day through blood transfusions. These infants receive among the highest doses of DEHP from medical devices.

Schneider, et al. (1989) found that the rate of extraction of DEHP during ECMO resulted in “unprecedented neonatal exposure to DEHP.” Serum levels of DEHP found in two infants after 14 and 24 days of ECMO support were 26.9 and 33.5  $\mu\text{g}/\text{ml}$ , respectively. DEHP levels of 3.5, 1.0 and 0.4  $\mu\text{g}/\text{gr}$  were found in the liver, heart, and testicular tissues, respectively, of an infant who had died 6 days after undergoing ECMO therapy for 7 days; trace quantities were found in the brain. The authors estimated that exposure of a 4 kg infant after ECMO support for 3-10 days would range from 42-140 mg/kg. This compares to 1.9 mg/kg

expected from hemodialysis and platelet transfusion and 0.5 mg/kg for whole blood transfusion. The authors concluded that alternative tubings for ECMO circuits should be considered. In a study of a larger group of infants (29 infants) supported with ECMO for various ailments, the same group of researchers (Schneider, et al., 1991) found DEHP serum levels ranging from 18-98 µg/ml after 3 to 15 days of therapy.

In a study involving six newborn infants receiving exchange transfusions for hyperbilirubinemia, Sjoberg, et al. (1985a) found that from 1.7 to 4.2 mg/kg body weight (per day) DEHP was infused into infants during the transfusions. Immediately after transfusions, plasma levels of DEHP in the infants ranged from 3.4 to 11.1 µg/ml. Concentrations of the DEHP metabolite MEHP infused into the infants ranged from 0.2 to 0.7 mg/kg body weight per transfusion, and post-transfusion plasma MEHP concentrations varied from 2.4 to 15.1 µg/ml. Exposures to infants, according to the authors, were similar to those expected in an adult receiving a blood transfusion. They concluded that until work has been done to determine whether the risks of deleterious effects from DEHP exposure are higher in infants than adults, "it seems logical to take measures to minimize DEHP exposure during early life."

In another study of infants receiving multiple exchange transfusions for erythroblastosis, these same researchers (Sjoberg, et al, 1985b) found that during a single exchange transfusion, the amounts of DEHP and MEHP infused ranged from 0.8 to 3.3 mg/kg and from 0.05 to 0.20 mg/kg body weight, respectively. Maximal plasma levels of MEHP were about 5 µg/ml, and the presence of MEHP in serum continued for a relatively long period following transfusions (24 hours or longer). The researchers noted that up to a few milligrams of DEHP per kilogram body weight may be transferred to a newborn infant during an exchange transfusion. Those infants who are given blood products (as a result of surgery) or ECMO in addition to exchange transfusions may be exposed to large cumulative amounts of DEHP. Since as much as 30% of the infused DEHP may have originated from parts of the transfusion set other than the blood bag, the authors recommended the use of alternative materials in extension tubing and blood warmer units in addition to blood bags.

Plonait, et al. (1993) examined sixteen newborn infants receiving exchange transfusions for levels of DEHP. The researchers found that DEHP levels were undetectable before exchange but ranged from 6.1 to 21.6 µg/ml of serum after a single exchange transfusion. Between 12.5%-26.5% of the plasticizer was eliminated with the waste blood. In one preterm infant, DEHP could be detected in plasma even 94 hours after transfusion. No correlation was found between the serum DEHP concentration immediately after each transfusion and the blood volume exchanged.

Hillman, et al. (1975) examined levels of DEHP in heart and gastrointestinal tissue of stillborn infants and infants who underwent intensive neonatal care using umbilical catheters, but who subsequently died up to six months after birth. The researchers found significantly higher concentrations of DEHP in heart tissue from the intensive care study group (1.27 µg/g) than in the stillborn controls (0.07 µg/g). Significantly higher levels were associated with larger amounts of blood products and more extensive use of catheters. Three children who died of necrotizing enterocolitis and who had received arterial umbilical catheterization had gut residue DEHP levels ranging from 0.16 to 0.63 µg/g. One infant studied had a heart residue DEHP level of 0.80 µg/gr after five months, indicating that clearing may not occur rapidly in this population. The researchers hypothesized that prematurity and low postnatal age may alter rates of clearance. The authors concluded that while the adverse effects of DEHP are being evaluated, "thought should be devoted to possible alternatives that do not make potentially toxic substances available to tissue."

Roth, et al. (1988) studied DEHP migration from PVC respiratory tubing systems in five mechanically ventilated preterm infants.<sup>6</sup> This was the first study to examine DEHP loss from a respirator tubing system with heated and humidified air flow. The researchers found concentrations of DEHP in condensate contained in the water traps of respirator tubes ranging from <1 to 4,100 µg/l. They estimated inhalation

DEHP exposure to range from 1 to 4,200 µg/hour. DEHP appeared to have accumulated in the lung tissue of one infant studied at autopsy.

The researchers found that at temperatures of approximately 30 degrees Celsius, DEHP showed a significant transition into the gaseous phase and was apparently swept off the inner surface of the tubes by the air stream. They concluded that because of the possible association between DEHP exposure from respiratory tubing and adverse respiratory and other outcomes in infants, "...it seems appropriate to limit the use of DEHP containing plastic tubing systems for mechanical ventilation of preterm infants and neonates until this matter has been investigated satisfactorily (Roth, et al., 1988)."

In their analysis of DEHP health risks, Huber, et al. (1996) prepared a summary of available studies on the leaching of DEHP from medical devices into the human body (Table 3). These results are corroborated by previously described in-vitro studies demonstrating variable levels of DEHP extraction from dialysis, transfusion, and ECMO therapy. The highest exposures to patients originate from hemodialysis, although ECMO and blood transfusions might lead to a higher short term DEHP burden. Hemodialysis results in long term exposure. The studies examined found that 23% to 70% of the DEHP that entered the patients' bodies through dialysis or blood transfusion remained after treatment (Huber, et al., 1996).

**Table 3: 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        |
| Blood transfusions in newborns            | NR                  | 0.05-0.7          | Treatment period |
| Extracorporeal oxygenation in infants     | NR                  | 42.0-140.0        | Treatment period |
| Cardiopulmonary bypass                    | 2.3-168             | 0.03-2.4          | Treatment day    |
| Artificial ventilation in preterm infants | NR                  | 0.001-4.2         | Hour             |
| Peritoneal dialysis                       | 40                  | 0.8               | Year             |
| Platelet concentrates in adults           | 26-175              | 0.4-2.5           | Treatment period |
| Clotting factors in hemophiliacs          | 2                   | 0.03              | Day              |
| Exchange transfusions in infants          |                     | 0.8-4.2           | Treatment        |

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

Several investigators have found that DEHP has a membrane stabilizing function that prolongs the storage time of red blood cells. By binding to red cell membranes, DEHP appears to have a protective effect against hemolysis in red blood cells. This binding, according to Rock, et al. (1986), means that previous estimates of the levels of plasticizers to which patients are exposed may have been underestimated, because calculations were based primarily on plasma concentrations, without considering sequestering on the surface of red blood cells.

As previously noted, human exposure to DEHP in the general population is reported to range from 0.5 to 2.0 mg DEHP per day (Wams, 1987). However, a single 4-hour-hemodialysis session may expose a patient to 180 times more DEHP than these general population levels. For example, the Swedish Chemical Inspectorate (KemI, 1997) cited sources that calculated that acute exposure through blood and plasma transfusion can result in up to 120 mg DEHP per liter of blood; treatment on a heart/lung machine can result in exposure to DEHP of up to 14 mg/kg per day; and chronic exposure via dialysis can result in 370 mg per treatment.

## Toxicity of DEHP in Animals and Humans

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The previous section has shown that patients can be exposed to DEHP during dialysis, transfusions, ECMO and ventilation therapy. This section reviews the adverse effects of DEHP and its metabolites, in particular MEHP, on several organ systems including the reproductive system, the kidney, the heart, the lungs, and the liver. These correspond with the organs where DEHP has been found following blood transfusions. Results from some key studies on the toxicity of DEHP on different organ system are summarized in Table 4.

Most of the information about the toxicity of DEHP comes from toxicological studies on animals, with DEHP administered usually at relatively high doses. To determine whether an exposure to a chemical is harmful to humans, direct human evidence is the most useful, but this is very hard to come by because it is obviously not ethical to conduct experiments in humans, and, observation of humans exposed through daily life is difficult for a variety of reasons. Moreover, it is difficult to link delayed effects with earlier exposures.

As previously noted, despite its high volume use in PVC products, the effects of long term human exposure to DEHP from medical devices is not well understood. This is true even though scientists contracted by the National Institutes of Health in the 1970s noted this lack of data and recommended to government agencies that studies be undertaken to follow dialysis patients for adverse health effects (Petersen, et al., 1975). The lack of evidence of harm in humans does not indicate that DEHP is safe. Cairns (1999) stated that “while high uncertainty may obscure both the probability of a risk and the magnitude of harm, uncertainty does not eliminate risk.” Failure to accumulate sufficient human evidence of an effect is not the same as evidence that no such link exists. The nature of exposures may be hard to find (or highly variable) and adequate follow-up of all exposed people throughout their lifetimes may not occur (Davis and Gerry, 1999).

Because epidemiologic data are rarely available to determine whether a substance might cause harm to human populations, scientists turn to toxicological data, generated in controlled experiments in laboratory animals. In such experiments, scientists can control exposures to laboratory animals and follow them over time to identify adverse effects. A fundamental precept of toxicology is that a researcher must test a substance at high doses to ensure that the study has sufficient “power” to find adverse health effects should they exist. Rare diseases caused by toxic substances are difficult to identify without high dose testing in very large numbers of animals. The results from animal testing at high doses are then extrapolated to human exposures at lower doses. In toxicology, the results obtained from animal testing, supplemented by in-vitro (in the test-tube or dish) testing on human and animal cell lines, are generally considered relevant to humans, though the magnitude and types of effects may vary between species. When a substance has been shown to be toxic in laboratory animals, it is often later shown to be toxic in humans unless metabolic pathways in animals are very different.

**Table 4: 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/<br>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             |

## **Disposition of DEHP**

The absorption, distribution, metabolism and excretion of DEHP have been extensively studied in rats, primarily after oral exposure, although disposition following inhalation, dermal, and intravenous exposures have been studied to a limited degree. Primates absorb DEHP from the gut less readily than rodents (Rhodes, et al., 1982). Younger animals may absorb DEHP to a greater degree than adults (Gray and Gangolli, 1986). Once absorbed, DEHP is widely distributed throughout the body. Fat, absorptive organs (gastrointestinal tract) and excretory organs (liver, kidney, gastrointestinal tract) are the major initial repositories for DEHP (Kluwe, 1982 and KemI, 1998). The heart, spleen, reproductive organs, lungs, muscles, and brain have also been shown to be repositories for DEHP and its metabolites (KemI, 1998, Jaeger and Rubin, 1972). Distribution of DEHP appears to be qualitatively similar across species (KemI, 1998). Distribution of the primary DEHP metabolites, while less well studied, is likely to be similar to that of DEHP (Klewe, 1982, KemI, 1998).

Several studies indicate that DEHP can cross the placental barrier and distribute into fetal tissues. After a single dose of DEHP was administered to pregnant female rats, DEHP appeared in the placenta, fetal tissue and amniotic fluid within 24 hours (Singh, et al., 1975, as cited in USCPSC, 1985 and KemI, 1998). DEHP can also be distributed through breast milk into infants (KemI, 1998).

Metabolism is the process of modifying a substance in the body so that it is more easily excreted (for example, breaking it down into smaller molecules or making it more water soluble). The extent to which different DEHP metabolites are produced and excreted depends upon the species, the age of the animal, prior exposure to DEHP, the amount of DEHP administered, and the administration route (KemI, 1998). High levels of administered DEHP may saturate liver biotransformation capacity (Syracuse Research, 1982).

DEHP is initially broken down to mono-ethylhexyl phthalate (MEHP) and 2-ethylhexanol (2-EH), primarily by hydrolysis in the lining of the intestinal tract. However, hydrolysis also occurs in the kidneys, lungs, plasma, pancreas and fat. Researchers have proposed that the toxicity of phthalates is governed to a great degree by the properties of these hydrolysis products, particularly MEHP (Lake, et al., 1977, Foster, 1997, Li, et al., 1998). Lake, et al. (1977), concluded that the hydrolysis of phthalates is qualitatively similar between the rat, the ferret, the baboon, and humans, though it may differ somewhat quantitatively. These researchers suggested that all three animal models studied would be suitable for assessing the toxicity of phthalate diesters to humans.

Approximately 80% of an oral dose of DEHP in rats undergoes hydrolysis into MEHP and 2-ethylhexanol, while only about 1% of intravenously administered DEHP is converted (Pollack, et al., 1985). This means that intravenous exposure to DEHP may lead to less MEHP exposure and therefore less toxicity than an orally administered dose. Despite this, DEHP in stored blood has been demonstrated to undergo at least some hydrolysis to MEHP (Vessman and Rietz, 1978, Sjoberg, et al., 1985a,b, Huber, et al., 1996). MEHP has also been identified in the blood and tissues of human adults undergoing hemodialysis and neonates undergoing exchange transfusions (Pollack, et al., 1985a, Sjoberg, et al., 1985 a,b). Pollack et al. (1985a) found that time averaged circulating concentrations of MEHP during dialysis were similar to those of DEHP, which might be explained by altered metabolism of DEHP during renal failure or slow biotransformation after systemic intake of DEHP. Thus, humans are exposed to MEHP as a result of exposures from DEHP-containing medical devices.

The liver appears to be the main organ for further metabolism of MEHP and 2-EH, occurring through many pathways, which differ across species. The organ toxicity of each of these metabolites, numbering more than 10, is largely unknown. Rats and mice metabolize MEHP and 2-EH primarily by

oxidation while in primates, and to some degree mice, glucuronidation is the primary pathway (Ganning, et al., 1984, KemI, 1998, Klewe, 1982, Crocker, et al., 1988). Research indicates that metabolite profiles of DEHP, as measured in urine and feces, are roughly similar across species, although metabolites are excreted in different quantities (Rhodes, et al., 1986, KemI, 1998). Animal studies are thus likely to be useful in understanding the consequences of human exposure to DEHP.

The metabolism of DEHP appears to be age-dependent. Several studies have identified differences in DEHP metabolism between adults and neonatal and elderly animals (Roth, et al., 1988 and Gollamudi, et al., 1983). Infants, with immature metabolic pathways, can differ significantly from adults in their glucuronidation capability (Kawade and Onishi, 1981). Plasma levels of MEHP decreased more slowly than DEHP levels in infants receiving exchange transfusions (Sjoberg, et al., 1985 a,b). A preterm infant may experience much higher post-transfusion plasma MEHP levels than one born at term (Sjoberg, et al., 1985 a,b). Animal studies have shown that the additional metabolism of MEHP into simpler breakdown products in the fetal rat liver is less efficient than in the neonatal or adult rat liver (Plonait, et al., 1993). The implications of these age-related differences in metabolism not fully understood, but it is likely that they contribute to the susceptibility of the developing organism to DEHP toxicity (see page 25).

The effects of impaired renal function and other illnesses on DEHP metabolism and excretion are largely unexplored.

## Acute toxicity

The acute toxicity of DEHP is relatively low, with an LD<sub>50</sub> (the amount of the substance required to kill 50% of laboratory animals in an experiment) of greater than 25 g/kg in rats and 30 g/kg in mice (Lundburg and Nilsson, 1994). Much lower LD<sub>50</sub> values (200-250 mg/kg) were reported following intravenous administration to rats. However, Petersen, et al. (1975) identified an LD<sub>50</sub> of 1400 mg/kg for mice and 2080 mg/kg in rats administered DEHP intravenously. They found the acute toxicity of MEHP to be approximately five times that of DEHP (240 mg/kg in mice and 415 mg/kg in rats). A sub-acute LD<sub>50</sub> of 355 mg/kg was identified in mice fed DEHP 3 times per week over a one month period (Petersen, et al., 1975). Data on adult animals indicate that the liver is the primary target tissue for toxic effects following acute oral exposure, although the kidney and testes may also be affected. Single non lethal oral doses of DEHP (2 g/kg) caused an increase in liver and brain weight in rats after 7 days, although the weights and gross pathology of other organs was not affected (Syracuse Research, 1982).

## Reproductive and developmental toxicity

Reproductive toxicity testing identifies effects on reproductive systems that may result from exposure to environmental agents. Adverse effects may include altered onset of puberty, gamete production and transport, reproductive cycles, sexual behavior, fertility, gestation, lactation, pregnancy outcomes, or reproductive senescence. Developmental toxicity testing examines a broad range of endpoints, beginning with fertilization and continuing throughout maturation into adulthood. In their most complete form, developmental toxicity studies examine functional as well as structural abnormalities.

Studies undertaken since the 1940s have demonstrated the toxicity of DEHP to the reproductive tract and developing fetus in laboratory animals. These effects, generally observed at high doses, range from decreased or complete loss of spermatogenesis in male mice and rats, to inhibition of the function of

estrogen-producing granulosa cells in female rats, to developmental and teratogenic effects in the offspring of rodents exposed in utero. They may not be identifiable until well after the birth of the organism and may be passed on to offspring. Although most studies of reproductive and developmental effects of DEHP attempt to identify a threshold of exposure below which adverse effects are not seen, recent work demonstrates that subtle effects, not previously examined for, occur at even lower levels.

### *Testicular toxicity*

DEHP has been recognized for decades as a testicular toxicant (Autian, 1972, Syracuse Research, 1982, Agarwal, 1986; Douglas, 1986). Evidence of testicular toxicity related to DEHP reported in the literature includes: reductions in relative testis weight; decreases in the production and quality of sperm; depletion of testicular zinc; testicular, seminiferous tubule and epididymal atrophy; and testicular interstitial-cell tumors. The testicular toxicity of DEHP appears to be mediated by MEHP (Foster, 1997). Studies indicate that the Sertoli cells (the nurse cells to immature sperm cells and critical to the blood testis barrier) are the likely target for male reproductive toxicity of DEHP and MEHP.

While most of the effects of DEHP on the male reproductive tract have been demonstrated at high doses, some studies have found testicular effects at lower levels, near those at which a human might be exposed from medical devices (Arcadi, et al., 1998). Studies have found a greater sensitivity of DEHP-induced testicular toxicity in immature animals than adults, indicating that testicular development during the fetal and neonatal period may be particularly sensitive to relatively low levels of DEHP (Li, et al., 1998, Gray and Gangolli, 1986). Moreover, while adverse effects on the testes identified in adult animals appear to be reversible (Huber, et al., 1996), this may not be the case when animals are exposed to DEHP in utero or as neonates (Oishi, 1985, Arcadi, et al., 1998).

### *Studies in adult animals*

Early studies conducted on adult animals found DEHP exposure to result in atrophy to the seminiferous tubules and testes. For example, one study found these effects when rats were fed from 0.9 to 1.9 g/kg body weight per day DEHP in diet for 90 days (Shaffer, et al., 1945 as cited in Autian, 1972). A review of the literature identified six studies prior to 1980 where rats fed high doses (0.2% to 2.0% of the diet) of DEHP over short periods of time developed a wide range of dose-dependent male reproductive abnormalities ranging from absence of spermatogenesis and atrophy of the testes, to seminiferous tubular atrophy (Syracuse Research, 1982). Another study (Agarwal, et al., 1986) reported a dose-dependent and significant reduction in testes, epididymis and prostate weights at a dose of 5,000 mg/kg in diet for 60 days. At 20,000 mg/kg severe atrophy of the seminiferous tubules, sperm abnormalities and a loss of spermatogenesis were observed. The researchers suggested that DEHP exerts its testicular toxicity by causing a zinc deficiency (by selectively removing testicular zinc from spermatids) which in turn reduces the production of gonadotropins including testosterone, resulting in gonadotoxicity. Testicular toxicity led to a decrease in litter size when male rats exposed to DEHP were mated to virgin and unexposed female rats (Lamb, et al., 1987).

One study (Kurata, et al., 1997) reported no change in testis/body weight ratio or blood levels of testosterone in mature marmosets fed high levels of DEHP (100-2500 mg/kg per day for 13 weeks). Hormone levels were not reported.

### *Studies in neonatal animals and the developing fetus*

Several studies indicate that DEHP testicular toxicity is an age-dependent event (Gray, 1980; Gray and Gangolli, 1986; Sjöberg, 1986). Immature animals appear to exhibit more severe effects at lower doses,

and with earlier on-set, and these effects appear to be less reversible than in adult animals (Foster, 1997, Arcadi, et al., 1998). For example, one study reported that seminiferous tubular atrophy and reductions in seminal vesicle and prostate weight occurred when 4-week-old rats were fed 2,800 mg/kg per day DEHP in diet, but it did not affect 15-week-old mature rats (Gray and Gangolli, 1986). The basis of the age-related susceptibility is not completely clear. Sjöberg and colleagues (1986) proposed that age differences in testicular toxicity might be due to differences in the metabolism and absorption patterns of DEHP and MEHP. They proposed that immature animals have higher MEHP absorption rates than mature ones. However, others have noted that an intrinsic difference in tissue susceptibility cannot be ruled out (Gray and Gangolli, 1986).

Research indicates that in-utero and neonatal exposure to DEHP can lead to multiple, irreversible effects in offspring, sometimes at relatively low doses. A single high dose of 750 mg/kg per day in diet from day 14 of gestation to day 3 of nursing resulted in a wide range of adverse effects on the male reproductive tract (Gray, et al., 1999). These included: 90% of offspring with testicular or epididymal atrophy or agenesis and 67% with hypospadias. The researchers noted that the testis is a direct target of DEHP, which affects the reproductive system by a mechanism that is distinct from many other reproductive toxicants.

Studies at lower doses have also led to demonstrable adverse effects, raising concerns about medical treatment during pregnancy and for premature infants and neonates. Poon, et al. (1997) found that young male rats fed 37.6 mg/kg body weight per day DEHP for 13 weeks experienced some Sertoli cell vacuolation. Animals receiving 375 mg/kg per day had atrophy of the seminiferous tubules with complete loss of spermatogenesis. Arcadi, et al. (1998) found that the male offspring of female rats exposed to 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 severe dose-dependent histological damage to the testes at both dose levels. These abnormalities included disorganization of the seminiferous tubule structure and the absence of spermatocytes and were only slightly reversible. They were not observed in adult male rats exposed to the same concentrations of DEHP.

#### *In-vitro studies*

Various *in-vitro* studies provide some indication as to the mechanisms by which male reproductive toxicity occurs. The target for male reproductive toxicity of DEHP is the Sertoli cell, resulting in a subsequent detachment of germ cells from the Sertoli cell monolayer (Gray and Gangolli, 1986, Foster, 1997). The Sertoli cell is the principle testicular site of action for follicle stimulating hormone (FSH), which is necessary for the initiation of spermatogenesis and many of the normal functions of Sertoli cells. *In vitro* exposures in the range of 1 to 100  $\mu$ M (approximately 270-27000  $\mu$ g/l) MEHP inhibit the ability of FSH to stimulate the second messenger CAMP (cyclic adenosine monophosphate), essential for Sertoli cell function. The effects on Sertoli cell structure and function lead to loss of spermatogonia, causing a subsequent impairment in fertility (Gray and Gangolli, 1986, Foster, 1997).

Li, et al. (1998) found that low level MEHP exposure can affect neonatal rat Sertoli cell/gonocyte interactions in an *in-vitro* system. This interaction is essential to the normal maturation of sperm. At concentrations of 0.01, 0.1, and 1.0  $\mu$ M MEHP, the investigators found that gonocytes began detaching from Sertoli cells in the cell-culture prematurely (within hours) and that Sertoli cell proliferation was lowered. Importantly, none of the concentrations used showed any change in the morphology of the Sertoli cells; the effect was on the interaction of the Sertoli cells with the gonocytes. The lowest effective dose in this experiment was 0.1  $\mu$ M, which corresponds to about 27  $\mu$ g/l. While the implications of MEHP interference with the Sertoli Cell/gonocyte interactions during critical developmental periods are not well

understood, the importance of this period to long term sperm development is generally accepted, and any adverse functional outcome would not become apparent for years.

### *Ovarian toxicity*

Adverse effects on the female reproductive tract related to DEHP exposure have been observed in laboratory animals. Exposure of adult, regularly cycling female rats fed 2 g/kg DEHP for 1 to 12 consecutive days resulted in: prolonged estrous cycles, suppressed or delayed ovulation, smaller preovulatory (PO) follicles, and suppressed estradiol production (Davis, et al., 1994). The researchers proposed that DEHP exerts its effects by affecting preovulatory follicle granulosa cells, which are the primary source of estradiol in the fertile rat, leading to a cascade of effects that ultimately suppresses or delays ovulation but does not appear to lead to direct ovarian toxicity. They concluded that these results in adult female rats raise concern for effects in humans because the ovarian functions of women follow a similar ovulatory cycle.

Younger, six week old mice raised on a diet containing 0.1% to 0.3% DEHP (both males and females) for seven days prior to and during a 98 day cohabitation period experienced dose-dependent decreases in fertility and in the number and proportion of pups born (Lamb, et al., 1987). Mating of exposed females with unexposed males resulted in a lack of fertility and significant decreases in the weights of the female reproductive organs (ovaries, oviducts, and uterus), although histological lesions in the reproductive tract were not observed.

An *in vitro* study suggested that MEHP is the active metabolite responsible for a decrease of estradiol production in preovulatory follicles (Davis, et al., 1994a). The researchers proposed that MEHP alters the existing levels or availability of aromatase, an enzyme responsible for the transformation of testosterone into estradiol in the granulosa cells, which may explain the decreased estrogen levels *in-vivo*. This occurs independent of follicle stimulating hormone (FSH) activity. The authors also proposed that MEHP suppresses the production of follicle-stimulating hormone (FSH) which stimulates cyclic adenosine monophosphate (c-AMP) in cultured rat granulosa cells. The accumulation of c-AMP is necessary for the production of progesterone, a hormone that plays a crucial role in implantation and pregnancy maintenance in both rodents and human beings. Treinen, et al. (1990) found that rat granulosa cells lost up to 40 percent of their ability to stimulate c-AMP accumulation when these cells were exposed to 100  $\mu$ M (approximately 27,000  $\mu$ g/ml) of MEHP for 24 hours.

### *Embryotoxicity/fetotoxicity*

Numerous studies have shown that DEHP is capable of crossing the placental barrier and can be toxic to the developing fetus. These effects generally occur at relatively high doses. The types of fetotoxic and teratogenic effects induced by DEHP include: a decrease in kidney and testes weights in offspring; histological damage to kidneys, liver and testes; developmental (learning) difficulties; spontaneous abortions; decreased implantation; heart malformations; hydronephrosis; misplaced digits; open neural tubes; exencephaly; and fetal death. Some of these effects may be subtle and difficult to recognize until later in life.

DEHP may be metabolized in the mother's body with its metabolites then passed through the placenta, rather than being hydrolyzed in the fetus (Tomita, et al., 1986). MEHP, 2-EH, and a secondary DEHP metabolite, 2-ethylhexanoic acid (2-EXHA), are thought to be responsible for DEHP's embryotoxicity (Ritter, et al., 1987, Tomita, et al., 1986). DEHP administration resulted in alterations in both maternal and embryonic zinc metabolism, suggesting a possible mechanism for its embryotoxic effects (Peters, et al., 1997). These effects are consistent with those observed in studies of experimentally induced zinc deficiency. Research indicates that these effects may not be reversible by supplementing the diet with zinc (Oishi et al., 1983).

One review identified nine embryotoxicity and teratogenicity studies on DEHP prior to 1980 (Syracuse Research, 1982). High doses of DEHP fed during certain days of or throughout gestation resulted in a range of embryotoxic and teratogenic effects. At least two studies (one oral and one peritoneal administration) identified embryotoxic and teratogenic effects at doses ranging from 2.5 to 10 mg/kg per day during days 5 to 15 of gestation. However, one study administering DEHP intravenously at doses ranging from 1.3 to 4.7 mg/kg per day on days 6 to 15 of gestation did not identify any adverse embryotoxic or teratogenic effects (Syracuse Research, 1982).

In one study, single oral doses of 0.1, 0.5 or 1 ml/kg administered to pregnant mice resulted in dose- and time-dependent adverse outcomes in the fetus, including a marked decrease in the litter size (number of live births) and malformation in all live fetuses (gross and skeletal abnormalities) (Tomita, et al., 1986). The researchers noted that a single injected dose of MEHP resulted in a significantly higher incidence of somatic mutations in the coat hair of offspring of mice. In another study, pregnant mice fed 1000 mg/kg DEHP on gestational days (GD) 8 and 9 had reduced mean maternal body weight on GD 18 and a significantly lower number of live pups compared to controls (Peters, et al., 1997). More than 40% of the fetuses of treated animals had external abnormalities, mainly exencephaly. The mean number of embryos examined on GD 10 with a visible heartbeat was significantly lower in the DEHP treated mice; mean crown-rump length was shorter; the percentage of live embryos was lower; and the incidence of open neural tubes was higher in exposed compared to unexposed mice.

Two studies show that DEHP exposure combined with exposure to other common toxicants may result in additive or synergistic effects. Narotsky, et al. (1995) found DEHP to exert synergistic fetotoxic and teratogenic effects on rats when administered by gavage with two common chemicals, trichloroethylene (an industrial solvent) and heptachlor (a pesticide). Each chemical demonstrated developmental toxicity by itself, with differing toxicological profiles. The DEHP-heptachlor combination was synergistic for maternal toxicity. The DEHP-trichloroethylene combination showed synergistic effects on prenatal loss, maternal weight gain, pup weight, and full litter resorption. No three way interactions were detected. In study on rats given a single dose of DEHP and its metabolites 2-EH and 2-EHXA, Ritter, et al. (1987) found that the teratogenic effects of all three compounds are potentiated by caffeine when administered orally to pregnant rats. For example, maternal exposure to caffeine, in addition to DEHP, increased the percentage of malformed fetuses from 20.8% to 72.9%.

## **Nephrotoxicity of DEHP**

Since the 1950s, research has suggested a role for DEHP in renal toxicity. Two research groups found that long term, low dose experimental animal exposure to DEHP resulted in kidneys that were described at autopsy as being “swollen” and “cloudy” (Crocker, et al., 1988). Early studies also found renal cysts in the offspring of mice who had been fed phthalates (Onda, et al., 1974 as described in Crocker, et al., 1988).

Oral dosing of rats at approximately 2.15 mg/kg body weight of DEHP three times per week over one year resulted in significantly reduced kidney function (as measured by creatinine levels) and increased focal cysts when compared to controls (20 controls/25 exposed) (Crocker, et al., 1988). These exposure levels were designed to mirror upper bound exposure levels for a dialysis patient undergoing a 5 hour dialysis session. In a large mouse study, animals fed high concentrations of DEHP in their diet (12,000 ppm) showed renal toxicity after 4-8 weeks of feeding and moderate lesions after 24 weeks. Lesions included focal tubular degeneration, atrophy and regenerative tubular hyperplasia, and cystic renal tubules. No lesions in other tissues indicative of renal failure were observed (Ward, et al, 1988).

An examination of DEHP levels in normal and pathological human kidneys at autopsy found only two of 15 normal kidneys had measurable levels of phthalates, but phthalates were found in the two nephrosclerotic kidneys examined (Overturf, et al, 1979). While the significance of this observation is unknown, the researchers noted that effects observed in laboratory animals indicate a possible relationship between phthalate exposure and adverse effects on the kidney.

In an examination of the nephrotoxic effects of DEHP metabolites on cultured kidney epithelial cells (opossum kidney cells), researchers found that MEHP caused a dose-dependent decrease in cell viability and that MEHP concentrations greater than 25  $\mu\text{mol/l}$  (approximately 6.8 mg/l). resulted in a dose-dependent shrinkage of the cells and a high occurrence of cell death (Rothenbacher, et al., 1998). These effects were not observed for 2-EH. The authors speculated that MEHP primarily causes a loss in cell membrane integrity.

Based on a 104 week rat study finding an increase in absolute and relative kidney weight in both sexes and increased mineralization of the renal papilla in males, the Swedish Chemical Inspectorate (KemI, 1998) has reported that the lowest no observable adverse effects level (NOAEL) for kidney toxicity in from DEHP is 28.9 mg/kg/day.

## Cardiotoxicity of DEHP

Several studies have indicated that DEHP and its metabolite MEHP may be toxic to the heart. Cardiac surgery patients may receive direct cardiac exposure to DEHP through the cardiac bypass circuitry. As early as 1960 in isolated rat heart experiments, scientists noted that certain types of PVC tubings would release additives that would affect the heart (Autian, 1972).<sup>7</sup> Jaeger and Rubin (1972) reported that DEHP levels of 0.4 mg/100ml were lethal to chick-embryo beating heart cells maintained in tissue culture. More recent *in-vivo* and *in-vitro* studies have indicated that MEHP causes dose-dependent and possibly reversible effects on the heart and vascular systems. The mechanism by which DEHP and MEHP exert their effects on the heart are not well understood.

An examination of the acute cardiac effects of MEHP in five anesthetized rats injected via the femoral artery found a steady and significant decrease in heart rate beginning after a total dose of 20 to 30 mg and a decline in blood pressure after a total dose of 40 to 50 mg of MEHP (Rock, et al., 1987). This resulted in eventual cardiac arrest. No observable effects levels were established at 10 mg for heart rate (28.5 mg/kg body weight) and 55 mg for blood pressure. Based on an estimated safety level (with safety factors) for cardiotoxic effects of 0.03 mg/kg, the researchers estimated that a hemorrhaging patient in a well-equipped trauma unit might receive a dose considerably higher than this level (up to 1.3 mg/kg for a 70kg male).

These results have been confirmed in *in-vitro* studies. A study on the isolated rat heart found that DEHP concentrations from 0.05 to 0.5% pumped through the heart affected both the rate and amplitude of heart beats (Petersen, et al., 1975). Higher concentrations immediately produced a sharp decline in heart rate and amplitude, eventually stopping the heart after several minutes. Longer contact with test solutions resulted in longer recovery times. A study examining MEHP effects on pulmonary artery pressure (PAP) in a rat heart lung preparation found that MEHP exerts a significant hypertensive effect on the pulmonary vasculature ending in constriction and edema (swelling and leakage) (Labow, et al., 1990). The concentration of MEHP in the rat lungs after perfusion varied from 20 to 40  $\mu\text{g/g}$ . Despite the results of these studies, the relevance of these *in-vitro* results to human toxicity remains unclear.

In a human study of the health effects of DEHP exposure, (Plonait et al. 1993) failed to identify notable changes in blood pressure or heart rate among infants receiving exchange transfusions from a PVC circuit. Serum DEHP levels in these infants ranged from 6.1 to 21.6  $\mu\text{g/ml}$ .

## Pulmonary Toxicity of DEHP

Several studies indicate that DEHP may reach the lungs during infusion and mechanical ventilation. For example, Jaeger and Rubin (1972) measured DEHP in tissues of humans at autopsy. The subjects had received cardiopulmonary bypass or multiple transfusions. Lung tissue concentrations of the chemical were among the highest of any tissue sampled. Other studies have shown that MEHP and DEHP accumulate in the lungs of rats after intravenous administration (Oie, et al., 1997).

Studies in animals have demonstrated that DEHP is toxic to the lungs at sufficiently high doses. Research indicates that MEHP may be responsible for these effects (Oie, et al., 1997). 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). Histological damage was observed at doses of 50 mg/kg body weight (Huber, et al., 1996). The pulmonary pathology was characterized by an inflammatory state commonly referred to as “shock lung.” Huber and colleagues (1996) have noted that in the course of mechanical ventilation, infants might receive levels of DEHP exposure similar to those causing effects in laboratory animals.

Researchers have hypothesized that MEHP causes pulmonary toxicity by mimicking the inducing prostaglandins and thromboxanes (inflammatory mediators) in the lungs, affecting bronchial contracting receptors and increasing inflammation in the airways (Oie, et al., 1997).

A study examining the effects of DEHP exposure from PVC respiratory tubing systems on three mechanically ventilated preterm infants found that, after initial improvement due to the respiratory therapy, all three developed pathological changes in the lungs resembling those observed in hyaline membrane disease (Roth, et al., 1988). The condition was characterized by a significant increase in inspired oxygen concentration, respiratory rate and maximal inspiratory pressure. It could not be explained as the usual lung damage after artificial ventilation, leading the researchers to suggest the possibility of a causal relationship between worsening of the condition of the patients and inhalation exposure to DEHP. There were no indications of shock lung, pulmonary hemorrhage, or pneumonia in the patients. Inhalation exposures ranged from one to 4200 µg/hour. Symptoms in two of the infants subsided after PVC tubing was substituted with DEHP-free ethylene vinyl acetate tubing.

In a matched case-control study comparing 251 children with bronchial obstruction to controls without this condition Jakkola, et al. (1999) found a statistically significant association between risk of bronchial obstruction in the first two years of life and the presence of PVC flooring (an 89% increased risk of bronchospasm/wheezing if the floor covering of the residence contained PVC) and textile wall coverings, adjusting for potential confounders.<sup>8</sup> Further analysis revealed an exposure-response relationship between the estimated amount of PVC and other plasticizer-containing surface materials in the home and the risk of bronchial obstruction. The researchers concluded that plasticizers emitted from PVC materials may increase the risk of early childhood bronchial obstruction.

## Hepatotoxicity of DEHP

The liver is one of the most important and common targets of DEHP toxicity. It is the site of DEHP accumulation and the major site for DEHP metabolism in the body. Studies in various animal species have demonstrated that when animals are fed DEHP or its metabolites, a variety of liver effects occur, changing the structure and function of the organ. These occur through changes in various aspects of liver cells including: the formation of peroxisomes — organelles in cells that carry out numerous biochemical func-

tions; induction of mitochondria; and protein and lipid turnover (influencing the synthesis and breakdown of macromolecules in the liver) (Ganning, et al., 1984, 1987). DEHP exposure also leads to the formation of liver tumors in animals. Timing and chronicity of dosing appears to play a role in the liver toxicity of DEHP (Ganning, et al., 1984, 1987). Some studies have identified non-carcinogenic liver abnormalities in primates and humans undergoing medical treatment for life threatening illnesses.

### *Non-carcinogenic effects on the liver*

Researchers have identified several non-carcinogenic liver abnormalities in rodents, rhesus monkeys and humans related to DEHP exposure. One study found that DEHP administered in diet to adult male rats at 2.0, 0.2 and 0.02% for 102 weeks, resulted in changes in liver lipid metabolism resulting in cell membrane destabilization (Ganning, et al., 1984, 1987). These effects were found to be dose and time dependent and cumulative (low doses over time exert effects similar to higher doses given over shorter periods). Moore (1996, as referenced in Keml, 1999) found that the lowest observable adverse effects level and no observable adverse effects level for non-carcinogenic liver abnormalities (peroxisome proliferation and increased liver weight) in mice fed DEHP in diet for 104 weeks were 98 and 19 mg/kg body weight per day, respectively.

Studies on immature rhesus monkeys receiving plasma transfusions from DEHP-containing PVC blood bags over a six month or one year period resulted in a trend of abnormalities in liver histology (cell damage) and function that persisted up to 26 months after treatment (Jacobson, et al., 1977 and Kevy and Jacobson, 1982). The researchers did not observe these effects in either control monkeys or those receiving the same transfusions using polyethylene-stored platelets (another plastic not containing DEHP). The monkeys in this study, designed to mimic clinical conditions, received total yearly doses of DEHP ranging from 50 to 1500 mg. While the number of subjects was small (5 exposed, 5 controls in one experiment and 7 exposed, 7 control in another), the researchers calculated that human hemodialysis patients would be exposed to as much as 10 to 20 times as much DEHP than that which produced hepatic toxicity in the rhesus monkeys.

A study of liver biopsies from patients undergoing hemodialysis two to three times per week found that after one year of dialysis peroxisome proliferation did occur in the human liver. Such liver abnormalities were not observed after one month of dialysis, and the patients had not received any drugs known to have peroxisome proliferating effects. Based on their observations and review of the literature, the researchers suggested “the possibility that even small doses of phthalate esters may have a cumulative effect reaching the effect level of high doses if intake is continued over a sufficiently long time period.”

A study of infants receiving extracorporeal membrane oxygenation therapy (ECMO) raised the question of whether cholestasis (a condition characterized by impaired excretion of bile from the liver into the biliary system), which is found in many infants supported by ECMO, might be directly or indirectly related to DEHP exposure from ECMO tubing (Schneider, et al., 1991). In a study of 29 infants with serum DEHP levels of 18 to 98 µg/ml DEHP following a 71 to 300 hour ECMO treatment period, the researchers found that total hemoglobin, maximum free hemoglobin, and DEHP levels were significantly associated with the degree of cholestasis, though these did not correlate with duration of ECMO support. Other clinical factors that were hypothesized to be potential risk factors for cholestasis were not found to be related to the observed degree of cholestasis. The researchers concluded that DEHP may be related to cholestasis secondary to hemolysis (breakdown of red blood cells), resulting in a large bilirubin load with inhibited excretion.

However, Plonait, et al. (1993) failed to find an increase in cholestasis among 15 infants undergoing single or multiple exchange transfusions, though the children in their study were exposed to lower plasma levels of DEHP over a shorter period of time than those reported by Schneider, et. al (6.1 to 21.6 µg/ml measured in blood after a single transfusion).

### *Carcinogenic effects*

Early studies to investigate liver carcinogenicity failed to demonstrate an association in rats (Carpenter, 1953; Harris, 1956). These investigations suffered from inadequate study designs. In 1982, the U.S. National Toxicology Program (NTP) conducted a study with an improved study design (including, for example, more animals and better survival rates) and found that DEHP caused hepatocellular tumors in rats and mice of both sexes (Kluwe, 1982). The results of this bioassay represented the beginning of a new set of concerns about DEHP hazards. Subsequent studies have confirmed these findings and identified DEHP as a liver carcinogen in rodents.

However, DEHP is a member of a class of compounds called peroxisome proliferators. Exposure to these chemicals causes the development of peroxisomes in the liver of rodents much more readily than in higher mammals, and many investigators believe that peroxisome proliferation is an essential requirement for the subsequent development of liver cancer (Huber, et al., 1996). Studies in mice bred to lack one of the receptors necessary for peroxisome proliferation show much less hepatic response to DEHP exposure (Ward, et al., 1998). Consequently, many investigators believe that DEHP may be a liver carcinogen in rodents but that it does not pose the same hazard in humans because of this fundamental species difference. Some regulatory agencies, for example, in the European Union, have taken DEHP off their lists of likely human carcinogens for this reason. However, uncertainty about the absolute necessity for peroxisome proliferation as a step toward cancer development remains. This matter is further discussed in the next metabolism section.

But despite this concern, and based on animal cancer data, the U.S. Agency for Toxic Substances and Disease Registry has determined that DEHP “may reasonably be anticipated to be a carcinogen” (ATSDR, 1993) in spite of the absence of any direct human data linking DEHP exposure to cancer. According to ATSDR, the majority of animal cancer bioassays have shown dietary DEHP to be hepatocarcinogenic in both rats and mice at doses ranging from 0.3% to 0.6% in feed, comparable to doses of approximately 350 and 700 mg/kg respectively (because of food spillage, these figures are imprecise). A composite analysis of the data available through the early 1980s concluded that DEHP “has been shown to be carcinogenic to rodents in a valid chronic test, indicating that it should be considered as a potential carcinogen in humans (Kluwe et al, 1983).”

A Chronic Hazard Advisory Panel for the U.S. Consumer Product Safety Commission (US CPSC, 1985) concluded that the evidence is sufficient to establish the carcinogenicity of DEHP for rats and mice and that in the absence of adequate data on humans, “it is reasonable to regard DEHP as presenting a potential carcinogenic risk to humans.” These conclusions were also reaffirmed by the International Agency for Research on Cancer (IARC) in their labeling DEHP as a class 2B carcinogen (limited evidence of carcinogenicity). An expert panel convened in 1988 (Schulz, 1989) concurred that the results of the carcinogenicity bioassays of DEHP in rats and mice showed that it was carcinogenic, and that it is appropriate to classify the chemical as a “probable human carcinogen.” The panel members could not justify, on scientific grounds alone, the selection of any particular model for dose-response or estimation of a virtually safe dose. The panel found the body of evidence incomplete regarding whether the carcinogenic response in rodents is predictive of a similar response in humans (i.e., the mechanism of effect).

The most recent and comprehensive analysis of the carcinogenicity of DEHP in rodents is contained in a draft risk assessment conducted by the Swedish Chemical Inspectorate for the European Union (KemI, 1999). In this review, KemI analyzed some 12 different cancer bioassays in adult rats and mice exposed to DEHP through diet over a large percentage of their lives. The authors reviewed the recent large long term bioassays conducted by Moore (1996 and 1997, as cited in KemI, 1999) which confirmed the increased incidence of cancers in both male and female mice and rats exposed to DEHP. In these bioassays,

researchers observed a significant dose-dependent increase in hepatocellular neoplasms in male mice at a dose of 98.5 mg/kg per day and an increased incidence of hepatocellular adenomas in rats at 146.6 mg/kg per day, compared to controls. Based on their analysis the Swedish National Chemical Inspectorate concluded that DEHP is a hepatocarcinogen in mice and rats. KemI noted that the relevance of these results to humans are not fully elucidated.

## **Mechanisms of effects of DEHP**

The mechanisms by which DEHP may cause various adverse effects in diverse organs of laboratory animals and humans of varying ages are not well understood. These mechanisms are likely to be multiple and variable, depending on the health endpoint, the organ, the age, and species studied. In this section, a proposed mechanism of DEHP carcinogenicity, called “peroxisome proliferation” and its relevance to non-cancer health effects are discussed.

DEHP belongs to a class of chemicals called “peroxisome proliferators.” This class includes a diverse set of some 70 substances, including: industrial chemicals, such as trichloroethylene; herbicides, such as lactofen; other plasticizers such as diethylhexyl adipate; and hypolipidemic drugs (to lower the risk of cardiovascular disease) such as clofibrate (Reddy and Lalwai, 1983, Citron, 1995). Peroxisome proliferators differ widely in their quantitative ability to induce peroxisome proliferation.

Peroxisomes are cell membrane organelles, present in all cells, that contain enzymes responsible for the oxidation of fatty acids, the biosynthesis of cholesterol, and other biochemical pathways (Reddy and Lalwai, 1983, KemI, 1997, 1999). These enzymes include: hydrogen peroxide generating oxidases, catalase (which catalyses the degradation of hydrogen peroxide), and a fatty acid oxidation enzyme (KemI, 1999). Respiration, gluconeogenesis, lipid metabolism, and other metabolic functions have been attributed to peroxisomes (Reddy and Lalwai, 1983). Peroxisome proliferation is characterized by an increase in the volume of peroxisomes (in number and possibly size), changes in peroxisome morphology, and induction of peroxisomal enzymes, leading to a cascade of effects that can ultimately lead to organ toxicity (Reddy, et al., 1984, KemI, 1999). The role of peroxisomes in organ toxicity and mechanisms by which peroxisome proliferation ultimately leads to cancer and other effects are less well understood.

At least two theories have been proposed for the mechanism by which peroxisome proliferators, such as DEHP, cause liver cancer in laboratory animals: (1) through the induction of peroxisome proliferation, leading to oxidative stress and the generation of electrophilic free radicals, ultimately indirectly causing damage to DNA; and (2) through increased hepatocyte proliferation and suppression of hepatocellular apoptosis (programmed cell death) which could lead to proliferation of previously existing DNA damage (KemI, 1999, Gonzalez, et al., 1998). Controversy over the mechanism of effects of peroxisome proliferators has centered primarily on their ability to induce liver tumors. Mechanisms by which peroxisome proliferators might induce toxicity in organ systems other than the liver have not been generally proposed.

One of the proposed theories for the mechanism by which peroxisome proliferators cause hepatic tumors is by causing genetic mutations indirectly by increasing intracellular hydrogen peroxide (Gonzalez, et al., 1998). Peroxisome proliferators markedly increase peroxisome fatty acid beta-oxidation as well as the peroxide generating enzyme acyl-CoA but only slightly increase catalase (which degrades hydrogen peroxide) (Gonzalez, et al., 1998). This leads to a sustained oxidative stress due to an imbalance in the production and degradation of hydrogen peroxide (KemI, 1999). Thus, hydrogen peroxide could escape the peroxisome and react with cellular macromolecules causing genetic mutations (Gonzalez, et al., 1998).

However, there is evidence suggesting that the level of oxidative damage in animals may be too low to account entirely for the carcinogenicity of peroxisome proliferators (KemI, 1999). Also, although peroxide-modified lipids have been found in the hepatocytes of peroxisome proliferator treated rats, more sensitive indicators of oxidative damage have not consistently been affected. While oxidatively damaged DNA in the form of 8-hydroxydeoxyguanosine (a specific and sensitive indicator of oxidative DNA damage) has been detected in the livers of rats chronically exposed to different peroxisome proliferators, a quantitative relationship between peroxisome proliferator induced carcinogenicity and oxidative DNA base damage was not found (Cattley and Glover, 1993).

If the generation of hydrogen peroxide were required for carcinogenesis, one would expect a direct relationship between the potency of the chemical for peroxisome proliferation and its potency for hepatocarcinogenesis; such a relationship was not found when the strong peroxisome proliferator, WY-14,643 was compared to the weaker peroxisome proliferator DEHP (Gonzalez, et al., 1998). At doses that caused similar levels of peroxisome proliferation, WY-14,643 induced an earlier and much greater liver tumor response than DEHP (Melnick and Kohn, 1996). These results, taken together, have led researchers to conclude that oxidative DNA damage cannot fully explain the carcinogenic responses of peroxisome proliferators, and, as such, other hepatic responses may be more critical features of the mechanism of peroxisome proliferator carcinogenicity (Cattley and Glover, 1993, Gonzalez, et al., 1998, KemI, 1999, Melnick and Kohn, 1996).

The second of the proposed theories for peroxisome proliferator-induced carcinogenicity involves replication of hepatocytes and disruption of normal cell cycle regulation. This appears to occur independent of peroxisome proliferator-induced oxidative damage and may not be entirely regulated by the cellular receptor (peroxisome proliferator activated receptor) thought to mediate peroxisome proliferator-induced effects (see below) (Gonzalez, et al., 1998). Peroxisome proliferators appear to inhibit programmed cell death (apoptosis), a process by which genetically damaged cells self-destruct (Gonzalez, et al., 1998, KemI, 1999, Reddy and Lalwai, 1983). Inhibition of apoptosis could be responsible for the carcinogenic effects of peroxisome proliferators if genetically damaged cells destined for programmed cell death continue to replicate (Gonzalez, et al., 1998). An increased rate of cell proliferation caused by peroxisome proliferator-induced disruption of cell cycle regulation could lead to an increased frequency of spontaneous mutations and a promotion of initiated cells before they can be repaired (KemI, 1999). Both DEHP and MEHP have been shown to induce DNA synthesis and inhibit hepatocyte apoptosis in rats and mice in both in-vitro and in-vivo experiments (KemI, 1999). This cell proliferation appears to be dependent on the continuous administration of a peroxisome proliferator (Gonzalez, et al., 1998).

As previously noted, DEHP and other peroxisome proliferators have not been thought to be directly genotoxic. The reversibility of peroxisome proliferator induced carcinogenesis has been described, suggesting that DEHP may act as a tumor promoter rather than a tumor initiator (Cattley and Preston, 1995). However, genotoxic actions of DEHP cannot be completely ruled out. For example, 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. Mononuclear cell leukemia does not appear to be related to peroxisome proliferation (KemI, 1999). DEHP metabolites, MEHP and 2-EH, can be mutagenic under some circumstances and have also been associated with chromosomal damage including the induction of dominant lethal mutations in mice bioassays (Huber, et al., 1996). French researchers showed that DEHP is capable of inducing an enzyme (ornithine decarboxylase) which has been linked to the malignant transformation of cells (Dhalluin, et al., 1997).

Recent research has indicated that a class of nuclear receptors, called the peroxisome proliferator

activated receptors (PPAR) plays a central role in mediating the effects of peroxisome proliferators. In the presence of a peroxisome proliferator, the PPAR receptors induce the regulation of peroxisome proliferator responsive genes (KemI, 1999). Three PPAR receptors have been identified, the most important of which, and most studied, for hepatocarcinogenicity is PPAR-alpha, which is expressed at high levels in the liver and kidney, primary sites of peroxisome proliferation (Gonzalez, et al., 1998). The function and importance of the other PPAR receptors is relatively unknown. Studies in mice bred without the PPAR-alpha receptor ("knock-out" or PPAR null mice) indicate that, in the mouse, hepatocarcinogenicity of DEHP and other peroxisome proliferators is dependent on PPAR-alpha (mice without the receptor did not develop hepatic tumors) (Gonzalez, 1998, Ward, et al., 1998). This suggests that other PPAR receptors have a minimal role in mouse hepatocarcinogenesis.

The results of studies in "knock-out" mice raise questions as to whether hepatocarcinogenic responses observed in rodent studies are relevant to humans. Marked species differences in peroxisome induction following exposure to peroxisome proliferators has been observed (KemI, 1999, Cattley and Preston, 1995). Rats and mice appear to exhibit high sensitivity to peroxisome proliferators; non-human primates are weakly responsive; and guinea pigs and marmosets are not responsive, even to potent peroxisome proliferators (KemI, 1999, Gonzalez, et al., 1988). Nonetheless, one comparative study in cats, chickens, pigeons, and two species of monkeys (Reddy, et al., 1984) found that peroxisome proliferation occurred in all five species and that it was a dose-dependent rather than species-specific phenomenon.

Humans are relatively insensitive to peroxisome proliferators, although the mechanisms by which humans are resistant are not understood. The human response has been studied in patients taking peroxisome proliferating drugs. Liver biopsies of patients treated with hypolipidemic drugs did not reveal evidence of peroxisome proliferation (KemI, 1999, Gonzalez, et al., 1998). No evidence of hepatocarcinogenicity has been observed in limited clinical trials involving the hypolipidemic drugs clofibrate and gemfibrozil (KemI, 1999). It is unclear if the length of time during which patients were followed was sufficiently long to observe latent effects. Nonetheless, Ganning, et al. (1984, 1987) observed peroxisome proliferation in liver biopsies of patients undergoing dialysis through DEHP-containing PVC tubing. Also, peroxisome proliferators invoke a potent lipid-lowering response in humans that is the basis for the therapeutic efficacy of the fibrate drugs (Gonzalez, et al., 1998). This suggests that humans may have different levels of hepatic expression of PPAR-alpha, as lipid-lowering responses of fibrate drugs in rats are PPAR-alpha dependent (Gonzalez, et al., 1998). Research has shown that humans have less than one-tenth the levels of PPAR-alpha expression observed in mice (Gonzalez, et al., 1998, KemI, 1999). The spectrum of genes activated by PPAR-alpha may be dependent on cellular levels of the receptor. However, as humans do possess the PPAR-alpha receptor, lack of the receptor cannot explain the lack of peroxisome proliferation in humans after treatment with fibrate drugs (Gonzalez, et al., 1998). While quantitative species differences in peroxisome proliferation activity and hepatic effects following administration of peroxisome proliferators is generally accepted, the relevance to humans of peroxisome proliferator-induced effects in rodents and the mechanisms by which they occur are not fully elucidated.

In a review article on non-genotoxic carcinogens, Melnick and Kohn (1996) noted that interindividual variability in peroxisome proliferator receptors potentially could lead to different responses to these chemicals, as humans are responsive to peroxisome proliferators, albeit to a much lesser degree than rodents. They concluded that the mechanism by which peroxisome proliferators induce liver cancer is not fully understood, and it is thus not possible to conclude at this time that peroxisome proliferation alone is the cause of DEHP-induced liver cancer. According to Melnick and Kohn, attributing a chemical's

carcinogenicity solely to its ability to induce one effect (peroxisome proliferation) may obscure important contributions to its carcinogenic mechanism.

Activation of the PPAR-alpha cannot fully explain DEHP's effects in other organ systems and on the developing fetus. Two studies involving knock-out mice (Peters, et al., 1997, Ward, et al., 1998) demonstrated that DEHP can cause fetotoxicity, teratogenicity, and effects on the testis and kidneys in male mice independent of the PPAR-alpha receptor. That is, mice bred to lack PPAR-alpha still exhibit toxic effects associated with DEHP exposure. In the adult mouse, PPAR-alpha appeared to mediate the "early" toxicity of DEHP in the kidney and testes but signs of chronic toxicity in the knock-out mice were observed (Ward, et al., 1998). In the fetotoxicity study, similar effects were observed in mice with and without the PPAR-alpha receptor (Peters, et al., 1997). The authors in this study found that the mechanisms underlying alterations in maternal and embryonic zinc levels (proposed as a mechanism of fetotoxicity and teratogenicity) were not dependent on PPAR-alpha.

Some hypotheses about the testicular toxicity of DEHP metabolite MEHP have been proposed. Li et al. (1998) presented data which suggest that MEHP interferes with the important interaction between immature Sertoli cells and germ cells, but the mechanism by which that occurs is unclear. Other studies in young animals with more mature Sertoli cells suggest that MEHP interferes with the binding of follicle stimulating hormone (FSH) to its receptor on Sertoli cells (Lloyd and Foster, 1988). It may be that the mechanism of testicular toxicity of MEHP in the fetus or neonate differs from the adult.

While the mechanisms of reproductive, developmental, liver, kidney, and lung toxicity associated with DEHP exposure are actively being investigated, a thorough review of available evidence indicates that it is premature to conclude that these mechanisms of action are not relevant to humans. Multiple mechanisms of toxicity appear to exist for DEHP, and their relevance to each species or individuals within the species (depending on age and other potential determinants of susceptibility) is unknown.

Reproductive and developmental toxicity occur at least partly independent of the PPAR receptor. Thus, some other mechanism or mechanisms of action are operative and their relevance to humans cannot be ruled out. Mechanisms of pulmonary, kidney, and cardiac toxicity have been only minimally studied, although it appears that they are also independent of peroxisome proliferation. Liver toxicity appears to be the only toxic endpoint of DEHP for which there remains substantial debate about the relevance of animal studies to humans. Even liver carcinogenicity may well occur via more than one direct or indirect mechanism, about which there remains substantial debate (Citron, 1995).

In a recent analysis, the California Office of Environmental Health Hazard Assessment (OEHHA) stated:

OEHHA acknowledges that a substantial body of scientific literature concerning DEHP and the class of compounds known as peroxisome proliferators has developed in recent years, particularly with regard to the role of the peroxisome proliferator activated receptors (PPARs) and cell proliferation may play in the carcinogenic process. At this point...OEHHA does not find this new body of evidence 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 (OEHHA, 1999).

OEHHA based its decision on evidence that PPARs mediate a multiplicity of effects, evidence that humans have and express PPAR genes, and evidence that cellular events mediated by PPARs other than peroxisome proliferation and oxidative damage may be operative.

## **Calculating human risk from DEHP exposure**

Attempting to quantify the magnitude of human risk from exposure to DEHP is inappropriate at this time because of wide and poorly quantified variabilities in human exposures, a wide range of effects observed in different organ systems with differing dose-response curves, and differences in age-related susceptibility. Qualitatively, the data indicate that a wide range of toxic effects occur in laboratory animals, some near levels of DEHP exposure to which an individual patient might be exposed from PVC medical devices. It is unclear whether thresholds (exposure levels below which no adverse effects occur) for some of the types of organ toxicity observed in laboratory experiments exist.

Few risk assessments have been performed on the health effects of DEHP exposure from medical devices, other products or general environmental exposure. Those that have been done have focused almost entirely on cancer effects. Thus, risk assessments conducted to date have not generally considered non-cancer effects in humans, such as damage to the testes, ovaries, kidneys, heart, and lungs, particularly when exposure occurs in the fetus or developing infant. Most have failed to consider the full range of DEHP exposures (medical devices, food, consumer products) to which an individual might be exposed or varying susceptibilities depending on age or infirmity.

Some researchers have attempted to conduct partial cancer risk assessments of DEHP. For example, Wams (1987) estimated that the exposure of the average citizen to DEHP is of the same order of magnitude as an estimated safe level for cancer effects (116 mg/kg per day). The author noted that high risk groups, such as hemodialysis patients, may exceed this exposure level. In their 1985 risk assessment, the Consumer Product Safety Commission (USCPSC, 1985) found that, assuming no threshold and based on animal data, dietary DEHP exposure could represent a substantial portion of the total liver cancer deaths in the U.S. — 100-150 per year. The risks to dialysis patients and hemophiliacs from intravenous exposures to DEHP were estimated to be 10 to 30 times higher.

Huber and colleagues (1996) estimated the risk of liver cancer to maximally exposed dialysis patients. They found that these patients would have an exposure at least 15 fold below the lowest observable adverse effects level of any characterized peroxisome proliferation-specific effect and approximately 100-fold below this level for DEHP-related tumorigenesis. These results assumed that peroxisome proliferation is the main mechanism of liver carcinogenesis in humans. However, as previously noted, Melnick and Kohn (1996) and others have stated that serious uncertainties remain as to whether peroxisome proliferation is the sole carcinogenic mechanism of DEHP. This matter is important because Huber et al. made the assumption that a threshold model for carcinogenesis should be used. Melnick and Kohn found that the lack of a threshold cannot be ruled out. Based on an alternative linear no-threshold dose-response model that was later rejected, Huber et al. calculated a risk to highly DEHP exposed dialysis patients of 84-144 cancers per 10,000 at an exposure of 1 mg/kg body weight DEHP per day.

Even if it were ultimately determined that there is a threshold level of DEHP exposure below which peroxisome proliferation does not occur, and even if peroxisome proliferation were indeed the only mechanism by which one or more toxic effects associated with DEHP exposure occur in humans, it is likely that this “safe” level of exposure would vary among individuals in the population. Like all other physiologic properties, it would have a distribution – some people with “high” thresholds and some with “low” thresholds – requiring attention to the most sensitive member of the population for public health protection.

However, it now seems likely that DEHP toxicity is mediated, at least in part, by mechanisms other than peroxisome proliferation and that adverse effects may well be occurring in people who are particularly susceptible or excessively exposed.



# Risk Management Options for DEHP in Medical Devices

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In this section, a series of possible risk management options are presented which address the hazards posed by human exposure to DEHP from medical devices. These range from what might be termed a “permissive” approach to a “materials” approach. Each is progressively more protective of public health as far as phthalate risk is concerned.

Risk management options include:

- **Study phthalates more thoroughly and take no action at this time.**  
This option involves new or continued research on the health impacts caused by patient exposures to DEHP. It would involve continued exposure to humans at current levels as scientific evidence is gathered. This approach would include: determination of mechanism of action and its relevance to humans, measurements of the toxicity and exposure to phthalates; study of health effects in humans; the taking of action depending on results of studies; and a policy of action only when science provides clear, convincing evidence of risk to patients.
- **Reduce permissible exposure limits to phthalates and improve processes/products to reduce leaching or shift away from the use of more toxic types of phthalates (control approach).**  
This option involves establishing a “safe” level of exposure to patients from DEHP. After such a safe level is established, manufacturers would be required to keep leaching below that level. If exposures did not surpass that safe level, patients would be considered protected against effects. Specific uses of DEHP in medical devices (e.g., fatty nutrient supplements) might be prohibited. Also, switching to alternative phthalates or adding polymer layers or other additives to medical devices to reduce leaching might be considered.
- **Mandate/encourage replacements for phthalates in PVC medical devices (prevention).**  
This option could be considered a prevention-oriented approach. It involves replacing phthalates with other plasticizers in PVC medical devices. This option would eliminate the health risk posed by DEHP and other phthalate plasticizers. Some alternative plasticizers, such as citrates, appear to be safer from an environmental and health point of view. Citrate plasticizers are made from citric acid, which in turn is made from plant material. They have been used widely for years as plasticizers in packaging and medical devices. They are biologically based and bio-degradable. However, the health effects from long term exposure to citrate plasticizers in medical devices have not been widely studied. While they appear to leach less than DEHP, it is unclear whether exposures from medical devices might pose a risk to patients. Citrates have been shown to cause respiratory irritation, nervous system effects, effects on blood pressure, and on calcium metabolism in animal studies (HSDB, 1999).<sup>9</sup>

Another alternative PVC plasticizer, tri(2-ethylhexyl) trimellitate (TETM), has also received scant attention in the scientific literature. Nonetheless, it would appear that TETM leaches less into medical devices or humans than DEHP. It would be premature and inadvisable, however, to substitute TETM for DEHP without a better understanding of its full range of health effects

The alternative plasticizers are more costly than DEHP. Price information has not been obtainable, but an indication of the prohibitive costs at present comes from Baxter Healthcare which investigated the possibility of replacing DEHP in its PVC blood bags (an indication, perhaps, of concern over DEHP leaching). But the American Red Cross, the largest consumer of blood bags, refused to pay the difference in price (Kennedy, 1999).

Most importantly, this option does not address the environmental and health impacts posed by PVC production and disposal. These effects, beyond the scope of this report, are substantial and should be considered by medical device manufacturers, purchasers, and hospitals in their choices regarding materials. Some of these effects, which extend beyond concerns over the health effects associated with DEHP, are briefly described below.

PVC production and disposal (through incineration or burning) has been linked to the creation of the highly toxic by-product dioxin because of PVC's chlorine content (Moller, et al., 1995, Green, 1992, Hasselriis, 1992, Evers, et al., 1988). This link has been extensively studied in the literature, though the quantitative relationship between PVC production and disposal and dioxin creation is still under debate. A more detailed description of dioxin toxicity and links to PVC production and disposal is presented in an appendix to this report. PVC, more than any other commodity plastic, requires a large quantity of additives (such as stabilizers), some of which are toxic and can leach out of medical devices. Finally, the PVC monomer, vinyl chloride monomer (VCM), is a known human carcinogen.

- **Find suitable alternatives for PVC.**

If safer alternatives to PVC exist, which require no plasticizers, then this approach would have important advantages. It would completely eliminate the health hazards associated with DEHP exposure and the PVC lifecycle, resulting in multi-risk reduction. It would focus industry and government resources on innovation in the development of safer materials, and encourage long term, comprehensive planning, rather than require the dubious task of establishing safe levels of risk for the entire population. This approach would seek to identify and develop materials that are safer, cleaner and more resource conserving throughout their lifecycles.

An analysis of alternatives to PVC and characteristics needed in those alternatives is provided in Chapter 5.

# Alternatives to PVC in the Medical Bags and Tubing Markets

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Because it is cheap, clear, and flexible, PVC remains the most widely used material by manufacturers and end users of medical bags and tubing. Yet, PVC is beginning to face serious competition from other polymer-based products that are potentially safer and cheaper. Baxter International's recent announcement to phase-out PVC use in intravenous (IV) bags reflects the trend in the industry toward non-PVC materials.<sup>10</sup> The recent announcement by United Health Services that they will seek to replace PVC medical supplies with cost effective alternatives reflects this trend within the healthcare provider community.<sup>11</sup> This section reviews the medical bags and tubing market, identifies alternatives to PVC and their manufacturers, and summarizes some of the major environmental and public health concerns with alternatives. Although some of these concerns are briefly discussed, a more thorough analysis of any risks posed by alternative materials is warranted.

## Market profile: PVC in hospitals

Medical bags and tubing, rigid containers, respiratory equipment, examination gloves, packaging, and other patient care products define the wide array of PVC products in hospitals (Table 5). Flexible uses of PVC, which require the use of large quantities of plasticizers to impart flexibility to the polymer (30% or more by weight), include medical bags and tubing, respiratory equipment, examination gloves, and film packaging. Medical bags and tubing are of particular interest because they directly expose patients to DEHP.

The demand for PVC in medical bags and tubing in the U.S. totaled 273 million pounds in 1994: 110 million pounds for bags and 163 million pounds for tubing. The leading consumers of medical bags and tubing are Baxter International and Abbott Laboratories, which together accounted for almost 80% of PVC use in medical bags and 75% of PVC use in medical tubing. Baxter and Abbott consumed 211 million pounds of PVC in 1994 (Chemical Market Resources, 1995, pp. 29 and 31). In both medical bags and tubing, Baxter and Abbott compete with corporations with much smaller PVC market share (Table 6). Another competitor of Baxter and Abbott's, B. Braun/McGaw, uses PVC-free materials in its IV bags (the materials used are discussed below).

Analysts of the medical bag market divide it into three broad use categories: 1) IV solution, 2) blood, and 3) other bags — such as collection and specimen bags. IV bags represent the largest end-use, with 55% of the U.S. PVC medical bag market, followed by blood bags (25%) and other bags (20%) of the market. See Table 7 for more details.<sup>12</sup>

Used in multiple product lines, medical tubing cannot be categorized into a few clear-cut use categories. Medical tubing products include IV solution tubing, irrigation tubing, extension tubing, catheter tubes, blood/enzyme tubing, drainage tubing, suction tubing in oxygen lines, perfusion equipment tubing, tubing for short term implants, infusion tubing, and tubing for other medical devices. These diverse product lines consumed 163 million pounds of PVC in the U.S. in 1994 (Chemical Market Resources, 1995).

**Table 5: PVC in the health care industry**

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**Flexible Bags**

- Blood bags
- Intravenous (IV) bags
- Other bags, including collection and specimen bags

**Rigid Containers**

- Mixing containers
- Sharp containers (for needles)

**Tubing**

- Catheters
- Enteral feeding tubes
- IV, dialysis, and respiratory tubing

**Respiratory Equipment**

- Masks
- Oxygen tents

**Examination Gloves**

**Packaging**

**Other Patient Care Uses**

- Anti-embolytic therapy
  - Bed pans
  - Basins
  - Drip chambers
  - Inflatable splints
  - Mattress and pillowcase covers
  - Patient identification bracelets and cards
  - Shower curtains
  - Thermal blankets
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**Table 6: U.S. Market Shares of PVC Medical Bags and Tubing (1994)**

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| Corporation         | Total use of PVC in medical bags (% by company) | Total use of PVC in medical tubing (% by company) |
|---------------------|---|---|
| Baxter Healthcare   | 52.0  | 43.75   |
| Abbott Laboratories | 27.0  | 32.50   |
| Huls                | 7.0   | 0   |
| Achilles            | 5.0   | 0   |
| O'Sullivan          | 4.0   | 0   |
| Ellay               | 3.0   | 0   |
| Teknor-Apex         | 2.0   | 0   |
| Sherwood            | 0   | 9.0   |
| Colorite            | 0   | 3.7   |
| Norton              | 0   | 2.5   |
| Rehau               | 0   | 1.8   |
| Others              | 0   | 6.75  |

Source: Chemical Market Resources, 1995.

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**Table 7: PVC Demand in the U.S. Medical Bag Market (1994)**

| Type of Bag        | Pounds of PVC (millions) | Percent of PVC Bag Demand |
|--------------------|--------------------------|---------------------------|
| IV solution bags   | 60.5                     | 55%                       |
| Blood bags         | 27.5                     | 25%                       |
| Other medical bags | 22.0                     | 20%                       |
| <b>Total</b>       | <b>110</b>               |                           |

Source: Chemical Market Resources, 1995.

PVC’s rise to dominance, especially in the bag market, is part of a larger trend in the displacement by plastics of glass, aluminum, and metals. Lightweight, shatter-resistant, and easy-to-handle, plastics have pushed aside the traditional materials for holding, storing, transferring, and dispensing liquids. Among the plastics, PVC has trumped alternative polymers because of its transparency, flexibility, capacity to withstand steam sterilization (up to 121°C — also referred to as autoclaving), ability to form tight seals through radio frequency (RF) sealing, biocompatibility<sup>13</sup> with a range of solutions and body tissues, and low cost.

In the manufacture of tubing, where PVC remains the dominant polymer,<sup>14</sup> resistance to kinking is an especially important characteristic of PVC. Most hospitals reject non-PVC tubing because it lacks comparable flexibility, transparency, biocompatibility, and cost-effectiveness (Greenpeace Austria, 1998).

Low cost is the big factor in PVC’s favor and the major hurdle to alternatives. PVC and its companion plasticizers and additives<sup>15</sup> create a low cost material. Other polymers can compete with PVC on technical terms, often exceeding PVC on technical performance, but seldom match it on a cost basis. In addition to competing with PVC on a per pound of material cost-effectiveness basis, manufacturers of new materials also encounter the challenge of developing alternatives that large manufacturers like Baxter and Abbott can use with existing production equipment. Stuck with existing production equipment (“sunk costs” to use the jargon of economists), product manufacturers are loathe to shift to materials that do not fit within existing production systems. Along with the economic advantages, PVC has the “experience” advantage. Product designers, production engineers, and line workers are familiar with the polymer, and are reluctant to switch to alternatives. Product manufacturers thus enjoy two cost advantages over competing materials: it is a cheap polymer on a per pound basis, and its production is supported by sunk capital investments. But it is likely that the costs of PVC alternatives would come down as innovation in processing and production grows, through learning curves and economies of scale.

## Non-PVC polymers and their attributes

The polymers that will fit most comfortably within existing large-scale production systems are the ones most likely to succeed, at least in the near term (over the next few years), in displacing PVC. Abbott and Baxter alone use machinery that rolls out over 210 million pounds of PVC products per year. The most appropriate polymers are those that can be processed on existing production equipment.

Table 8 lists the different polymers that currently compete or are likely to compete with PVC in the near future and provides a qualitative picture of how they compare with PVC. “Polyolefins” are a class of polymers that include the polyethylenes and polypropylenes. The polyolefins, especially those based on metallocene technology, are most likely to compete with PVC in the long-run because they meet all the criteria critical to PVC.

Polyolefins are currently the most widely used commodity plastics in the world because of their ease of processing, cost and durability. The polyolefins can be made into products of varying hardness by modifying the polymer, without the use of additives. Development of new polymerization techniques allow the production of several polymer blends and alloys (polymer mixtures) in the production reactor itself. This allows the manufacturer to produce a broad range of materials that can be tailored to suit various applications and performance qualities, including improved crack resistance and toughness, improved processability, and minimal additive use.

New advancements in catalyst research has lead to the development of metallocene polyolefins which have a narrow molecular weight distribution leading to low additive use, low leachability and improved physical qualities. Polyolefin elastomers made with metallocene catalysts have better flexibility, clarity, and tensile strength than PVC. Because of their tensile strength, metallocene-based polyolefin products can be “downgauged.” That is they can be made thinning for the same strength, and so up to 40% less material is needed to provide equivalent strength of to PVC. Polyolefin laminates<sup>16</sup> and blends also have this property, lowering their production costs. Metallocene polyolefins also have a lower melt processing temperature, much lower injection molding cycle times (up to 25% less than PVC) and offer potential price savings of 25%-50% in five to eight years (Wilson, 1997 and Rothman, 1997). Downgauging also reduces disposal costs for hospitals by reducing the tonnage of waste. Finally, metallocene polyolefins can likely be produced using the same equipment as PVC.

Ethylene vinyl acetate (EVA) also competes with PVC. It is used in higher-end markets, often as a layer in a laminate. A performance advantage of EVA over PVC is the polymer’s ability to retain its properties over time. EVA can range from the thermoplastic (conventional plastic) to elastomeric (rubbery) state by modifying the vinyl acetate content of the polymer, also increasing polymer impact strength. This means that EVA can be processed for a wide variety of uses without the use of additives. Because EVA does not use plasticizers, no plasticizers are available to leach out and lower the material’s performance.<sup>17</sup> Its polarity means that sheets can be easily welded and its low sealing temperatures mean that it can be quickly processed at lower cost. A disadvantage of EVA in manufacturing is that because it is a “tacky,” it can be difficult to work with. This problem can likely be overcome with processing innovation.

## **PVC-free products in the medical bag market**

PVC-free IV, dialysis, and enteral feeding bags are already on the market and competing with PVC today. These and other alternative products are made from polyolefins, thermoplastic elastomers, ethylene vinyl acetate, ethylene vinyl alcohol, and/or liquid silicone rubber. In some bag and tubing uses, such as red blood cell storage, where PVC continues as the dominant material, manufacturers concerned with DEHP are currently searching out alternative plasticizers (see below).

Many manufacturers use alternative polymers to package their medical solutions. Notable among them is B. Braun/McGaw, which claims to have 18 percent of the IV solution market (Zawaideh, 1999). Along with B. Braun/McGaw are the large producers, like Baxter, that use PVC-free alternatives to package a few solutions, and a host of small manufacturers, like CharterMedical, that have little market share. In addition to the manufacturers of solutions, some major polymer producers like Dow are developing alternative materials for use in medical applications.

### ***IV solution bags***

In the largest medical bag use category, B. Braun/McGaw sells IV solutions in PVC-free Excel<sup>a</sup> and PAB<sup>a</sup> plastic

**Table 8: Comparison of PVC to Alternative Polymers Based on Critical Medical Application Function Criteria**

| Polymer                        | Clarity | Flexibility | Steam Sterilizable (autoclaving at 121 C)                               | Radio Frequency Seal Compatible | Low Cost in Production   | Comments  |
|--------------------------------|---------|-------------|---|---------------------------------|--|---|
| PVC                            | Yes     | Yes         | Yes   | Yes                             | Yes  | Need for and leaching of plasticizers                                 |
| Polyolefin blend               | No      | Yes         | Yes   | No                              | No   |   |
| Polyolefin laminate            | Yes     | Yes         | Depends. PP <sup>1</sup> cannot be autoclaved, but PE <sup>2</sup> can. | No                              | No   | Sterile fill process compatible                                       |
| Polyolefins, metallocene-based | Yes     | Yes         | Yes   | Yes                             | Yes. Cost-competitive because of "downgauging" (less material needed per unit of product than w/PVC) | May be compatible with existing production equipment                  |
| Polyester                      | Yes     | Yes         | Yes   | Yes, but with difficulty        | No   |   |
| Ethylene Vinyl Acetate (EVA)   | Yes     | Yes         | Alone, no. With other polymers as part of a laminate, yes.              | Yes                             | Relatively low cost  | More difficult to use in production because it is a "tacky" material. |

<sup>1</sup> = PP = polypropylene. <sup>2</sup> = PE = polyethylene.  
Source: Len Czuba, Flexpo '98.

bags and in glass containers.<sup>18</sup> B. Braun/McGaw uses a three-layer laminate for its Excel<sup>a</sup> bags — 1) a polypropylene and polyethylene copolymer blend at the solution contact layer, 2) a polyester layer, and 3) a synthetic elastomer. B. Braun/McGaw IV solutions are competitively priced and reduce hospital disposal costs because the bags weigh 28-49% less than PVC bags with an overwrap.<sup>19</sup> The cost competitiveness of the polyolefin/polyester laminates is attested to by market analysts, who noted that "Specialty polypropylene (PP) based films compete with PVC films in medical bags on a price and performance basis. Specialty PP films, which are manufactured by McGaw, offer very comparable properties to PVC (Chemical Marketing Report, 1995)."

A significant new development in the IV bag market is Baxter International's pledge to phase-out PVC use in IV solution bags (Freudenheim, 1999). According to the Memorandum of Understanding signed on 5 March 1999 by Baxter and the Retirement Plans for the Employees of the Sisters of Mercy Regional Community of Detroit, the Sisters of Charity of Cincinnati and the Service Employees International Union, Baxter "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."

While Baxter remains the leading user of PVC for bags and tubing, it also uses PVC-free materials in some applications. For example, Baxter uses polyolefin plastic containers for the storage of blood platelets and pre-mixed drugs for intravenous injection; uses EVA containers for nutritional lipid solutions and bone-marrow banking; and uses other PVC-free polymers for the storage of blood plasma and frozen blood cells (Baxter, 1999a and 1999c). In 1997, Baxter purchased an Italian corporation, Bieffe Medital, which manufactures dialysis, IV therapy, and irrigation solution products using PVC-free materials.

Baxter is also developing a polypropylene/polyethylene blend for extreme temperature medical applications. The ultra-low density polyethylene is manufactured using a metallocene catalyst. This new material will allow for the storage and transportation of human plasma, bone marrow, and other biologically active materials that require extremely low temperatures, from minus 78°-minus 195°C (-172°F-384°F); PVC is very brittle at these very low temperatures (Esposito, 1997).

In the dialysis market, Fresenius Medical Care produces a PVC-free peritoneal dialysis set — both dialysis bags and tubing are PVC-free — made with a polymer marketed under the tradename, Biofine<sup>®</sup>.<sup>20</sup> Their hemodialysis units, however, use PVC bags and tubing. Hemodialysis and peritoneal dialysis are the two principal dialysis methods, with hemodialysis the dominant technique.<sup>21</sup>

A handful of other corporations produce PVC-free IV bags for specialty solutions. For example, CharterMedical (Lakewood, NJ) manufactures bags from a three-layer laminate consisting of a center layer of ethylene vinyl alcohol (EVOH) sandwiched between two layers of an ethylene vinyl acetate (EVA) copolymer.<sup>22</sup> The CharterMedical bags, unlike the PVC and Braun/McGaw bags, cannot be steam sterilized.<sup>23</sup> This greatly reduces their applications.

With the IV solutions market dominated by Baxter, Abbott, and B. Braun/McGaw, some U.S. manufacturers of PVC-free alternatives have turned to overseas markets. For example, the Cryovac Division of Sealed Air Corporation (Duncan, S.C.) manufactures a multi-layer PVC-free bag that includes a polypropylene copolymer. The bag is in commercial use in Europe, but not in the U.S. A few potential U.S.-based customers are testing Cryovac's multi-layer product in clinical trials. The multi-layer bag can withstand steam sterilization (Sizemore, 1999), but its multi-layer structure will add to production costs.

In Europe, manufacturers and suppliers are also using and developing PVC-free alternatives. For example, Serum-Werk Bernburg (a German corporation) recently began producing PVC-free IV bags using Propylex<sup>®</sup>, a three-layer plastic containing an outer layer of polypropylene, a blend of polypropylene and styrene, ethylene, butadiene and styrene (SEBS), and a blend of polypropylene and SEBS. Serum-Werk Bernburg plans to use the material to package 25 different medical liquids and to manufacture PVC-free tubing for the solutions. The tubes will be made with an inner layer of EVA and an outer layer of a polypropylene-elastomer blend (Butschli, 1999).

PVC-free alternatives should be in demand for containing and conveying lipid solutions because high fat solutions can increase DEHP leaching. Some medical product manufacturers and suppliers to the industry have been attentive to this issue. For example, Bayer Corporation (Pittsburgh) has developed a lipid-resistant, transparent, polycarbonate polymer that meets FDA biocompatibility requirements and can be sterilized using steam autoclaving, radiation, or ethylene oxide (Anonymous, 1997). As noted above, Baxter uses EVA containers for nutritional lipid solutions. And CORPAK MedSystems (Wheeling, IL),<sup>24</sup> manufactures a PVC-free enteral feeding bag. These bags deliver enteral formulas that, in most cases, have a high lipid content. CORPAK's Polar Enteral Feeding Bags are made from a polyethylene/nylon laminate and EVA (Shaughnessy, 1999).<sup>25</sup>

### ***Blood products and bags***

“Blood bags,” like “IV bags,” is a catchall term that obscures the many different products contained by the bags. Red blood cells, plasma, platelets, cryoprecipitated AHF (anti-hemophilic factor),<sup>26</sup> cryoprecipitated-poor (cryo-poor) plasma,<sup>27</sup> white blood cells, and plasma derivatives<sup>28</sup> are among the many products derived from human blood. And like IV bags, the appropriate container depends on the blood product. PVC dominates the market as the material most widely used: PVC with either a phthalate (DEHP) or trimellitate (TETM) plasticizer can be used to store all blood products.<sup>29</sup> A polyolefin alternative is available for many blood products, but not for red blood cells.

When a donor gives blood (called “whole blood”), it is initially stored in DEHP plasticized PVC bags.<sup>30</sup> Shortly thereafter, usually within eight hours, a centrifuge separates the whole blood into red blood cells and platelet-rich plasma. Red blood cells are stored in DEHP plasticized PVC bags and platelet-rich plasma is stored in polyolefin bags or TETM plasticized PVC. Red blood cells are usually stored fresh in refrigerators at temperatures ranging from 1°-6°C and have a shelf-life of 35-42 days. Red blood cells can be frozen and have a shelf-life up to 10 years (AABB, 1999). However, less than one percent of red blood cells are frozen.

To our knowledge, no commercially available substitutes have been identified for PVC to date in the storage of red blood cells. An advantage of DEHP plasticized PVC in the storage of red blood cells is that DEHP actually binds to red blood cells, preserving them and extending their shelf-life. DEHP’s preservation of red blood cells is an unintentional result: DEHP was not added to PVC to increase the shelf-life of blood cells, rather it was a serendipitous discovery. But if leaching of DEHP into red blood cells is to be viewed as a benefit of PVC bags, it would seem appropriate to consider DEHP as a drug - with specific pharmacologic properties - that should be subjected to the same scrutiny as any new drug.

Fenwal Laboratories (a division of Baxter) — which dominates the blood bag market with roughly 80 percent market share — does market a non-DEHP plasticized PVC bag (named “PL 2209”).<sup>31</sup> Instead of DEHP, PL 2209 uses citrates as a plasticizer. The bag has little market share due to higher cost and little or no value added in terms of increased shelf-life.<sup>32</sup> Shelf-life is a critical factor driving material selection for packaging blood products because a container with a longer shelf-life reduces product losses.

Citrates are a logical choice for use in blood storage because they have been used for years as anti-coagulants.<sup>33</sup> Beginning in the 1940s, anti-coagulants made from citrates been added to whole blood and red blood cells to enhance separation of blood products and extend shelf-life. Approved anti-coagulants include anti-coagulant citrate dextrose (ACD) solution, citrate phosphate dextrose (CPD) solution, and citrate phosphate dextrose adenine (CPDA-1) (AABB, 1999b; and FDA, 1999).

Platelet-rich plasma is often further refined in a centrifuge, which separates the platelets from the plasma. The PVC formulation most widely used for storing platelets and platelet-rich plasma is TETM plasticized PVC; platelets stored at room temperature (20-24°C) in this material are constantly agitated and have a shelf-life of five days. DEHP plasticized PVC bags can be used to store platelets, but few blood banks use them because platelets only have a shelf-life of three days in these bags.

Polyolefin bags compete with the TETM plasticized PVC bags in the storage of platelets and platelet-rich plasma. The polyolefin bag can also store platelets for five days and is cheaper than the TETM plasticized bag. Despite being cheaper, Fenwal Laboratories sells more PVC than polyolefin bags.<sup>34</sup> The TETM plasticized PVC bags may be more popular because they are more gas permeable: they allow greater oxygen transmission into the bag than polyolefin. While the better gas transmission rate does not result in a longer shelf-life, it may increase the percentage of platelets that can be stored in a TETM/PVC bag and maximizes plasma production from a unit of blood.

Most plasma is frozen to increase its shelf-life. Frozen plasma — called “fresh frozen plasma” (FFP)

— has a shelf-life of a year. To qualify as “fresh frozen,” plasma must be frozen within six hours of collection from a donor (FDA, 1999). FFP can be stored in DEHP plasticized PVC or polyolefin bags, but the cheaper PVC bags dominate the market. Freezing of PVC may lead to cracking if leaching has occurred to a significant degree. Table 9 summarizes the primary blood products, the materials they are stored in, and their shelf-life.

**Table 9: Blood Products and Their Storage Containers**

| Blood Products                     | Storage Bag(s)   | Comments   |
|------------------------------------|--|--|
| Whole blood                        | ▶ DEHP plasticized PVC   | Whole blood usually is centrifuged, within eight hours of a donation, into separate blood products   |
| Red blood cells (fresh)            | ▶ DEHP plasticized PVC<br>▶ BTHC plasticized PVC                     | Shelf-life for fresh red blood cells, in either bag = 35-42 days. “BTHC” is a citrate-based plasticizer. BTHC bags have little market share. |
| Platelet-rich plasma and platelets | ▶ Polyolefin bag<br>▶ TETM plasticized PVC<br>▶ DEHP plasticized PVC | Shelf-life for PO and TETM plasticized PVC bags = five days and for DEHP plasticized PVC = three days.                                       |
| Fresh frozen plasma (FFP)          | ▶ DEHP plasticized PVC<br>▶ Polyolefin bag                           | Shelf-life for both bags = one year. DEHP plasticized PVC is used most often to package FFP.   |

Sources: Association of American Blood Banks, 1999; Hakani, et al, 1998.

### *Collection and specimen bags*

Collection and specimen bags have been tough markets for PVC-free products to enter because they are extremely cost-competitive. With less demanding technical requirements, as compared to IV and blood bags, materials for use in collection and specimen bags compete on the basis of material cost. However, the low technical demands also create opportunities for polymers that otherwise could not compete with PVC because they cannot, for example, withstand steam sterilization or accept an RF weld. For non-PVC polymers to compete in the collection and specimen bag markets they must be stronger than PVC, that is, require less material per unit of product (downgauging).<sup>35</sup>

Dow Plastics is seeking to break PVC’s dominance in collection bags through its Affinity<sup>®</sup> film, which is a metallocene-based polyethylene product. Dow is working with medical device manufacturers to use Affinity<sup>®</sup> in ostomy and urology collection bags and hopes to have its film on the market by the end of 1999. The advantage of Affinity<sup>®</sup> over PVC is in downgauging: “The combination of lower film density and improved properties results in a thinner, lighter weight product that meets the performance needs while reducing the volume of material required (Lipsitt, 1998).” The Affinity<sup>®</sup> film can be gamma or ethylene oxide sterilized, but cannot be autoclaved.

### *Medical tubing*

PVC has advantages in tubing because of its resistance to kinking, transparency, and low cost. With the large suppliers of medical devices only using PVC-free tubing in narrow applications — for example, where unique infusion requirements are present, as with Taxol or Insulin — PVC-free tubing remains on the margins of the tubing market. However, this is not for lack of alternative polymers that meet the technical qualities necessary for tubing.

EVA, polyolefins, polyurethane, and silicone are the primary alternative polymers to PVC in medical tubing. Norton Performance Plastics Corporation, Sealed Air Corporation, CORPAK, and JPS Elastomerics are among the U.S. corporations that manufacture PVC-free medical tubing. Norton Performance Plastics Corporation offers a wide range of PVC-free tubing products through its Tygon and Sil-Med divisions.<sup>36</sup> Tygon's High Purity Tubing is made from an EVA-polyolefin laminate (formulation 2275) and is "ideal for handling sensitive fluids such as pharmaceutical or biological solutions."<sup>37</sup> The polyolefin in Tygon's High Purity Tubing is metallocene-based and manufactured by DuPont Dow Elastomers under the tradename Engage<sup>®</sup>. Silicone tubing is also made by Norton Performance Plastics divisions including Tygon's Sanitary Silicone Tubing<sup>38</sup> and Sil-Med's tubing for use in closed-wound drainage systems, chest drainage, passive drainage, and peritoneal dialysis catheters.<sup>39</sup> Silicon tubing has also been used for years in endotracheal applications for children (Greenpeace Austria, 1995).

Depending on the application, enteral feeding tubing is made from polyurethane, silicone, or PVC. "In-dwelling" tubing (tubing that remains in the body for days) is made from polyurethane or silicone because it does not turn brittle over time, as does PVC tubing. External enteral feeding tubes are, however, often made from PVC. CORPAK manufactures a polyurethane tube for both external and internal uses (Shaughnessy, 1999). Stevens Urethane, a division of JPS Elastomerics, is another manufacturer of polyurethane tubing for medical applications.<sup>40</sup>

In Europe, B. Braun-Melsungen<sup>41</sup> manufactures a PVC-free tubing using polyolefins. Because the tubing is not mass-produced it costs more, although just a few cents more per unit of product, than comparable PVC-based tubing. The added cost of the polyolefin tubing has kept its market share down (Greenpeace Austria, 1998). Sealed Air Corporation also sells PVC-free tubing in Europe (as well as in Asia and Latin America, but not in the U.S.) through its Cryovac division.<sup>42</sup> Cryovac manufactures a laminate tubing, with an inner layer of EVA and an outer layer of an EVA-polypropylene copolymer.

Some tubing manufacturers, such as the Natvar Company, have developed PVC laminates that place PVC on the outside of the tube and a non-PVC polymer on the inside to reduce the potential for plasticizer leaching. Natvar manufactures a multi-layer tubing, using low-density polyethylene (LDPE) on the inside and PVC on the outside. Called Surepath/151<sup>®</sup>, it is used in applications where contact with PVC is problematic, like Taxol and Insulin. Natvar uses a non-DEHP plasticized PVC, but refuses to reveal the plasticizer.

## **A short assessment of different polymers**

Many polymers have been identified as alternatives to PVC in medical applications. To decide if one or more of these represent safer alternatives to PVC, an analysis of the lifecycle of each polymer should be performed to assess the relative environmental and health impacts of each. Lifecycle analyses are difficult to do thoroughly because of data gaps and the lack of consistent methods for comparing the relative impacts of different chemicals. "Data gaps" refer to the lack of data on pollutants from different production processes as well as the lack of toxicological data on many pollutants. The lack of "consistent methods" refers to the challenge lifecycle analyses confront in trying to aggregate many different pollutants together — for example, nitrogen oxides, benzene, carbon dioxide, and dioxins — with the goal of offering a common unit of analysis for comparing total "impacts" of a product or material.

Nonetheless, careful comparisons need to be conducted on PVC and its alternatives. Earlier sections of this report have shown that DEHP exposure can present a risk to patients that should be avoided if possible. In this section, it is shown that approved non-PVC medical devices are already on the market and

more will likely make it to the market in coming years. Thus, shifting away from DEHP can begin immediately without waiting for “final proof” that an alternative is better. These alternatives may be safer than PVC throughout their lifecycle but careful, thorough analysis is needed as the basis of final material choice. Below, an overview of the types of environmental and health and safety considerations that should be taken into account when considering the choice of alternative materials for medical devices is provided. Continuous monitoring of all alternative materials will help ensure that any unforeseen impacts are quickly mitigated.

PVC requires large concentrations of plasticizers and other additives to achieve flexibility and other characteristics, while these can often be achieved in other polymers through additional monomer or polymer chain modification. None of the alternative polymers listed below requires phthalate plasticizers. Nonetheless, all plastics require additives to some degree to impart particular qualities on the polymer. These may be less leachable, however, than PVC additives. As previously noted, the production and disposal of PVC has been linked to the formation of dioxins.

Polyurethanes use several very hazardous intermediates and create numerous hazardous by-products. Their production has been linked to numerous occupational health problems including heart disease, asthma, and reduced sperm quality. For example, toluene diisocyanate — which is used in their production — is a strong respiratory sensitizer. Their incineration releases numerous hazardous chemicals including isocyanates and hydrogen cyanide. Polyurethanes are also potentially more hazardous in the work environment than PVC.

Polycarbonate (PC) is used for products like CDs and refillable milk bottles and is usually made using highly toxic phosgene derived from chlorine gas. PC does not need additives but does need solvents, such as methylene chloride, a carcinogen, for its production. A number of processes have been developed to reclaim polycarbonate from CDs, milk and water bottles, but only for downcycling into lower quality products. The monomer for polycarbonate, bisphenol-a, is a suspected endocrine disrupting chemical and possible carcinogen. It has been found to leach from baby bottles and laboratory equipment.

Ethylene vinyl acetate is made by the co-polymerization of ethylene and vinyl acetate by free radical polymerization initiated either by a peroxide or perester. Vinyl acetate is produced by one of three methods: by reacting acetylene and acetic acid; by passing mixed vapors (acetylene gas with acetic acid vapor) over a catalyst of zinc acetate; or by reacting ethylene with acetic acid and oxygen in the presence a catalyst. These raw materials are relatively harmless. However, the raw material vinyl acetate has been demonstrated in at least one study to cause thyroid tumors in laboratory animals, raising suspicions about hormone disrupting qualities.

Polyolefins include both polyethylene and polypropylene and the “metallocenes.” The raw materials used in these plastics are relatively harmless, but can be flammable or explosive. Also, the cracking of hydrocarbon feedstocks generates persistent organic substances, such as polyaromatic hydrocarbons (PAHs). Petroleum production also generates dioxins due to the use of chlorine catalysts. Finally, the burning of these plastics can generate many volatile compounds, including formaldehyde and acetaldehyde, both identified as probable carcinogens. Despite hazards from polyolefin production, these can be considered among the least harmful of plastics. Polyolefin plastics can be made biodegradable by creating weak links in the polymer chain so that bacteria and other microorganisms can break it down (this plastic has already been used in some medical devices

## **Summary – DEHP and PVC-free alternatives exist**

DEHP plasticized PVC will confront many market challenges in the near future in most medical device and other product markets from non-PVC polymers and non-DEHP plasticized PVC polymers. Non-PVC polymers, especially the polyolefins, are beginning to push PVC out of the IV bag market and have the potential to make serious inroads in plasma and platelet packaging in the near future. B. Braun/McGaw already has almost 20 percent of the IV market and uses polyolefin-based, multi-layer bags. Baxter, the leading user of PVC bags with almost 50 percent of total PVC medical bag consumption, plans to phase-out PVC use in IV bags. In the blood bag market, polyolefins pose a serious threat to PVC in the plasma and platelet markets where they already have significant market share.

PVC is holding strong in red blood cells packaging, “other” bags, and tubing. For the time being it would appear that the only threat to PVC in red blood cells packaging is another PVC product based on a citrate plasticizer instead of DEHP. No non-PVC alternative is currently on the market for packaging red blood cells, and it is unclear whether any is in the research and development pipeline. The “other bag” market, dominated by low value end uses such as collection and specimen bags, has seen little activity in alternatives development and use, with the notable exception of metallocene polyolefin manufacturers. Because metallocene-based products are in the commercial pipeline, but not on the market, they offer a longer term threat to PVC in other bag uses.

Although an array of alternatives to PVC are available in the tubing market, PVC still shows significant strengths in this market. Outside of a few specialized uses such as Taxol infusions and enteral feeding, PVC is holding strong in the tubing market. Moreover, neither B. Braun/McGaw nor Baxter have made any commitments to move away from PVC altogether in their tubing use. If anything, there are signs of a turning toward non-DEHP plasticizers, including trimellitate, or polyolefin lined PVC instead of a move toward non-PVC alternatives for tubing on a large scale.

Despite the difficulty in entering the market, viable, approved non-PVC alternatives currently exist for all uses of PVC in medical devices except red blood cell storage. With the rapid development of polymer technology, however, this alternative may be available in relatively short order. Given growing concerns about DEHP and the PVC lifecycle, any company that developed and successfully produced a PVC-free alternative for red blood cell storage would be at a unique market advantage. These increasing concerns, coupled with regulatory or government policy declarations, and market trends away from PVC in certain flexible applications will, in the short term, lead to increased research and development into alternative polymers.<sup>43</sup> Nonetheless, with the exception of packaging IV solutions and some blood products, some manufacturers (especially the market leaders) will also turn to non-DEHP plasticized PVC, relying on trimellitate and citrate plasticizers as they may offer medical device manufacturers lower per pound and unit costs, as well as compatibility with existing production equipment. While this development would reduce human exposure to DEHP, other hazards associated with the PVC lifecycle exist, as noted earlier.



## Conclusions

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The objective of this report was to review the evidence on the health risks posed by the use of DEHP in medical devices. A thorough review was conducted of the literature on human exposure to DEHP through its leaching into medical devices and the toxicology of DEHP including its metabolism and evidence of adverse effects demonstrated in laboratory experiments (animals and *in-vitro*) and in humans. Alternatives to PVC in medical devices were also reviewed, as this is an essential part of the consideration of the weight of evidence that the DEHP health data represent.

The weight of the evidence indicates a significant potential for serious adverse effects to human health from DEHP-containing medical devices. 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 appear to vary widely. Often this leaching can result in high dosages of DEHP to an individual patient.

Toxicological testing in animals, *in-vitro* tests, supported by limited human data, provide different types of evidence linking DEHP and its metabolites to a wide range of adverse effects in the liver, reproductive tract, kidneys, lungs, and heart. Some of the effects observed in laboratory experiments have occurred near levels of exposure to which a patient might be exposed from these devices.

Uncertainties remain as to how relevant the results in laboratory experiments are to actual conditions of exposure. Intravenous dosing leads to reduced formation of one potentially toxic metabolite, MEHP. However, MEHP has been found in human sera and in patients undergoing medical treatment. At least one intravenous study in non-human primates found abnormal liver histology and reduced liver function at levels of exposure which a human might experience. Whether intravenous administration of DEHP, rather than oral administration, reduces risk to humans unclear.

Another important set of uncertainties are differences in the metabolism of DEHP between animals and humans and the mechanisms by which DEHP causes disease. It appears that DEHP metabolism is qualitatively similar between rodents and humans. It also appears that the monoester, MEHP, is the compound responsible for many of the toxic effects demonstrated in laboratory animals, though the relevance of other primary and secondary metabolites is less understood. However, metabolism will likely vary within the human population as well. For example, infants do not have fully developed metabolic pathways. Because it is not known what the safe level of DEHP exposure is for any given individual (particularly if that person is already infirm), small amounts of DEHP and its metabolites may eventually result in adverse effects.

Mechanisms of action may differ for toxic endpoints and more than one mechanism might be operating for a single endpoint, causing cellular damage directly or indirectly. Although our knowledge of the mechanisms by which DEHP causes adverse effects or disease are evolving, so are new sources of uncertainty. For example, is peroxisome proliferation the only mechanism by which DEHP causes cancer in laboratory animals, and if so, what is the importance of the quantitative differences between rodents and

humans in their ability to generate peroxisomes? Some toxic effects of DEHP have been shown to occur independent of peroxisome proliferation. Due to these uncertainties, inadequate evidence exists to state conclusively that the mechanisms of toxicity found in laboratory animals do not occur in humans.

Rather than trying to assess the risk from DEHP exposure only to a particular organ in a particular individual, the total picture of toxicity from this chemical (the risk to all organs together and the whole population of individuals exposed) has been assessed. Certain populations, including dialysis patients and hemophiliacs may have long term exposures to relatively high doses of DEHP, while others, such as neonates and the developing fetus, may have exposures at critical points in development. Also, individuals receiving medical treatment through PVC devices are often doing so because they are ill or injured, possibly compromising their detoxification systems. The precise magnitude of the risk of adverse health effects to these individuals cannot be ascertained with confidence at this time.

The conclusions reached in this report regarding DEHP exposure and its toxicity in animals, are conclusions that have been reached by various researchers and regulatory bodies over a period of more than 30 years. While there is no conclusive proof of adverse health effects in humans, based on the available evidence, it would seem prudent to avoid exposure to DEHP wherever possible. This does not mean that DEHP-containing medical devices should be precipitously removed from service. These medical devices serve a critical role in medical care settings. However, the challenge is to identify alternative materials which do not contain DEHP or other similar plasticizers and which have the potential to be safer alternatives to DEHP-containing PVC.

Alternatives should be considered in terms of the possible 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 dioxins. Given these other hazards in PVC production and disposal and the need for medical care providers to consider the health hazards posed by the products they produce or sell, a prudent and thoughtful course of action is to identify materials that pollute less throughout their life cycles and provide necessary properties for the product being made. The availability of alternatives presents a compelling argument for moving assertively, but carefully to the substitution of other materials for PVC in medical devices.

A review of the literature and supplier interviews suggests that PVC alternatives are widely available for use in most medical devices and may be cost-competitive. Several U.S. and European medical device manufacturers have already developed PVC-free alternatives for IV bags, tubing, and platelet storage, some of which commend a substantial share of their product market. Additional efforts towards innovation in red blood cell storage and medical tubing will be needed, as PVC offers material advantages for these product uses. Exxon, one of the largest phthalate ester manufacturers in the U.S., is investing billions of dollars in the development of metallocene polyolefin plastics, which are widely predicted to enter the market as replacements for flexible PVC in coming years.

In conclusion, a review of the literature found that humans are exposed to substantial levels of DEHP through PVC medical devices and that, based on evidence from scientific studies in animals and cell cultures and some limited human evidence, this exposure may lead to adverse health effects. Long term medical care patients such as hemophiliacs and dialysis patients, as well as neonates and the developing fetus are at particular risk. Therefore, a precautionary approach should be applied to minimize the risk to humans from exposure to DEHP through medical devices. Where alternative materials do exist that meet existing performance requirements at reasonable costs, these materials should be considered as potentially safer substitutes for DEHP-containing PVC medical devices. Where such materials do not exist, research and development efforts should to be undertaken to ensure their availability in the future.

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# Appendix: The Links Between PVC Production and Disposal and the Creation of Dioxin

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It has been argued that in considering the population health effects of a product's use, one must consider the potential effects of the product throughout its life cycle, from production, through use, to disposal. During both its production and disposal, PVC is associated with the production of dioxins, one of the most toxic classes of chemicals known.<sup>44</sup> This appendix will examine the links between PVC production and disposal and the creation of dioxin. Although the amount of dioxin created in PVC production and disposal by incineration is disputed, a general scientific consensus has formed that the creation and combustion (as noted from measurements after accidental fires) of PVC creates dioxin. This is due to PVC's chlorine content.

Dioxins are a group of 75 chemicals known as polychlorinated dibenzo-p-dioxins (PCDDs). Polychlorinated dibenzofurans (PCDFs), a closely related group of 135 compounds, are often found together with dioxins in the environment. PCDD/Fs are not intentionally produced and have no useful purpose. PCDD/Fs are produced as byproducts of manufacturing and combustion processes where organic carbon, oxygen and chlorine are present. The various forms of dioxins and furans (called congeners) are generally considered together in regard to their production, measurement, disposition in the environment, and toxicity. Since the toxicity of the PCDD/Fs congeners varies by a factor of one thousand, the concentrations of PCDD/Fs are often expressed as international toxicity equivalents (ITEQs). This allows the focus to be on the potential health effects of the total amounts of dioxin released. PCDD/F concentration is not a particularly accurate measurement of the potential health effects of PCDD/Fs in the environment since a very low concentration of a very toxic congener can have the same potential effect as a much higher concentration of a low toxicity congener. ITEQs are expressed as the equivalent mass of the most toxic of the PCDD/Fs congeners: 2,3,7,8-tetrachloro- dibenzo-p-dioxin.<sup>45</sup>

Dioxins (PCDD/Fs) are very potent toxicants and have a wide range of potential effects. In its Draft Dioxin Reassessment, the U.S. Environmental Protection Agency noted that dioxins have been shown to have effects on the immune system, male and female reproductive systems, hormonal processes involving insulin, thyroid hormones and steroids, and have been shown to cause birth defects, including fetal death (US EPA, 1994a). PCDD/Fs are considered probable human carcinogens by the U.S. EPA (US EPA, 1994a) and are classified as confirmed human carcinogens by the International Agency for Research on Cancer (IARC) (McGregor, et al., 1998). Contributing to the potential health effects of PCDD/Fs is their resistance to breakdown by normal chemical, physical, and biological processes in the environment (stability) and their strong tendency to accumulate in biological tissues and increase in concentration in organisms higher up in a food chain (biomagnification). The stability of PCDD/Fs, along with their association with very fine particulate matter, allows dioxins to be widely dispersed through the global environment. Dioxins and other persistent pollutants have been detected on both the northern and polar ice caps, even though the major sources of dioxins are thousands of miles away in the middle latitudes. PCDD/Fs, once unleashed in the environment, tend to disperse widely and remain toxic. Individual exposures to PCDD/Fs

tend to accumulate in the body of exposed animals, and dioxin concentrations in body tissues tend to be higher in animals high on the food chain, such as predators, raptors, and humans. Thus, any particular dioxin source can act both locally and globally.

PCDD/Fs accumulate in fatty tissues within the body; most notably, PCDD/Fs have been found at high concentrations in human breast milk (US EPA, 1997). The high toxicity and large bioaccumulation potential of PCDD/Fs has led the U.S. EPA to state in its reexamination of the health effects of dioxin that nearly everyone in the United States may already have received and accumulated a dose of PCDD/Fs sufficient to give rise to adverse health effects (US EPA, 1994b). In this sense, all humans have reached, or exceeded, the threshold dose for dioxin toxicity. Additional exposures will result in additional adverse effects. The daily dose that is thought to result in a one-in-a-million cancer risk in humans is between 0.5 and 4 picograms per kilogram per day (Andrews, 1992). One picogram is one millionth of a millionth of a gram (1,000,000,000,000 picograms equals one gram).

PVC contains two of the three chemical elements required for formation of PCDD/Fs: organic carbon and chlorine - chlorine in abundance relative to the rest of the environment (the third element, oxygen, is introduced during incineration). Chlorine is important in both the toxicity and persistence of PCDD/Fs. It is the relatively large amount of chlorine in PVC that makes it an important contributor to sources of PCDD/Fs. PVC is 45 to 54 % chlorine by weight (Green, 1992, Hasselriis, 1992), and roughly 30 to 40% of the world's chlorine production contributes to the manufacture of PVC (Moller, et al., 1995). PCDD/Fs can be formed during PVC production and PVC disposal. For a number of reasons, determining the extent of the link between PVC and PCDD/Fs is not an easy matter. First, the chemical formation of PCDD/Fs is very complex. Except for research purposes, dioxins are not intentionally created. The conditions of the processes that create PCDD/Fs are generally controlled to maximize output of the desired product (e.g., destruction of infectious agents and volume reduction of the waste), not to minimize PCDD/F production. Even when process changes can be made to limit PCDD/F production, the complexity of their formation often leads to unpredictable results, sometimes shifting PCDD/F from one part of the process to another or from one waste stream to another, rather than actually limiting PCDD/F formation. Even the use of air pollution control (APC) equipment to remove PCDD/F and other pollutants from the stack gases can result in a net increase in total dioxin production. The difficulties in pinning down the mechanisms that lead to PCDD/F formation in incineration make it difficult to control. One point remains clear: the chlorine in the waste contributes to PCDD/F production and emissions and, since PVC contributes 90% of the chlorine in medical wastes (Green, 1992), PVC is making significant contributions to the amounts of PCDD/Fs produced in medical waste incineration.

## **PCDD/Fs in PVC production**

The manufacture of PVC occurs by four primary steps. The precursors, ethylene and chlorine are combined to produce ethane dichloride (EDC). The EDC is then pyrolyzed to form the vinyl chloride monomer (VCM). Each of these steps in the process produces some PCDD/Fs that remain in the product (Carroll, 1988) and are passed onto the next production step, or are captured in a waste stream and treated (Moller, et al., 1995). VCM is then polymerized to produce raw PVC, which is molded and formed with the addition of stabilizers and plasticizers, to produce the variety of PVC products. PCDD/Fs are formed during production of EDC and VCM, during the part of the production process called oxychlorination (Moller, et al., 1995). Most of these PCDD/Fs produced in these processes are captured in waste (Moller, et al., 1995). Water waste streams are generally treated with activated carbon. Solid wastes streams, such

as still bottoms and spent activated carbon, are generally treated by incineration, which, paradoxically, can produce more PCDD/Fs than were present in the original solid waste (Moller, et al, 1995). Dioxin contamination found in the Rhine river has been attributed in part to EDC/VCM production, recognizable by the congener pattern (Evers, et al., 1988).

## PCDD/Fs in PVC disposal

One point about PCDD/F formation is generally agreed: PCDD/Fs are formed in all combustion processes where organic carbon, oxygen, and chlorine are present (Fiedler, 1998). However, the conditions of combustion strongly influence the amount and the character of the PCDD/Fs that are formed. Combustion conditions known to have an influence on PCDD/F formation include:

(1) the combustor type and configuration; (2) the composition of the material being burned, with the amount of chlorine in the material being the primary issue; (3) the temperature of combustion, (4) temperatures in post-combustion zones and within air pollution control (APC) equipment; and (5) material feed rate (Moller, et al., 1995, Fiedler, 1998, Rigo, et al., 1997).

Although scientists generally acknowledge that all of these factors have an effect on the production of PCDD/Fs, they do not agree on which of these parameters are important and to what extent each affects the formation process. Even the role of chlorine is not entirely clear. While chlorine is clearly required for the formation of dioxins, the relationship between the amount of chlorine in the waste and the amount of dioxin produced is not direct. It may be that small amounts of chlorine contribute proportionately more to dioxin formation than do larger amounts of chlorine (Kanters, 1996, Moller, et al., 1995).

Among the larger studies to look at this issue is one sponsored by the American Society of Mechanical Engineers (ASME) (Rigo, et al., 1997). It was conducted under the auspices of the ASME, but the primary financing came from the Vinyl Institute and Chlorine Chemistry Council. The Canadian Ministry of the Environment provided a small amount of funding.

The purpose of the study was to look at the relationship between chlorine input in various types of waste incinerators and PCDD/F output. The study included an analysis of historical data from municipal, medical and hazardous waste incinerators, boilers and industrial furnaces, and cement kilns. The data were available from 450 facilities comprising 1900 sets of PCDD/F measurement data. The data include measurements of combustor operational parameters, such as air temperatures at various points in the process stream, oxygen levels, feed rate and composition, hydrogen chloride (HCl) emissions, and PCDD/Fs in combustion air at various locations within the incinerator systems. No direct measures of chlorine input were used in the Rigo, et al. analyses of municipal or medical incinerators. Percent chlorine was presented for HWIs and boilers and industrial furnaces, but no feedrates. Biomass combustor data were a mixture of HCl emissions, percent chlorine in feed and chlorine feedrate.

In compiling the report, Rigo, et al. analyzed data from 59 municipal waste combustors (MWCs), 24 medical waste incinerators (MWIs), 23 cement kilns, 32 hazardous waste incinerators (HWIs), 5 boiler and industrial furnaces (BIFs), and 8 biomass combustors. Rigo, et al. statistically analyzed data from 22 MWCs; 18 MWIs; and 24 HWIs. For HWIs, BIFs, and biomass combustors, the report concluded that the data were insufficient to determine a correlation between chlorine input and PCDD/F output. Yet the report went on to conclude that no correlation between chlorine input and output in these types of facilities could be inferred, despite the lack of supporting data. For cement kilns, the report concluded that chlorine feed rate has no discernible effect on the nature or quantity of PCDD/Fs emitted from the stacks of these facilities.

For both municipal and medical waste incinerators the authors employed more data for analysis. Using the concentration of uncontrolled HCl in stack gas as a surrogate for chlorine feed rate, the authors concluded that no correlation between the chlorine feed rate and the amount or quality of dioxin output from the stack could be shown.

Subsequent to the release of this report, Greenpeace (Costner, 1997) published a re-analysis of the Rigo et al. data and a critique of the report methods and conclusions. Some of the significant findings of the re-analysis are:

1. The Rigo, et al. report used composite measurements, in some instances combining data from different process areas of an incinerator (e.g., averaging of post-combustion and post APC measurements), that may have tended to minimize the actual changes in PCDD/F output related to chlorine input.
2. The measures of chlorine input, percent chlorine in feed and uncontrolled HCl in stack gas, are poor surrogates for chlorine feed rate, which is more likely to be related to PCDD/F formation. Chlorine feed rate includes the total waste feed rate and the percent chlorine content together.
3. PCDD/Fs measured in process and stack gases were the only media to be considered in the report. The report did not account for PCDD/Fs that may be going to fly ash or bottom ash.
4. The Greenpeace re-analysis of the statistical data presented in the report appendix showed that (while not directly reported): on a facility-by-facility basis, a positive relationship between HCl and dioxin concentrations in stack gases was apparent at 15 of 22 municipal waste combustors. This positive correlation was statistically significant at confidence levels of >95 percent at five facilities; >90 percent at two; and <80 percent at the remaining eight. The reanalysis also showed that concentrations of HCl and dioxin in stack gases exhibited a positive correlation at 10 of 15 medical waste incinerators. Among these, confidence levels were >95 percent at two facilities, >90 percent at one, >80 percent at two, and <80 percent at five.

Overall, the Greenpeace report concluded that the data presented in the Rigo, et al. report indicated a predominantly positive correlation between surrogates for chlorine input and PCDD/F in stack gases of municipal and medical waste incinerators. As explained in the Greenpeace report, the statistical analyses presented in the Rigo, et al. report do not show that there is a strong connection between the amount of chlorine going into the incinerator and the amount of PCDD/Fs coming out the other end. They do make it clear that chlorine in incinerated wastes is contributing to the PCDD/Fs in the process outputs, but the degree to which they are linked is not established. Nonetheless, many studies do find a connection between chlorine in and dioxin out but the degree of association varies.

The Swedish Environmental Protection Agency (SEPA) has found that when both chlorine and carbon sources are present in combustion processes, PCDD/Fs can be formed (SEPA, 1996). The U.S. EPA's dioxin reassessment states that dioxin-like compounds can be formed when chlorine donor compounds are present in combustion (USEPA, 1994b). A recent study of a variety of combustion facilities indicated that a clear link exists between PCDD/F emissions and the chlorine content of the waste feed (Thomas, 1995). This connection has been observed most clearly in studies of municipal waste incineration. Dutch incinerator and laboratory studies have shown that emissions of dioxins and dioxin-like compounds are reduced significantly when the amount of PVC feed is reduced (Kanters, 1996)

The mechanism of PCDD/F formation in combustion processes is not fully understood (Moller, et al., 1995). The relationship between reductions in waste content of PVC and reductions in PCDD/F formation are complex, depending on a variety of combustion conditions as well as chlorine content of the waste stream. The evidence to date indicates that when chlorine is present in an incinerator waste stream, PCDD/Fs will be produced and any reductions in chlorine content in the waste will contribute to a reduction in the formation of PCDD/Fs (Moller, et al, 1995).

Most of the demonstrations of the contributions of PVC to PCDD/F formation have been in municipal waste incinerators. The same processes that lead to the formation of PCDD/Fs are active in medical waste incinerators, although the amount of PVC, and chlorine, in medical waste is much higher. Medical waste is 5 to 6 % PVC (2.5 to 3% chlorine) by weight compared to about 1% PVC (0.5% chlorine) by weight in municipal waste (Hasselriis, 1992, Moller, et al, 1995). The higher chlorine content increases the opportunity for PCDD/F formation (Kanters, 1996), making medical waste incinerators a large potential source of PCDD/Fs in the environment. Medical waste incinerators are consistently ranked among the largest environmental sources of PCDD/Fs. While new medical waste incinerator emissions standards will likely reduce the emission of dioxins from MWIs, they will not be able to completely eliminate dioxin emissions from this source.

A shortcoming of many studies attempting to quantify the link between chlorine and dioxin in incineration is that they do not directly compare chlorine input and dioxin output. Instead, they often compare chlorine input and dioxin in stack emissions. The latter measure is only one small fraction of the total dioxin output and can be ensconced as emissions are passed through various pollution control devices that are designed to remove dioxins from the stack gases. Comparing chlorine input to total dioxin output may be the only way to fully understand the chlorine/dioxin relationship.

## Addressing dioxin creation

A limited number of control options are available for reducing PCDD/F emissions from PVC incineration. Air pollution control equipment is installed in many incinerators, but these controls are not fully effective, are expensive to install and maintain, and may simply shift the PCDD/Fs from one waste stream to another. The dioxins shifted to another waste stream may not be effectively destroyed. Also, incineration may produce more PCDD/Fs if improperly done or, as with end of stack controls, may shift the problem to yet another waste stream. The effective use of these controls is dependent upon the regulations that govern allowable emissions and drive the regulated community. However, in a recent ruling from the District of Columbia Circuit Court of Appeals, the court expressed “serious doubts” about EPA’s regulatory approach to medical waste incinerators and declared that “EPA’s method looks hopelessly irrational (US Court of Appeals, 1999).” Further, these types of controls, even at their most effective, allow some dioxins to be released, adding to the threshold level of exposure that we are already experiencing.

The most effective control measure for PCDD/Fs is to not produce them. This means identifying and developing alternative products that do not contain materials that may lead to the production of dioxin in production or disposal. Material substitution is a viable option for replacement of PVC in many of its uses, including medical applications. Given the availability of viable, and perhaps safer, substitute materials for medical applications of PVC in direct patient care, hospitals, physicians, and medical care providers need to consider the public health impacts of PVC production and disposal.



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# Endnotes

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1. While all plastics use a variety of additives to some extent, PVC uses more additives than other commodity plastics. For example, PVC consumes the vast majority of metal stabilizers because of its susceptibility to dehydrochlorination. This is due to the fact that PVC is made up of large percentage of a chlorine. The impacts of this chlorine content is discussed in an appendix to this report.
2. For example, many companies in the toy industry switched to the use of di-isononyl phthalate (DINP) in the mid to late 1980s. Unfortunately, it may cause a similar range and magnitude of adverse health impacts in laboratory animals as DEHP. Recent concerns about DINP have led several toy companies to eliminate the use of this plasticizer, and several European governments have also initiated actions to restrict the use of DINP in toys intended for children under three years of age.
3. Products tested in this study, conducted by Stat Analysis, Chicago, IL, included blood bags, IV bags, medical tubing, and syringes. A non-PVC IV bag contained less than 0.2% DEHP (a detectable amount), possibly the result of contamination.
4. For example a dialysis patient may suffer from impaired excretory pathways (Crocker, et al., 1988); and infants have immature metabolic pathways. The importance of route of exposure, DEHP metabolism and distribution in the body are discussed in the next section.
5. ECMO is provided to pre-mature infants to provide oxygenation support for underdeveloped lungs.
6. According to these researchers, the use of disposable PVC respiratory tubing systems began in 1980.
7. The authors note that these effects may also be due to leaching of organotin stabilizers from the PVC tubing.
8. Oie, et al. (1997) identified the predominant plasticizer emitted from PVC flooring as DEHP
9. Duke and Vane (1968) found that the pulmonary blood-vessels in isolated perfused cat lungs do not respond to hypoxia when the perfusion circuit is made from PVC tubing. The tubing in their experiments used acetyl-tri-n-butyl citrate in epoxy soya-bean oil as a plasticizer. In additional experiments, perfused cat lungs did have a pulmonary pressor response to anoxia when tubing was made out of silicone or red rubber. The researchers hypothesized that the octyltin stabilizer used in some of the PVC tubing tested had some effect but could not explain the entire effect of the PVC tubing on the lung preparations.
10. Baxter is the largest supplier of IV medical devices in the U.S. and the largest consumer of PVC in the medical device sector (for use in its bags and tubing).
11. Universal Health Services is the third largest hospital management company in the U.S. UHS recently acknowledged that “polyvinyl chloride (PVC) plastic, a component in various medical products, may result in damage to the environment.” UHS plans to investigate the amount of PVC it is currently using and formally ask its suppliers to develop non-PVC alternatives.
12. Within the IV solution bags segment, the biggest product categories are saline solutions, dextrose injections, and electrolyte solutions.
13. “Biocompatibility” refers to the ability of a medical device to work “harmoniously” (or at least without negative observable effects) with solutions and patient tissues. To determine the biocompatibility of medical devices, analysts use analytical chemistry tests, in-vitro tests using cell cultures, and animal models. A device’s biocompatibility depends on the nature of its component materials, the types of patient tissue exposed to the device, and the duration of exposure.
14. For example, B. Braun McGaw, which markets PVC-free IV bags still uses PVC tubing.

15. "Additives" include impact modifiers, fillers, and processing aids, which are added to PVC to impart specific properties to the product.
16. A laminate is a material that includes layers of polymers.
17. As previously noted, because of DEHP leaching, PVC products will lose some of their flexibility over time. This may be problematic for longer use products and could lead to problems in use (e.g., warmed feeding or respiratory tubes losing their flexibility)
18. B. Braun/McGaw is not listed in Table 1 — U.S. Market Shares of PVC Medical Bags and Tubing (1994), because it is not a major user of PVC.
19. PVC bags usually have an overwrap to slow-down the diffusion of plasticizers and the breakdown of the bag.
20. Fresenius has not revealed the polymers used in Biofine.
21. Peritoneal dialysis is an older technique that relies on the patient's peritoneal membrane to filter out impurities. It used to work in the following way: fluid was put in the patient's abdomen where, through osmosis, it was cleansed and the "dirty" fluid was removed one half hour later. This process was done for 24 hours with a nurse changing the fluid every half hour. Now patients do it themselves: before falling asleep they plug in the tubing containing the fluid into their catheter and the fluid constantly flows into and out the abdomen during overnight hours. Hemodialysis uses artificial membranes, as opposed to the intact peritoneal membrane, to clean the blood. During hemodialysis the blood is taken out of the patient's body, passed into a membrane, and back to the body.
22. Dravon Medical (Clackamas, OR) also manufactures EVA-based bags for custom medical bag products.
23. They can only be sterilized by gamma radiation.
24. CORPAK is a division of Thermetics (Woburn, MA).
25. Most enteral feeding bags use PVC and are produced by Ross Laboratories (a division of Abbott Laboratories) and Sherwood Medical. PVC-free enteral bags produced by CORPAK hold roughly three percent of the market (Shaughnessy, 1999).
26. Cryoprecipitated AHF" is a small portion of plasma that contains specific clotting factors (AABB, 1999).
27. "Cryoprecipitated-poor (cryo-poor) plasma" is plasma that had the cryoprecipitated AHF removed (HemaCare, 1999).
28. "Plasma derivatives" are "concentrates of specific plasma proteins that are prepared from pools (many units) of plasma." They include factor VIII concentrate, factor IX concentrate, anti-inhibitor coagulation complex (AICC), albumin, immune globulins (including Rh immune globulin), anti-thrombin III concentrate, and alpha 1-proteinase inhibitor concentrate (AABB, 1999).
29. "TETM" is short for tri-(2-ethylhexyl)-trimellitate.
30. An alternative exists to taking whole blood from donors and processing it into different products. It is called apheresis (also called hemapheresis): the process of removing blood from a donor and separating it into various components at the donation site. During apheresis desired blood components are removed from a donor's blood and the remaining components are reinfused into the donor. This process, however, takes longer: 60 minutes versus 20 minutes for a whole blood donation (AABB, 1999).
31. Fenwal's DEHP plasticized PVC bag is called PL 146.
32. Though some experts feel that red blood cell shelf life is increased through the use of citrates as plasticizers (Kevy, 1999).
33. Citrates, as noted above, are made from the fermentation of corn, molasses, and other biomass materials (Reilly Industries, 1999a).
34. It is estimated that sales of platelet bags at Fenwal divide roughly into 60 percent TETM plasticized PVC and 40 percent polyolefin bags. Fenwal's TETM plasticized PVC bag called "PL 1240" and the polyolefin bag is called "PL 732."
35. This assumes that the price of PVC products will not rise because of their negative human and environmental health effects.
36. See "<http://www.nortonplastics.com/maretsdefined/medicaltubing.html>" and "<http://www.tygon.com/>".
37. See "<http://www.tygon.com/prod/2275prod.html>".

38. See "<http://www.tygon.com/prod/3370ibprod.html>".
39. See "<http://www.sil-med.com/products/index.html>".
40. See "<http://www.jpselestomerics.com/urethane/tubing.html>".
41. B. Braun is the same corporation that recently merged with McGaw in the U.S. to form B. Braun/McGaw.
42. Cryovac and Sealed Air are U.S.-based businesses. Cryovac is based in Duncan, South Carolina.
43. For example, in June 1998, Chemical Marketing Resources held a conference, called Flexpo, where more than 150 representatives from plastics and chemical companies, academia, and government convened to discuss PVC alternatives for flexible products.
44. The health effects posed by ethylene dichloride and vinyl chloride monomer, two building blocks of PVC, will not be examined in this report, as well as the adverse health effects caused by exposure to other additives in PVC, as well as their ancillary production.
45. For example, suppose a sample contained 1 picogram/cubic meter (pg/m<sup>3</sup>) 2,3,7,8-tetrachlorodibenzodioxin (ITEQ multiplier of 1; Dioxin ITEQ = 1 pg/m<sup>3</sup>), 1 pg/m<sup>3</sup> pentachlorodibenzodioxin (ITEQ Multiplier of 0.1; Dioxin ITEQ = 0.1 pg/m<sup>3</sup>), and 1 pg/m<sup>3</sup> octachlorodibenzodioxin (ITEQ multiplier of 0.001; Dioxin ITEQ = 0.001 pg/m<sup>3</sup>). The sample would have a total dioxin concentration of 3 pg dioxin/m<sup>3</sup> and a dioxin toxicity concentration of  $1 + 0.1 + 0.001 = 1.101$  pg dioxin ITEQ/m<sup>3</sup>.



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