Safety Assessment of Di(2-ethylhexyl)phthalate (DEHP) Released from PVC Medical Devices

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Executive Summary

Patients undergoing medical procedures such as IV therapy, enteral and parenteral nutrition support, blood transfusion, hemodialysis and peritoneal dialysis, cardiopulmonary bypass (CPB) and extracorporeal membrane oxygenation (ECMO) can be exposed to di-(2-ethylhexyl)phthalate (DEHP), a compound used as a plasticizer for polyvinyl chloride (PVC) medical devices. DEHP has been shown to produce a wide range of adverse effects in experimental animals, notably liver toxicity and testicular atrophy. Although the toxic and carcinogenic effects of DEHP have been well established in experimental animals, the ability of this compound to produce adverse effects in humans is controversial. As a result, the ability of DEHP and other phthalate esters to produce adverse effects in humans has been a topic of active discussion and debate in the scientific and regulatory communities. Since patients undergoing medical procedures can be exposed to DEHP, a safety assessment has been conducted by the FDA Center for Devices and Radiological Health (CDRH) to provide risk managers with information necessary for informed regulatory decision making regarding the safety of DEHP released from PVC medical devices. **This safety assessment should be viewed as a first step in this process. Other factors, such as the availability and safety of alternatives to DEHP and PVC, must also be considered in developing a risk management strategy to address this issue.**

This Executive Summary provides a brief description of the approach used to assess the risk posed by patient exposure to DEHP and describes the conclusions reached following a careful examination of the data.

Safety Assessment Approach Used

No attempt has been made in this document to quantitatively assess the risk posed by exposure of patients to DEHP. Instead, a safety assessment approach involving comparison of the doses of DEHP received by patients undergoing various procedures to Tolerable Intake (TI) values for DEHP was used to develop a general index of safety or risk with regard to patient exposure to DEHP. A TI value is defined as the dose of a compound that is not expected to result in adverse effects following exposure for a defined period. The process used to derive the TI values for DEHP is outlined in ISO/DIS 10993-17 standard, *Method for the Establishment of Allowable Limits for Leachable Substances.*

The approach used by FDA/CDRH to derive the TI values for DEHP is based on an international consensus standard and is essentially identical to the method used by other regulatory agencies and advisory bodies to establish health-protective exposure levels for DEHP (and other compounds). The approach used in this safety assessment can be characterized as health-protective or conservative, since worst-case estimates of dose are typically compared to TI values intended to be protective for even sensitive individuals in the population. As a result, the TI/dose comparisons derived for many clinical scenarios are likely to overestimate the risk to the majority of the exposed patient population.

Exposure assessment and selection of a critical toxicity study

A comprehensive review of the literature was undertaken to provide the data used to estimate the dose of DEHP received by patients undergoing various procedures and to identify the critical effects of DEHP in exposed experimental animals. These data are summarized in the main body of the safety assessment and more detailed exposure and toxicity assessments can be found in Annexes A and B, respectively. The exposure assessment was based on direct measurements of patient exposure to DEHP and on estimates based on the rate at which DEHP was released from various devices. In the latter case, every attempt was made to take into account current clinical practices that impact device use and subsequent patient exposure to DEHP.

The TI values for DEHP were derived from the results of studies conducted using experimental animals and are based on adverse effects produced by DEHP on the testes, an organ that appears to be particularly sensitive to DEHP, at least in rodents. Justification for the selection or rejection of the key toxicity studies is provided in the safety assessment. In addition to the usual criteria applied in selecting a critical study (e.g., adequate sample size, use of an appropriate vehicle), consideration was given to what constitutes an "adverse" effect with regard to DEHP toxicity, since a number of the effects produced by DEHP can be considered to be adaptive or subclinical. Although the parenteral TI value was based primarily on the results of one study (AdvaMed, 2001), similar no-observed-adverse-effect-level (NOAEL) and lowest-observed-adverse-effect-level (LOAEL) values were identified in other relevant studies, thereby increasing the confidence that the appropriate NOAEL in rodents was selected for this assessment.

Derivation of a TI value for DEHP

Uncertainty Factors (UFs) were applied to the NOAEL or LOAEL from the critical studies to derive the TI values. These UFs are intended to account for: 1) interspecies differences in the potency of DEHP, 2) variability in the response of the human population to DEHP and 3) deficiencies in the data available to derive the TI values. Explicit identification of the uncertainties associated with the data helps to define the magnitude of each UF and results in a more transparent approach for assessing the risk posed by patient exposure to DEHP. Application of UFs to the NOAEL from the AdvaMed (2001) study yields a parenteral TI value of 0.6 mg/kg/day and an oral TI value of 0.04 mg/kg/day. Exposure of patients to DEHP at these doses by parenteral or oral routes of exposure, respectively, is not expected to result in the development of adverse effects. The oral TI is consistent with the health-based exposure limit values for DEHP derived by the U.S. EPA, Health Canada, the OECD, and the EU Scientific Committee on Toxicity, Ecotoxicity and the Environment (CSTEE).

In addition to DEHP, patients can be exposed to the DEHP metabolite, MEHP. This compound is formed exogenously by lipase enzymes in stored plasma or blood or by hydrolysis in stored and heated IV fluid. As a result, some of the DEHP that is released into stored blood, plasma, or IV fluids will be converted to MEHP before reaching the patient. Exposure to MEHP is important since this compound is thought to be the toxic metabolite of DEHP and because it is more potent than DEHP in producing adverse effects. A method was developed to estimate the aggregate dose of DEHP and MEHP and to express this dose on the basis of DEHP-equivalents (Annex C). However, because of uncertainties associated with the relative potency of DEHP:MEHP and the resulting estimates of DEHP-equivalent dose, the TI/dose ratios based on the dose of DEHP-equivalents received by patients will not be used to support regulatory decision making. Despite these uncertainties, it is nevertheless important to point out that simultaneous coexposure to DEHP and MEHP can occur in some patients.

The conclusions reached in the safety assessment are based solely on the potential for DEHP to cause adverse systemic effects in exposed patients. However, the clinical significance of various nonsystemic effects produced by DEHP is explored in Annex D. For example, the ability of DEHP to alter the hemocompatibility of PVC tubing or result in adsorption of drugs to PVC tubing may be the most clinically important endpoints to consider in the risk management phase of the assessment, depending on the device.

Conclusions of the Safety Assessment

The following conclusions were reached by comparing the dose of DEHP by patients undergoing various medical procedures to the TI value for oral or parenteral exposure. Comments on the size of the exposed population are included, in some cases, since the size of the impacted population is a factor in determining the risk management options to be considered.

IV infusion of crystalloid fluids and drugs
Based on the results of the safety assessment, CDRH concludes that there is little to no risk posed by patient exposure to the amount of DEHP released from PVC IV bags following infusion of crystalloid fluids (e.g., normal saline, D5W, Ringers Lactate). Further, there is little risk posed by exposure to the amount of DEHP released from PVC bags used to store and administer drugs that require a pharmaceutical vehicle for solubilization, when label instructions are followed.

Total Parenteral Nutrition (TPN)
The dose of DEHP received by adult patients receiving TPN admixtures is estimated to be less than the TI, suggesting that there is little concern for DEHP-mediated effects in these patients. In addition, non-PVC bags and tubing are typically used to administer TPN, further lessening the concern about DEHP-mediated effects.

The dose of DEHP received by neonates undergoing TPN supplementation is uncertain. The results of one study suggest that neonates can receive a very high dose of DEHP, whereas another suggests that neonates receive doses of DEHP from TPN that are equivalent to the TI. Therefore, depending on the data used to derive the TI/dose ratio, neonates receiving TPN admixtures with lipid may be at increased risk of DEHP-mediated adverse effects.

Blood transfusion
Relatively high doses of DEHP can be received by patients who are transfused with large volumes of blood and blood products over a short period (e.g., trauma or surgical patients receiving massive transfusions). However, the TI/dose ratio for this procedure is likely to overestimate the actual risk to these patients, since the TI is intended to be protective for long-term exposures, compared to relatively short-term exposure in acute transfusions. In contrast, a patient undergoing a routine, elective surgical procedure typically receives about two units of packed red blood cells. Transfusion of this volume of blood will result in a DEHP dose equivalent to the TI value, approximately 0.5 mg/kg/day. Long-term transfusion of blood to patients with anemia results in a DEHP dose about an order of magnitude lower. Similarly, infants who receive replacement transfusions in the NICU receive relatively small DEHP doses from the transfusions. Apheresis donors are exposed to relatively little DEHP when the dose is time-averaged over an extended period. Consequently, there is little concern about DEHP-associated adverse effects developing in persons donating platelets or plasma.

Two subpopulations of patients that may be at increased risk from exposure to DEHP following transfusions are infants undergoing exchange transfusion and adults undergoing ECMO. However, neither of these procedures is done very often, so the patient population exposed to relatively large doses of DEHP via exchange transfusion or replacement transfusion of adults on ECMO is expected to be small.

Cardiopulmonary bypass and ECMO
The aggregate dose of DEHP received by adults undergoing cardiopulmonary bypass procedures may equal or exceed the TI in some patients. However, heparin-coated tubing is used in about half of “special” or high risk cases and about 17% of “routine” cases (Mejak et al., 2000). Since little DEHP is released from heparin-coated tubing (Karle et al., 1997), the dose of DEHP received by many patients undergoing cardiopulmonary bypass will be less than those undergoing the procedure where uncoated PVC tubing is used.

The dose of DEHP received by neonates undergoing ECMO may exceed the parenteral TI by more than 20-fold, based on the exposure estimate from one study. However, a TI/dose close to 1 for this procedure can be derived using dose information from another study. Therefore, the risk posed by patient exposure to the amount of DEHP released during ECMO is uncertain. It is important to point out that no acute effects were seen in neonates undergoing this procedure in

the recent study by Karle et al. (1997); however, it is equally important to point out that testicular toxicity (the assumed most sensitive effect in humans and other species) was not assessed in this study.

Hemodialysis and peritoneal dialysis

Based on recent data on the amount of DEHP retained by patients on hemodialysis, there is little concern regarding exposure to DEHP in patients undergoing this procedure. In addition, since very little DEHP is released into peritoneal dialysis fluid, the corresponding risk of systemic effects developing following exposure to this low dose of DEHP is also low.

Enteral nutrition and breastfeeding

Lipid in enteral nutrition solutions can leach out considerable doses of DEHP from PVC bags and tubing. As a result, these patients may be at increased risk of developing DEHP-mediated effects if PVC bags and tubing are used to deliver the enteral nutrition solutions.

Based on theoretical estimates, it is possible for nursing infants of mothers on hemodialysis to receive very high doses of DEHP; however the exact dose received by these babies is highly uncertain. Because of the level of uncertainty in this estimate, a TI/Dose ratio was not derived for this means of exposure to DEHP. Also, because women on hemodialysis are typically infertile, the population of infants exposed in this manner is thought to be very small.

Bags used to store breast milk following the use of a breast pump are typically made from polyethylene or nylon coated with polyethylene. Consequently, it is not expected that infants will be exposed to any DEHP released from a breast pump or milk storage bags.

Aggregate exposure to DEHP from multiple medical devices

DEHP dose estimates typically do not take into account exposure of patients to multiple PVC devices. Consequently, it is important to assess the potential risk of patients in various clinical scenarios by taking into account aggregate exposure to DEHP from multiple devices. For example, neonates in the NICU environment are exposed to DEHP from multiple devices. Based on the dose of DEHP received in such procedures as intravenous administration of sedatives, administration of TPN and replacement transfusion, all common procedures in the NICU, it is possible to estimate that a 4 kg infant could receive a DEHP dose on the order of 3 mg/kg/day for a periods of weeks or months. The resulting TI/dose ratio in this setting is 0.2. In other words, the dose of DEHP received by some infants from device-related sources could be 5-fold greater than the TI. If the neonate is also undergoing ECMO treatment, the TI/dose ratio drops to around 0.05, indicating that the dose of DEHP received by some infants from device-related sources could be 20-fold greater than the dose of DEHP that is not expected to result in adverse effects following intravenous exposure.

Are children at increased risk for the adverse effects of DEHP, relative to adults?

Executive Order 13045, issued on April 27, 1997, directs relevant Federal agencies to make it a high priority to identify and assess environmental health risks that may disproportionately affect children and ensure that its policies, programs, and standards address disproportionate risks to children from environmental health risks or safety risks. Accordingly, FDA/CDRH has examined this issue and has concluded that **children undergoing certain medical procedures may represent a population at increased risk for the effects of DEHP.** This decision is supported by three findings: 1) children undergoing some medical procedures receive a greater dose of DEHP, on a mg/kg basis, than adults do, 2) pharmacokinetic differences between children and adults may result in greater absorption of DEHP, greater conversion of DEHP to MEHP (the toxic metabolite of DEHP), and reduced excretion of MEHP in children compared to adults, and 3)

children may be more pharmacodynamically sensitive to the adverse effects of DEHP than adults are. This conclusion is consistent with that reached by the expert panel that was recently convened by the Center for the Evaluation of Risks to Human Reproduction (CERHR) of the National Toxicology Program. Specifically, the panel noted that: “The available reproductive and developmental toxicity data and the limited but suggestive human exposure data indicate that human exposures in this situation approach toxic doses in rodents, which causes the Panel serious concern that exposure may adversely affect male reproductive tract development.”

1.0 Introduction

Polyvinyl chloride (PVC) plastic is used to manufacture a number of medical devices, including IV and blood bags and infusion tubing, enteral and parenteral nutrition feeding bags, nasogastric tubes, peritoneal dialysis bags and tubing, and tubing used in devices for cardiopulmonary bypass (CPB), extracorporeal membrane oxygenation (ECMO), and hemodialysis. Unplasticized PVC is hard and brittle at room temperature. As a result, plasticizers are necessary to impart flexibility to the polymer. Various plasticizers (e.g., adipates, citrates, phthalates) have been used as plasticizers for PVC, but the plasticizer of choice for PVC medical devices is di-(2-ethylhexyl) phthalate (DEHP).

The potential for (DEHP) and other phthalate esters to produce adverse effects in humans has been the subject of considerable discussion and debate in the scientific community, as well as attention by the media. Although the toxic and carcinogenic effects of DEHP have been well established in experimental animals, the ability of this compound to produce these effects in humans is controversial.

Concerns over the potential adverse effects of DEHP in patients have prompted one group, Health Care Without Harm (HCWH), to submit a Citizens' Petition to the FDA Commissioner requesting that the agency initiate action to require labeling on PVC medical devices to warn users that these devices may expose patients to DEHP and to establish a program to expedite the development and usage of substitutes for PVC devices that leach phthalate esters. In addition, various expert panels have recently been convened to examine the likelihood that exposure to DEHP could result in the development of adverse effects in humans, including a panel convened under the auspices of the American Council on Science and Health (ACSH), chaired by Dr. C. Everett Koop and a panel convened by the National Institute of Environmental Health Sciences' (NIEHS) Center for the Evaluation of Risks to Human Reproduction (CERHR). The FDA Center for Biologics Evaluation and Research (CBER) also recently held a workshop to examine issues relating to the use of phthalates as plasticizers for blood storage bags.

The various panels described above have been convened largely to address a series of controversial issues regarding the potential health risk posed by human exposure to DEHP. Following a review of the available data, these groups have reached differing opinions regarding the health risk posed by exposure to DEHP. For example, expert panel chaired by Dr. Koop for the ACSH concluded that there is little or no harm posed by patient exposure to DEHP. This conclusion was also reached by trade groups associated with the manufacture of PVC medical devices or the production of phthalate esters, such as the Health Industry Manufacturers Association (HIMA), the Phthalate Esters Panel of the Chemical Manufacturers Association (CMA), the Vinyl Institute, and the American Plastics Council. In contrast, the expert panel convened by the CERHR felt that exposure of critically ill neonates to DEHP represented a "serious concern" and HCWH has concluded that the potential risks of associated with patient exposure to DEHP are significant enough to require regulatory initiatives including labeling of PVC devices and to move toward alternatives to PVC. Over the years, a number of individual investigators have also suggested that DEHP exposure may pose a risk to patients, whereas others have suggested that there is little or no risk, particularly with regard to the carcinogenic effects of DEHP.

The divergent opinions on the safety of DEHP are due, in part, to differences in the interpretation of the scientific data and, in part, to differences in philosophical approach toward safety. Industry, in part, points to the lack of effects observed in DEHP-exposed patients as evidence of the safety of DEHP, along with data that suggest that the mechanism by which DEHP exerts certain effects in rodents is not applicable to humans. In contrast, groups such as HCWH embrace a precautionary approach that argues that patient exposure to DEHP should be minimized in light of adverse effects seen in experimental animals exposed to DEHP. However, neither of these

approaches necessarily involves comparison of the dose of DEHP received by patients undergoing certain medical procedures to a Tolerable Intake (TI) value for DEHP. Such an approach was used in this safety assessment. This safety assessment has been prepared to provide risk managers with information necessary for informed regulatory decision making regarding the safety of DEHP released from PVC medical devices.

Safety Assessment Approach Used

No attempt has been made in this document to quantitatively assess the risk posed by exposure of patients to DEHP. Instead, a safety assessment approach involving comparison of the doses of DEHP received by patients undergoing various procedures to Tolerable Intake (TI) values for DEHP was used to develop a general index of safety or risk with regard to patient exposure to DEHP. A TI value is defined as the dose of a compound that is not expected to result in adverse effects following exposure for a defined period. The process used to derive the TI values for DEHP is outlined in ISO/DIS 10993-17, *Method for the Establishment of Allowable Limits for Leachable Substances*, and is described more fully in Section 3.0. Briefly, this process consists of three steps:

Step 1: Identification of data from critical studies to serve as the basis for the selection of no-observed-adverse-effect-level (NOAEL) and lowest observed adverse effect-level (LOAEL).
Step 2: Derivation of Uncertainty Factors (UFs) to account for: 1) variability in response in the human population, 2) differences in the potency of DEHP between experimental animals and humans, and 3) various other limitations in the database.
Step 3: The NOAEL and LOAEL values selected from the critical studies were then divided by the product of the UFs (known as the Modifying Factor) to derive the TI.

Justification for the selection of the critical studies and uncertainty factors is provided in Section 3.0. Tables summarizing the results of all of the studies considered for TI derivation are provided in Annex B. Other potentially clinically significant effects (e.g., DEHP-mediated effects on hemocompatibility of blood tubing, drug adsorption to PVC tubing) are also discussed briefly in Section 3.0.

To characterize patient risk from exposure to DEHP, the dose of DEHP received by patients undergoing various procedures (estimated in Section 2.0) is compared to the TI values for DEHP (estimated in Section 3.0). The results of this risk characterization process, which is described in Section 4.0, will allow CDRH to draw conclusions about the risk posed by patient exposure to DEHP in various clinical scenarios.

2.0 Exposure Assessment

DEHP is released from a wide variety of PVC medical devices. A partial list of these devices is provided in Table 2-1.

Table 2-1. PVC medical devices known to release DEHP

IV storage bags	Ventilator tubing
IV infusion sets	Endotracheal tubes
IV infusion catheters	Nasogastric tubes
Blood storage bags	Enteral and parenteral nutrition storage bags
Blood administration sets	Urinary catheters
PVC exam gloves	Suction catheters
Chest tubes	Nasal cannula tubing
Hemodialysis tubing	Syringes
Extracorporeal membrane oxygenation (ECMO) tubing	Cardiopulmonary bypass (CPB) tubing

In this section, an attempt is made to quantify the dose of DEHP received by patients undergoing various medical procedures. In most cases, exposure is represented as administered dose (mg/kg/day) and is time-averaged over a course of treatment. For example, if an adult patient receives 60 mg of DEHP in a hemodialysis session, and undergoes hemodialysis three times per week, the time-averaged dose of DEHP received by this patient would be 60 mg/session x 3 sessions/week x week/7 days x 1/70 kg = 0.37 mg/kg/day. It is necessary to represent exposure dose in units of mg/kg/day, time-averaged over the exposure period, so a common dose metric exists for comparison of the dose of DEHP received by patients and the TI values for DEHP.

This section briefly provides the rationale for the selection of the doses used to develop the TI/dose ratios presented in Section 4.0, Risk Characterization. A more complete assessment of patient exposure to DEHP can be found in Annex A..

2.1 Parenteral Exposure to DEHP

Parenteral exposure to DEHP can occur following intravenous infusion of crystalloid solutions (e.g., normal saline, D5W, Ringers Lactate) and drugs, administration of enteral nutrition and total parenteral nutrition (TPN) solutions, and transfusion of blood or blood products. In addition, patients undergoing cardiopulmonary bypass (CPB), extracorporeal membrane oxygenation (ECMO), hemodialysis or peritoneal dialysis can also be exposed to DEHP. The extent to which DEHP is released from PVC medical devices is largely a function of the lipophilicity of the fluid that comes into contact with the device. Substances like blood, plasma, red blood cell or platelet concentrates; IV lipid emulsion or total parenteral nutrition solution; and formulation aids (e.g., Polysorbate 80) used to solubilize IV medications can readily extract DEHP from PVC tubing and containers. In contrast, nonlipid-containing fluids, like crystalloid IV solutions, saline priming solution for ECMO and hemodialysis, and peritoneal dialysis solution, extract relatively small amounts of DEHP from the PVC constituents of the device. Estimates of the upper-bound doses of DEHP received by patients undergoing various medical procedures are provided in Table 2-2.

Table 2-2. Estimated upper-bound dose of DEHP received by adult and neonatal patients undergoing various medical procedures.

Procedure	DEHP dose (mg/kg/day)	
	Adult (70 kg)	Neonate (4 kg)
Infusion of crystalloid IV solutions	0.005	0.03
IV infusion of drugs requiring pharmaceutical vehicles for solubilization		
When administered according to manufacturer's instructions	0.04	0.03
When stored mixed and stored at room temperature for 24 hr	0.15	
TPN administration		
Without added lipid	0.03	0.03
With added lipid	0.13	2.5
Administered via EVA bag and PVC tubing	0.06	
Blood transfusion		
Trauma patient	8.5	
Transfusion/ECMO in adult patient	3.0	
Exchange transfusion/neonate		22.6
Replacement transfusion/neonate in NICU		0.3
Replacement transfusion/correction of anemia in patients receiving chemotherapy and in patients with sickle cell disease	0.09	
Replacement transfusion/surgical patient undergoing CABG	0.28	
Treatment of clotting disorders with cryoprecipitate	0.03	
Cardiopulmonary bypass		
CABG	1	
Orthotopic heart transplant	0.3	
Artificial heart transplant	2.4	
ECMO		14
Apheresis	0.03	
Hemodialysis	0.36	
Peritoneal dialysis	< 0.01	
Enteral nutrition	0.14	0.14

2.1.1 Intravenous solutions

In the absence of lipid-containing substances, the amount of DEHP that leaches from PVC storage bags into crystalloid IV solutions is generally very small. For example, little or no DEHP was found to leach into crystalloid solution (normal saline, D5W) stored in PVC bags for more than one year (Dine et al., 1991).

The upper-bound concentration of DEHP in crystalloid IV solutions, as reported by Corley et al. (1977) for non-agitated bags (0.344 mg/day) was used to develop the adult TI/Dose ratios for this procedure. Based on this value, the time-averaged dose of DEHP delivered to a 70 kg patient receiving 2 L of IV solution/day would be on the order of 0.005 mg/kg/day.

Neonatal patients do not typically receive IV fluid administration via a gravity feed, rather a syringe infusion pump is often used to administer IV fluids to pediatric patients. Although the syringe used is typically made from polypropylene, a small amount of DEHP can be released from the PVC administration tubing. Loff et al. (2000) found that infusion of a crystalloid IV solution through PVC tubing for 24 hours yielded a DEHP dose of 116 µg, equivalent to a dose of 0.03 mg/kg/day for a 4 kg neonate.

2.1.2 Intravenous administration of lipophilic drugs dissolved in pharmaceutical solvents

The package insert labeling that accompanies a number of drug products, notably antineoplastics (e.g., paclitaxel, docetaxel, tacrolimus, teniposide), cautions against the use of PVC containers and administration sets for delivery of the drug. If non-PVC containers and non-PVC infusion sets are used to administer the drug, DEHP exposure is expected to be minimal.

The labeling information provided with a number of other drugs (ciprofloxacin, cefoperazone sodium, fluconazole, metronidazole HCl, cimetidine) instructs the user to administer and store the reconstituted drug in PVC bags that release minimal amounts of DEHP, such as Baxter's PL-146 bag. The concentration of DEHP in these bags is assumed to not exceed 5 ppm (5 µg/ml). Based on the dosage requirements of the drug, the dose of DEHP received by patients receiving these drugs in PL-146 bags is not expected to exceed 3 mg/day (0.04 mg/kg/day), assuming the premixed solution is agitated for 24 hours at room temperature before administration to the patient. Since IV bags are not typically agitated for 24 hours, the actual DEHP dose received by most patients treated with these drugs will be much less.

Often, multiple drugs are co-infused in the same IV infusion. One such case is the co-infusion of quinine along with multivitamin preparations. Faouzi et al. (1999a) demonstrated little DEHP is released from PVC bags containing quinine alone in solution; however, the presence of the lipophilic multivitamin cocktail dramatically increased the extent of DEHP release from the bag. Following storage of quinine/multivitamin combinations for 48 hours at 45°C, the concentration of DEHP in the bags reached 21 µg/ml. Consequently, a patient receiving a 500 ml infusion of quinine with a multivitamin cocktail would receive 10.8 mg of DEHP, or 0.15 mg/kg/day for a 70 kg adult. Since the storage of drug-containing IV solutions at 45°C is unlikely, this value represents an upper-bound estimate of the amount of DEHP received by adults during IV drug administration.

Drug infusions are typically administered to pediatric patients using an infusion pump. Loff et al. (2000) measured the amount of DEHP that could be received by a pediatric patient receiving IV drug therapy (Table 2-3).

Table 2-3. Dose of DEHP received by neonates undergoing IV drug therapy (Loff et al., 2000)

Drug	Perfusion time (hours)	Concentration of DEHP after perfusion (µg/ml)	Amount in ml	Total Amount of DEHP (µg)	Total Dose of DEHP (mg/kg/day) for a 4 kg neonate
Imipenem	0.5	0.78	8	6.26	0.0015
Midazolam	24	1.13	24	26.4	0.007
Fentanyl	24	4.59	29	132.5	0.033
Propofol	24	656	10	6561	1.64

As shown in Table 2-3, relatively little DEHP is expected to be received by children undergoing drug therapy with imipenem, midazolam or fentanyl. In contrast, patients receiving propofol can receive a considerable dose of DEHP over a 24 hour period. However, propofol is not approved for sedation in pediatric ICU patients in the US (FDA, 2001). Therefore, for the purpose of this assessment, the upper-bound dose of DEHP received by neonates undergoing conscious sedation is assumed to be 0.03 mg/kg/day for a 4 kg infant, based on the DEHP dose received during fentanyl infusion.

2.1.3 Parenteral nutrition

Total parenteral nutrition (TPN) formulations are often administered to critically ill patients requiring nutritional supplementation. Parenteral administration involves infusion directly into the circulatory system. Typical TPN admixtures contain amino acids, dextrose, electrolytes and lipids. Mazur et al. (1989) have shown that the presence of lipid in the TPN solution increases the concentration of DEHP in the admixture when PVC bags are used. The estimated daily dose of DEHP received by an adult patient receiving 3 L of TPN admixture that is either lipid-free or that has a lipid concentration of 10% is 0.03 and 0.13 mg/kg/day, respectively.

Although PVC storage bags are still used for TPN administration, EVA (ethylvinyl acetate) bags are being increasingly used for this application. However, even EVA bags contain PVC components (Kambia et al., 2001), resulting in the release of some DEHP into the TPN solution. In addition, although plasticizer-free tubing can be used gravity infusion of lipid emulsions, the use of PVC tubing is required for pump assisted lipid administration. Pump-assisted administration is necessary to overcome hyperalimentation fluid-lipid density differences and variable central venous back pressures. Therefore, it is possible that a considerable amount of DEHP could be received by patients receiving TPN even though non-PVC bags are used to store the TPN solution. The amount of DEHP released into TPN solution stored for 24 hours in EVA bags ranged from 0.2 to 0.7 mg (Kambia et al., 2001); 0.8 to 2 mg was released from the bag and the PVC administration set, following flow of the emulsion through the tubing for 11 hours. Assuming the highest amount of DEHP released from the outlet of the tubing came from emulsions containing the highest concentrations of DEHP, then the amount of DEHP released from the tubing ranged from 0.6 to 1.3 mg/day, based on administration for 11 hours/day. Based on these values, up to 2.8 mg of DEHP could presumably be released from the tubing over a 24-hour infusion and up to 4.4 mg of DEHP total (EVA bag + tubing) could be received over a 24-hour period (equivalent to 0.06 mg/kg/day for a 70 kg adult).

Unlike adults or even older children, neonates typically receive TPN via a syringe infuser. Loff et al. (2000) recently reported that if PVC tubing is used to administer the TPN, an infant could receive over 10 mg of DEHP from the tubing over a 24-hour period (equivalent to 2.5 mg/kg/day for a 4 kg neonate). However, an upper-bound dose of DEHP received by neonates can be derived from the data reported by Kambia et al. (2001) as follows: 1600 ng/ml (maximum conc.

of DEHP measured at outlet of PVC tubing) x 150 ml/kg/day (upper-bound dose rate for administration of TPN to neonates) = 0.24 mg/kg/day.

2.1.4 Transfusion of blood and blood products

DEHP migrates from PVC storage bags and into blood and blood products (platelets, plasma, packed red blood cells) because of the lipophilic nature of these biological fluids and cells. To derive appropriately protective TI/Dose ratios, upper-bound concentrations of DEHP were used to derive administered dose estimates.

Current clinical practices in transfusion medicine have been taken into account in deriving these administered dose estimates. For example, whole blood is rarely administered clinically. Instead, patients usually receive RBCs, platelets, fresh frozen plasma (FFP) or some combination of these products. When estimating the dose of DEHP received by patients receiving blood or blood products, it is important to differentiate between two scenarios: 1) infusion of large amounts of blood or blood products over a short period and 2) chronic infusion of smaller volumes of blood over a prolonged period. Acute, large-volume blood transfusion is necessary in the treatment of acute blood loss in trauma patients, some patients undergoing surgery, patients with acute gastrointestinal bleeding and neonates undergoing exchange transfusion. Chronic administration of smaller volumes of blood or blood products is common in the treatment of patients with chemotherapy-associated anemia, blood disorders such as leukemia and aplastic anemia, and in the treatment of patients with clotting disorders.

Based on the results reported by other investigators, Sjoberg et al. (1985b) estimated that an adult receiving 2.5 L of blood stored for 21 days would receive a DEHP dose of 1.3 to 2.6 mg/kg. In cases of massive blood loss and transfusion of large amounts of blood, considerably more DEHP could be administered to a patient. For example, Jaeger and Rubin (1972) estimated that a gunshot victim receiving 63 units of blood would receive a DEHP dose of around 8.5 mg/kg. This value represents an upper-bound estimate of the dose of DEHP that is likely to be infused during short-term transfusion scenario. It is important to recognize that the actual dose of DEHP received by most critically injured patients from transfusion will be much less.

Patients on ECMO receive RBCs to correct anemia and they receive platelet concentrates, FFP, and cryoprecipitate to treat clotting disorders. It is possible for adult patients to receive over 600 units of blood products during the course of their ECMO treatment and hospitalization. Based on the concentration of DEHP in blood and blood products, it is possible for adults patients on ECMO to receive DEHP doses on the order of 3 mg/kg/day or greater, solely from the blood transfusions necessary to correct anemia and clotting disorders in these patients.

Infants receiving exchange transfusion could receive a DEHP dose up to 22.6 mg/kg, according to Plonait et al. (1993); however, the DEHP dose received by infants in the Sjoberg et al. (1985b) studies ranges from 0.84 to 4.22 mg/kg. It should be noted that exchange transfusion was once commonly performed for the treatment of hyperbilirubinemia, however, is rarely used today.

Critically ill neonates require repeated phlebotomies that may deplete their blood volume. Also, infants are susceptible to anemia of prematurity. As a result, critically ill neonates often require transfusions. Levy et al. (1993) reported that 80% of low birthweight infants in the United States will receive multiple transfusions. Ringer et al. (1998) reported that neonates in one neonatal intensive care unit (NICU) received, on average, 33.6 ml of RBCs and 2.4 ml of FFP in the first 14 days. Infants in this study weighed about 1 kg. The dose of DEHP received by neonates undergoing replacement transfusion with packed RBCs is shown in Table 2-4.

Table 2-4. Dose of DEHP received from replacement transfusion in neonates

Blood product	Volume[1] (ml)	Estimated DEHP concentration[2] (µg/ml)	DEHP dose[3] (mg/kg/day)
RBCs	33.6	123.1	0.3
FFP	2.4	26.7	0.004

[1]Mean volume infused over 14 days in one of two NICUs
[2]Upper-bound concentration as reported by Plonait et al. (1993) for packed cells and by Shintani (1985) for FFP
[3]Assumes mean body weight of 1.073 kg per Ringer et al. (1998)

Since blood used for replacement transfusions is typically drawn up from the storage bag with a syringe and injected into the patient, there is no need to account for DEHP released from infusion sets. However, if blood products are administered via an infusion pump, then the amount of DEHP received by a pediatric patient would be considerably greater. For example, Loff et al. (2000) found that up to 8.1 mg of DEHP was released from PVC infusion tubing following perfusion of 20 ml of fresh frozen plasma through the tubing for 1 hour. This would result in a DEHP dose of around 2 mg/kg/day for a 4 kg child.

Patients with some chronic illnesses and those receiving antineoplastic chemotherapy often become anemic and require blood transfusion. Jacobson et al. (1977) determined that patients with leukemia and aplastic anemia receiving red cells, whole blood, and platelets over the course of one year received a DEHP dose of 0.006 to 0.08 mg/kg/day, when the dose was time averaged over the year-long administration period. Patients with sickle cell disease are typically transfused with 1-2 units of packed cells every 2-4 weeks. Using the data from Plonait et al. (1993) as an upper-bound value for the concentration of DEHP in packed red cells (174 µg/ml), the dose of DEHP received by a patient with sickle cell disease would be approximately 0.09 mg/kg/day.

Anemia is a common problem in patients undergoing chemotherapy for cancer treatment. As discussed by Barrett-Lee et al. (2000), 33% of patients receiving chemotherapy will require blood transfusion during their course of treatment. Estrin et al. (1999) reported that an average of 5.1 red blood cell units were infused per patient undergoing chemotherapy. The upper-bound estimate of DEHP exposure in this scenario is about 0.03 mg/kg/day.

Cryoprecipitates containing clotting factors are administered to patients with clotting disorders. Marcel (1973) found that cryoprecipitate packs contained from 0.8 to 1.9 mg of DEHP each. Since patients with clotting disorders can receive up to 400 bags of cryoprecipitate in one year, the daily DEHP dose received by these patients is on the order of 0.03 mg/kg/day.

Patients undergoing routine, elective surgical procedures typically receive about two units of blood or blood products (Mallett et al., 2000). Assuming a mean DEHP concentration of 44.8 µg/ml for packed cells (Plonait et al., 1993) and a packed cell volume of 350 ml, transfusion in a typical surgery would result in administration of a DEHP dose of 0.5 mg/kg/day.

2.1.5 Cardiopulmonary bypass and ECMO

Cardiopulmonary bypass is used in a number of cardiac surgical procedures (e.g., heart valve replacement, CABG surgery, heart transplantation, correction of congenital defects) and is also used as a means to oxygenate the blood during cardiac or pulmonary failure. Cardiopulmonary bypass used as a means to supplement blood oxygenation is termed extracorporeal membrane oxygenation (ECMO). Since considerable lengths of PVC tubing is typically used in heart-lung bypass circuits (i.e., 600 cm of PVC tubing can be used in ECMO circuits) the potential exists for patients undergoing these procedures to be exposed to DEHP.

Barry et al. (1989) showed that levels of DEHP and MEHP increased dramatically in patients who had undergone cardiopulmonary bypass during cardiac surgery. Although the dose of DEHP or MEHP received by these patients only from the CPB device and PVC tubing was not calculated, the total dose of these phthalate esters from all sources (i.e., tubing, transfusions) was estimated (Table 2-5).

Table 2-5. Dose of DEHP received during cardiac surgery (Barry et al., 1989)

Procedure	DEHP dose (mg/day)[1]	MEHP dose (mg/day)[1]
Coronary artery bypass graft (CABG)	15.4 to 72.9	2.2 to 8.0
Orthotopic heart transplantation	2.3 to 21	0.45 to 2.5
Artificial heart transplantation	3.8 to 167.9	0.25 to 18.8

[1]in the first 24 hours following surgery

Two groups of investigators, Shneider et al. (1989) and Karle et al (1997), have estimated the dose of DEHP received by infants undergoing ECMO (Table 2-6).

Table 2-6. Dose of DEHP received by infants undergoing ECMO

DEHP dose range (mg/kg)	DEHP concentration in blood during ECMO (µg/ml)	Study
4.7 to 34.9	0 to 34.9[1]	Karle et al. (1997)
42 to 140[2]	26.8[3] 33.5[4]	Shneider et al. (1989)

[1]Depending on circuit, normalized to a 4 kg infant
[2]3 to 10 day course of treatment
[3]Following 14 days of ECMO
[4]Following 24 days of ECMO

Information is unavailable to accurately estimate the dose of DEHP received by these patients on a mg/kg/day basis, since the exposure period is represented as a range (3-10 days). However, if we assume that the larger DEHP doses were received by patients undergoing this procedure for 10 days, the time averaged dose of DEHP received by these neonates is expected to be 3.5 to 14 mg/kg/day.

Estimates of DEHP dose derived by Karle et al. (1997) are based on the rate at which DEHP is extracted from ECMO tubing by circulating blood *in vitro*. It is interesting to note that Karle et al. (1997) demonstrated that little or no DEHP was released from heparinized PVC tubing. Although data are not available on the dose of DEHP received by patients undergoing ECMO using a heparin-coated circuit, it is anticipated, based on the results of the Karle et al. (1997) study, that many patients currently undergoing this procedure will receive little or no DEHP from the ECMO tubing. Although heparin-coated tubing is available in the US, the FDA has not approved the use of heparinized ECMO circuits.

Based on the data collected by Roy et al (2000), it is assumed that fewer than 1000 infants undergo this procedure annually in the US.

2.1.6 Hemodialysis

Hemodialysis represents a medical procedure that has the potential to deliver considerable doses of DEHP to a patient. For example, Faouzi et al. (1999b) recently reported that, on average, 75.2 mg of DEHP was extracted during a single dialysis session, with a range of 44.3 to 197.1 mg. However, Faouzi et al. (1999b) pointed out that not all infused DEHP is retained by the patient. These investigators have estimated that 3.6 to 59.6 mg of DEHP is retained in a single dialysis session. Assuming 3 dialysis sessions per week, this dose is equivalent to a time-averaged dose of 0.02 to 0.36 mg/kg/day for a 70 kg patient.

2.1.7 Peritoneal dialysis

Since peritoneal dialysis fluids are crystalloid in nature, it is not surprising that little DEHP is delivered to a patient in this procedure. Nassburger et al. (1987) measured levels of DEHP in peritoneal dialysis solution ranging from 4 to 11 μg/L. Similarly, DEHP concentrations in peritoneal dialysis fluid ranged from 1.1 to 3.7 μg/L, as measured by Sugimura et al. (2001). However, Mettang et al. (1996) found DEHP levels in dialysis fluid that ranged from 21 to 130 μg/L. Assuming a patient undergoing continuous ambulatory peritoneal dialysis (CAPD) is dialyzed with 8 L of fluid/day, the upper-bound estimate of the daily dose of DEHP infused into the peritoneum would be on the order of 1 mg/day (0.13 μg/ml x 8,000 ml/day x 0.001 mg/μg). Since the majority of an intraperitoneally injected dose of DEHP is not be absorbed (Rhodes et al., 1983) the administered dose of 1 mg/day is likely to overestimate the absorbed dose. Furthermore, a considerable amount of the infused DEHP will be returned upon drainage of the perfusate from the peritoneum.

Although the dose of DEHP or MEHP absorbed across the peritoneum by patients undergoing CAPD is likely to be low, as compared to other procedures, the endpoint of concern in patients exposed to DEHP and MEHP from CAPD may be a “local” one - peritoneal sclerosis - an endpoint that is not affected by the systemically absorbed dose. This issues is discussed in more detail in Section 3.0.

2.1.8 Apheresis

Data are unavailable on the dose of DEHP received by donors undergoing apheresis. However, Doull et al. (1999) used two assumptions to derive an estimate of the DEHP dose received by individuals undergoing this procedure: 1) that data on the amount of DEHP released during hemodialysis provide an upper-bound estimate of DEHP dose for this procedure and 2) that leaching of DEHP from PVC apheresis tubing is linear over time. If 74 mg of DEHP are released during a hemodialysis procedure lasting 5 hours (a value consistent with that reported by Fauozi et al. 1999b), it was assumed by Doull et al. (1999) that 14.8 mg of DEHP could be released during one apheresis procedure lasting one hour. Further assuming that platelet/plasma donation occurs once/month, the time averaged dose of DEHP received by a donor would be around 0.5 mg/day. FDA regulations stipulate that patients cannot donate platelets more than twice per month. Also, 2 hours is a more realistic estimate for the duration of an apheresis procedure. Therefore, assuming the dose of DEHP received by an apheresis donor is probably more on the order of 1.97 mg/day. This dose is equivalent to 0.03 mg/kg/day for a 70 kg donor; however, it should be pointed out that there is considerable uncertainty associated with this estimate.

2.2 Oral Exposure

In the medical device context, oral exposure to DEHP can occur following release of this phthalate from enteral feeding bags and tubing or from nasogastric tubing used for aspiration of stomach contents and decompression of the stomach. An additional source of oral exposure to phthalate esters, release from denture material, is possible. Although DEHP has been detected in leachates from dental composites (Lee et al., 1998), phthalates other than DEHP are typically used as

plasticizers for this application.

2.2.1 Enteral feeding

Enteral feeding is preferred over parenteral nutrition as a means to provide nutrition to critically ill patients (Sigurdsson, 1997). Some patients, especially those receiving care at home or in nursing facilities, will receive nutritional support enterally (via the gastrointestinal tract) rather than parenterally. Exposure to DEHP can come from the PVC bag used to store the enteral nutrition solution and the nasogastric tube, if one is used to administer the solution.

No data are available on the extent to which DEHP is released from enteral nutrition storage bags; however, the assumption can be made that these bags release DEHP at the same rate as bags used to store TPN admixtures. The total amount of DEHP received by a patient receiving enteral nutrition can be estimated from is the sum of the amount released from the bag and from the tubing. Using the data from Mazur et al. (1989), and assuming that that the enteral nutrition admixture contains a similar amount of lipid as the parenteral admixture, an upper-bound estimate of this dose is 9.47 mg/day, or 0.14 mg/kg/day. A more typical daily dose from enteral nutrition would probably be on the order of 0.04 mg/kg/day. By comparison, estimates of the amount of DEHP received by the general population via food range from around 0.3 mg/day for typical individuals to around 2 mg/day for highly exposed individuals.

2.2.2 Breast milk

One means of exposure to DEHP and MEHP that seems to have been largely overlooked is lactational transfer from a nursing mother to her offspring. The rodent studies that demonstrate adverse effects in offspring following ingestion of milk from DEHP-exposed dams (e.g., Parmar et al, 1985; Dabholkar, 1988; Cimini et al., 1994; Stefanini et al., 1997) suggest that transfer of enough DEHP or MEHP can take place to cause adverse effects.

Some data are available on levels of DEHP in milk from healthy mothers and KEMI (2000) has estimated that the average daily intake of DEHP via nursing would be 0.021 mg/kg/day for infants aged 0-3 months and 0.008 mg/kg/day for 3- to 12- month-old children. However, experimental data are unavailable on levels of DEHP in milk from mothers who have undergone or are undergoing medical procedures such as hemodialysis. In the absence of data from these patients, it's possible to derive preliminary estimates the concentration of DEHP and MEHP in human milk from levels of DEHP in the plasma or patients undergoing hemodialysis and experimentally derived milk:plasma partition coefficients for rats reported by Dostal et al. (1987) or by using theoretical partitioning models, such as those developed by Begg and Atkinson (1993). Using either of these approaches, it is possible to estimate that the dose of DEHP received by nursing infants of mothers exposed to DEHP via hemodialysis could be as much as 90 mg/kg/day (see Annex A for more detail); however this value is highly uncertain. Because of the level of uncertainty in this estimate, a TI/Dose ratio will not be derived for this means of exposure to DEHP.

Bags used to store breast milk following the use of a breast pump are typically made from polyethylene or nylon coated with polyethylene. In addition, the expressed milk is not expected to come into contact with flexible PVC components of the breast pump. Consequently, it is not expected that infants will be exposed to any DEHP released from a breast pump or milk storage bags.

2.3 Inhalation Exposure

Since PVC tubing is used in respirators, it is theoretically possible for some amount of this plasticizer to be released from the tubing into the respiratory air stream and result in patient exposure. Based on the concentration of DEHP measured in the air stream passed through PVC respiratory tubing, Hill (1997) it is estimated that a patient undergoing respiratory therapy would receive a daily DEHP dose ranging from 28.4 to 94.6 µg, which is equivalent to a dose of 0.0004 to 0.001 mg/kg/day for a 70 kg adult.

2.4 Dermal/Mucosal Exposure

The potential exists for DEHP to be released from skin surface- or mucosal membrane-contacting PVC devices such as urinary catheters, drug delivery patches, occlusive dressings, oxygen masks, and endotracheal tubes. However, there are insufficient data to accurately characterize the amount of DEHP that would be released from these devices and taken up by the body. Although nasogastric tubes contact the esophageal mucosa, it is assumed that the majority of the DEHP released from these devices is extracted from the lumenal side of the tubing and is subsequently absorbed in the gastrointestinal tract.

Patients are assumed to have only incidental contact with PVC gloves worn by health care workers. Since this safety assessment deals only with potential health risks to patients, the potential risk to health care workers from dermal exposure to DEHP will not be assessed. However, it is useful to note that KEMI (2000) has estimated that a health care worker wearing gloves for 2 hours/day could receive a DEHP dose of 0.007 mg/kg/day.

2.5 Aggregate Exposure to DEHP from Multiple Medical Devices

In additional to estimating exposure to DEHP on a procedure-by-procedure basis, it is important to estimate the total or aggregate dose of DEHP received by patients following exposure to multiple PVC devices.

2.5.1 Neonates in NICU setting

Neonates in the NICU environment are exposed to DEHP from multiple devices. Based on the dose of DEHP received in such procedures as intravenous administration of sedatives, administration of TPN and replacement transfusion, all common procedures in the NICU, it is possible to estimate that a 4 kg infant could receive a DEHP dose on the order of 3 mg/kg/day for a periods of weeks or months (Table 2-7).

Table 2-7. Aggregate exposure of neonates to DEHP in the NICU environment.

Procedure	DEHP dose (mg/kg/day)[1]
IV administration of sedative	0.03
IV administration of TPN	2.5
Replacement transfusion	0.3
Total[2]	2.83

[1]4 kg infant

[2]Doesn't include DEHP does from endotracheal intubation, nasogastric tube or ECMO

2.5.2 Adult patients undergoing ECMO

The total dose of DEHP received by patients undergoing ECMO can be grossly underestimated if this dose is estimated simply from data on the extent to which DEHP is released from PVC tubing used in the device. Since these patients are multiply transfused and can receive over 600 transfused units (RBCs, platelet concentrates, FFP, cryoprecipitate) during their course of ECMO and hospitalization, a considerable amount of DEHP can also be received from transfused blood products as well as the PVC used in the ECMO device. Patients undergoing ECMO are also multiply transfused and may receive drugs (e.g., antibiotics, vitamins) solubilized in pharmaceutical surfactants that promote DEHP release from PVC bags. For example, an adult undergoing ECMO could receive a DEHP dose ≥ 4 mg/kg/day, if aggregate exposure from multiple devices is considered. The principle contribution to the total dose of DEHP received by these patients comes from the multiple transfusions needed by these patients, not the PVC tubing used in the ECMO device.

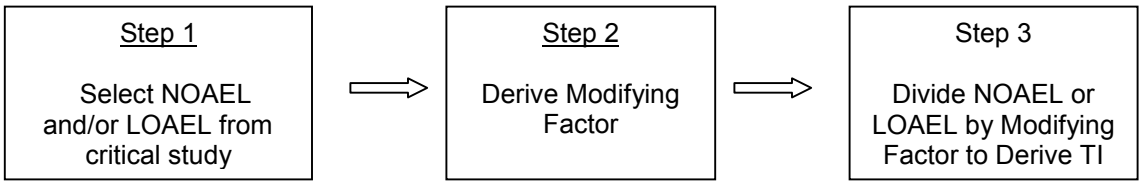
2.5.3 Adult patients undergoing surgical procedures

Adult patients receiving a coronary artery bypass graft surgery are can receive DEHP from a during a number of medical devices, including an endotracheal tube, IV bags and tubing (especially if a multivitamin solution is infused), chest tubes, hemodynamic monitoring catheters, nasal cannula, nasogastric tube, and blood bags and administration sets. The dose of DEHP received by these patients, as estimated by Barry et al. (1989), is based on the concentration of DEHP in the blood, and therefore, takes into account aggregate exposure.

3.0 Derivation of Tolerable Intake (TI) Values

The process used to derive the Tolerable Intake (TI) values for DEHP is outlined in ISO/DIS 10993-17, *Method for the Establishment of Allowable Limits for Leachable Substances*, and is illustrated in Figure 3-1.

Figure 3-1. Process for Deriving Tolerable Intake (TI) Values (from ISO/DIS 10993-17)



Briefly, this approach involves the following steps. Following a comprehensive review of the literature, data from critical studies were identified to serve as the basis for the selection of no-observed-adverse-effect-level (NOAEL) and lowest observed adverse effect-level (LOAEL) (Step 1). The complete database of studies reviewed for the safety assessment is summarized in Annex B; however, the merits and limitations of studies that reported the highest NOAELs and lowest LOAELs following parenteral administration of DEHP to experimental animals are reviewed in more detail in this section to illustrate how the critical values were selected. Once the most appropriate NOAEL and LOAEL values were selected, Uncertainty Factors (UFs) were derived to account for: 1) variability in response in the human population, 2) assumed differences in the potency of DEHP between experimental animals and humans, and 3) various other limitations in the database (Step 2). The NOAEL and LOAEL values selected from the critical studies were then divided by the product of the UFs (known as the Modifying Factor) to derive the TI (Step 3):

$$\text{TI (mg/kg/day)} = \frac{\text{NOAEL or LOAEL (mg/kg/day)}}{\text{Modifying Factor}}$$

Since the potency of DEHP differs across routes of exposure, separate TIs were derived for oral and parenteral exposure to the compound.

Although ISO/DIS 10993-17 instructs the user to derive a cancer-based TI when appropriate, there is considerable uncertainty with regard to the carcinogenic potential of DEHP in humans. Further, insufficient data exist to derive a cancer-based TI for DEHP for parenteral routes of exposure. As a result, a TI based on carcinogenicity will not be derived at this time for DEHP. Also, the methodology described in ISO/DIS 10993-17 allows the user to derive an Allowable Limit (AL) value from the TI value; however, derivation of an AL takes into account factors such as technical and economic feasibility that are beyond the scope of this safety assessment.

3.1 Selection of Appropriate NOAEL and/or LOAEL Values from Critical Studies (Step 1)

Table 3-1 summarizes the results of studies in which the lowest parenteral LOAEL values for DEHP were reported in the literature (parenteral studies listed in ascending order according to LOAEL). The reader should note that many studies other than those listed in Table 3-1 were reviewed in this safety assessment. The results of these additional studies are summarized in Annex B. The criteria for determining the applicability of these study results for derivation of TI values for DEHP are summarized in Table 3-2.

Table 3-1. Critical toxicity studies for DEHP

Study	Route	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Effect(s) at LOAEL
Jacobson et al. (1977)	IV		0.021	Histopathological changes in liver, altered BSP clearance kinetics
Fracasso et al. (1999)	IP		0.05	Peritonitis
Nair et al. (1998)	IP		0.75	Reduced levels of Vitamin E in the liver
Miripol et al. (1975)	IV	0.33	1.1	Reduced uptake of colloidal carbon
Komitowski et al. (1986)	IP		4.3	Morphological changes observed in hepatocytes using image analysis
Petersen et al. (1975)	IV		5.0	Reduced fertility
Rubin and Chang (1978)	IV		7.7 to 13	Pulmonary effects
Rutter (1973)	IV		21.4	Hepatomegaly, increased liver enzyme levels, increased lung weight
Rubin and Chang (1976)	IV		40	Reduced blood pressure
Curto and Thomas (1982)	IP		50	Reduced testicular Zn
Petersen (1975)	IV		50	Reduced litter size following exposure of treated males to untreated females
Greener et al. (1987)	IV	92	165	Reduced body weight gain, hepatomegaly, ↑SGOT
Sjoberg et al. (1985a)	IV	25	250	Altered Sertoli cells, degeneration of primary spermatocytes
Baxter et al. (2000)	IV	60		No adverse effects
AdvaMed (2001)	IV	60	300	Testicular atrophy, decrease in diameter of seminiferous tubules and depletion of germinal cells in testes, hepatomegaly

Table 3-2. Criteria to Determine Appropriateness of Study for TI Derivation

Criteria	Explanation
Relevance of the effect for humans	Hepatomegaly and other liver effects produced by DEHP in mice after oral (and presumably parenteral) administration have been shown to be mediated by PPARα in this species (Ward et al., 1998). Since humans are thought to be relatively refractory to the hepatic effects mediated by PPARα (Cattley et al., 1998; Roberts, 1999), studies reporting this endpoint were not used as the basis for TI derivation. In contrast, there is no mechanistic reason to believe that reproductive effects seen in DEHP-exposed rodents are not relevant for humans.
Dosage form of DEHP used	Neat (undiluted) DEHP is fairly viscous at room temperature. Consequently, when neat DEHP is injected intravenously, it may produce effects in "filtering" organs such as the lungs and liver by occluding capillary flow and not because of the intrinsic toxicity of the compound. As a result, studies in which DEHP was injected neat will not serve the basis of TI values for this compound.
Relevant routes of exposure	Since DEHP is converted to MEHP by lipase in the gastrointestinal tract, it is more potent when given orally than by parenteral routes of exposure. Therefore, studies in which DEHP was administered orally will not serve as the basis for parenteral TI values.
Effects should be considered to be adverse	Many of the effects described in Table 3-1 (e.g., changes in enzyme or antioxidant levels) are not typically considered to be "adverse" from a risk assessment perspective, but rather, are considered to be "subclinical" or "precursor" effects. Only studies with effects broadly considered to be adverse (histopathological or functional changes) will serve as the basis for TI derivation.
Publication form	Insufficient detail is provided in studies reported only in abstract form to evaluate their usefulness for TI derivation.

The rationale for accepting or rejecting each of the studies listed in Table 3-1 as the basis for the TI values for DEHP is explored below.

Jacobson et al. (1977)
Jacobson et al. (1977) reported that monkeys repeatedly infused (weekly for one year) with platelet-rich plasma (PRP) stored in PVC blood bags for 48 hours had impaired liver function and abnormal liver histopathology upon completion of the transfusions. The mean dose of DEHP received by two monkeys receiving PRP stored at 4^{o} C for one year was 0.021 mg/kg/day; the mean dose in three monkeys receiving PRP stored at 22^{o} C was 0.073 mg/kg/day. There are several factors that suggest that this study is relevant and appropriate for the development of the TI derivation. These factors include:

- use of a clinically relevant route and duration of exposure,
- manifestation of these effects in a primate model, not simply a rodent species,
- a clinically relevant means of introducing the DEHP into PRP (leaching from the PVC bag, not solubilization in a detergent),
- the finding that multiple, divergent, and clinically relevant hepatic endpoints (e.g.,
- BSP clearance, histopathology) are affected, and
- Since the study employed plasma instead of blood, there is no need to account adverse hepatic effects that could be caused by hemolysis of stored blood.

Despite these factors, the relevance of the findings of the Jacobson et al. (1977) study has been challenged by several groups, notably, Baxter (1999), HIMA (1999) and the authors of the Koop report (Koop et al., 1999). For example, the Baxter (1999) scientists point out:

- The authors (Jacobson and colleagues) conceded that the observed effects are mild and could be attributed to background effects.
- The study showed no change in standard liver function.
- A valid statistical analysis of the results was not performed because of the small number of animals used in the study.
- No liver pathology was evident in the animal with the highest hepatic levels of DEHP.
- Factors other than DEHP exposure, specifically, infection of the monkeys with tuberculosis and the possible reaction of the monkeys to foreign protein in the infused blood components from other monkeys, could be responsible for the effects seen.

Although effects in the liver of monkeys were seen at very low doses of DEHP in the study of Jacobson et al. (1977), there is considerable controversy about the relevance of these findings. As a result, the results of the study by Jacobson et al. (1977) will not be used at this time for the derivation of TI values for DEHP. This decision is consistent with that reached by other regulatory agencies (e.g. CalEPA/OEHHA) and advisory panels (CERHR, 2000).

Fracasso et al. (1999)
A recent study (Fracasso et al., 1999) demonstrated that peritoneal sclerosis was produced in rats following intraperitoneal injection of a DEHP dose of 0.05 mg/kg/day for 7 days. However, peritoneal sclerosis represents a “local” effect, not a systemic one. Therefore, the results of the Fracasso et al. (1999) study will not be used for the derivation of a TI based on systemic effects. In addition, DEHP was injected neat in the Fracasso et al. (1999) study, calling into question the relevance of the results for the clinical situation.

Miripol et al. (1975)
Miripol et al. (1975) found no difference in the rate at which carbon particles were cleared from the blood of rats administered DEHP-containing PVC extracts for 26 days; however, a reduced clearance rate was observed in rats that had received DEHP-containing PVC extracts at a dose of 1.1 mg/kg/day for 63 days (19 injections of plasma containing 3.7 mg DEHP/kg BW). This subtle effect is not typically considered to be "adverse" for the purpose of TI derivation.

Komitowski et al. (1986)
Subtle morphological changes were seen in hepatocytes using image analysis following a single IP injection of DEHP at a dose of 30 mg/kg, with sacrifice 7 days later (Komitowski et al., 1986). The time-averaged dose of DEHP in this study is equivalent to 4.3 mg/kg/day. Morphological changes seen using image analysis represent a subtle alteration that would not normally be considered to be adverse. Since no effects were seen in a more traditional histopathological examination of the tissue, the results of this study will not serve as the basis for TI derivations.

Petersen et al. (1975)
Although Petersen et al. (1975) reported reduced fertility in mice following IV injection of DEHP, some uncertainty exists about the actual doses that were used in the study. For example, Petersen et al. (1975) state: "Three levels 5 mg, 25 mg, and 50 mg per 100 cc of serum were used". If this concentration was correct, it would require administration of approximately 30 ml of serum to a rat to achieve the stated doses. This is obviously a physical impossibility.

Rubin and Chang (1976, 1978)
Rubin and Chang (1976) measured a fall in arterial blood pressure of 45 mm Hg following intravenous administration of a 40 mg/kg dose of DEHP to rats. However, the DEHP was solubilized in Tween 80, raising some concerns about the potentiating effect of the vehicle. In addition, the results were only published in abstract form. As a result, they will not be used for derivation of a TI for DEHP.

A LOAEL of 7.7 to 13 mg/kg was reported by Rubin and Chang (1978) for adverse pulmonary effects following intravenous administration of DEHP to rats that had undergone a period of hypovolemia followed by re-transfusion of blood. These results suggest that the injured lung may be more susceptible than a healthy lung to adverse effects produced by intravenous administration of DEHP. Although concerns about the physical effects of DEHP are minimized by the use of plasma-solubilized DEHP in this study, they cannot be completely dismissed. Also, since the data were only reported in abstract form, these results will not be used as the basis for TI derivation. However, the ability of hypovolemia with reperfusion to potentially increase the pulmonary toxicity of intravenously administered DEHP is intriguing and deserves further study.

Rutter (1973)
Changes in liver weight and hepatic enzyme levels were observed in dogs following intravenous administration of DEHP for 4 weeks. The following factors support the selection of this dose as the LOAEL upon which a TI value can be derived:

- The effects are seen in a non-rodent species, minimizing concerns about the relevance of these findings for humans.
- The study employs a clinically relevant route of exposure. Use of the intravenous route of administration also minimizes uncertainty about the extent to which the administered dose was absorbed.
- The endpoints observed (hepatomegaly, altered liver enzymes) are consistent with those seen in other studies following exposure of experimental animals to DEHP and in patients undergoing hemodialysis.
- The presence of both morphological and biochemical changes strengthen the conclusion that adverse hepatic effects are occurring, compared to the presence of only one of these effects.
- The changes seen in liver weight and alkaline phosphatase levels are dose-dependent.

However, there are concerns about the use of these results for establishing TI values for DEHP, notably, that the DEHP was administered neat, that a small number of dogs was used in each experimental group and that the study was unpublished.

Curto and Thomas (1982)
Decreased levels of prostatic and testicular zinc were observed by Curto and Thomas (1982) following intraperitoneal injection of rats with 100 mg/kg DEHP every other day for 20 days (50 mg/kg/day). Similar effects were not seen in mice exposed to the same dose of DEHP for 20 days, nor in mice or rats injected intraperitoneally with DEHP at doses of 50 or 100 mg/kg/day for 5 consecutive days. Histopathological examination of the tissues was apparently not carried out in this study. Since 100 mg/kg was the lowest dose administered in the 20-day study, a NOAEL for this effect was not identified.

Reduction in prostatic and testicular zinc levels is a hallmark of DEHP exposure. However, changes in enzyme activity in a tissue or concentrations of a cellular constituent do not represent an "adverse" event that should serve as the basis for a LOAEL. For example, the EPA (1996) Reproductive Toxicity Risk Assessment Guidelines instruct the user to consider biochemical evidence in a supporting fashion. The guidelines note:

> The LOAEL is the lowest dose at which there is a significant increase in the frequency of adverse reproductive effects compared with the appropriate control group in a database having sufficient evidence. A significant increase may be based on statistical significance or on a biologically significant trend. **Evidence for biological significance may be strengthened by mode of action or other biochemical evidence at lower exposure levels that supports the causation of such an effect** (emphasis added).

This statement implies that biochemical evidence itself should not serve as the basis for a LOAEL determination, but rather, could be used to provide mechanistic evidence for the effects that occur at higher doses.

The guidance provided by Moore et al. (1995) is more explicit with regard to this issue.

> *Biochemical markers of reproductive exposure and effect*. Various markers of exposure and effect have been investigated in male reproductive toxicology, including prosatein, androgens, and prolactin (65). Sertoli cell enzymes or biochemical secretory products, measured *in vitro* and *in vivo* as markers of cell function, are other examples of useful end points for studying target organ or cell responses. **Currently, however, they cannot be considered evidence of male reproductive toxicity** (emphasis added)**.**

Nevertheless, there are various factors that support the conclusion that altered zinc levels may at least represent a precursor effect in DEHP-exposed animals. For example,

- Reduced testicular zinc has been observed in a number of studies (not just Curto and Thomas, 1982), in multiple animal species (not just rodents), and following administration of DEHP or MEHP via various routes of exposure.
- Dietary zinc deficiency is associated with infertility in experimental animals.
- Reduced levels of seminal zinc are associated with oligospermia in infertile men.
- DEHP is thought to exert its teratogenic effect in rodents via induction of metallothionein in the liver, with subsequent binding of plasma zinc. This sequence of events results in reduced

levels of zinc in the fetus, a finding associated with developmental toxicity in offspring of exposed animals. It is reasonable to assume that a similar mechanism may serve as the basis for DEHP-associated testicular damage and infertility.

A zinc-deficient diet has been shown to produce a range of adverse testicular effects in rats including, degeneration of seminiferous tubules and interstitial tissue, necrosis of germ cell precursors, spermatic arrest, and testicular atrophy (Hafiez et al.,1990; Hamdi et al., 1997; Merker and Gunther, 1997) and levels of zinc in seminal fluid have been shown to be lower in oligospermic men than in normospermic, fertile men in some studies (e.g., Caldamone et al., 1979; Mohan et al., 1997), but not others (e.g., Madding et al., 1986; Adejuwon et al., 1996).

Zinc deficiency can increase the sensitivity of the testes to the toxic effect of other agents, such as cadmium (Oteiza et al., 1999). Since co-exposure of patients to DEHP and other testicular toxicants such as ethylene oxide (Kaido et al., 1992) can occur in various clinical scenarios (e.g., hemodialysis), the potential exists for DEHP to potentiate the adverse testicular effects of other compounds via a mechanism involving zinc depletion in the testes.

Mechanistically, reduced zinc could play a role in the etiology of DEHP-induced testicular toxicity, either through a reduction of angiotensin-converting enzyme activity (Rahman et al., 1999) or by failure to inhibit superoxide dismutase (SOD) activity which could lead to increased superoxide anion production (Gavella et al., 1999).

It is interesting to note that plasma (but not blood) concentrations of zinc are reduced in men undergoing hemodialysis. These patients are not only exposed to relatively high levels of DEHP, but also experience a high incidence of testicular atrophy and infertility. Therefore, the effects seen in rodents may have a clinical correlate in humans.

Despite these factors, it is appropriate to consider an endpoint such as altered zinc in the testes of DEHP-exposed animals to be a precursor event to more serious effects; however, it should not be considered to be an adverse effect in its own right for the derivation of a TI value.

Greener et al. (1987)
Greener et al. (1987) investigated the toxicity of DEHP administered intravenously to 3-day-old rat pups for 18 consecutive days at doses of 30.8, 91.7, or 164.8 mg/kg/day. A significant ($p < 0.01$) dose-dependent decrease in body weight gain and average weight gain per day was observed in DEHP-treated animals relative to controls. However, the body weight data in the Greener et al. (1987) paper were reported in bar graph form, not in a tabular format, so it is impossible to determine if there is a statistically significant difference in body weight between controls and any individual treatment group. Nevertheless, based on observation of the Figure 2 in the Greener et al. (1987) paper, it appears that mean (presumably) body weights of animals in the 30.8 mg/kg/day exposure group did not differ from those in the BSA control group. The difference in body weight may have reached statistical significance in the group administered DEHP at a dose of 164.8 mg/kg/day, as compared to BSA-injected controls. In addition to changes in body weight, there was a dose-dependent increase in absolute and relative liver weight in DEHP-exposed rat pups that reached statistical significance in the high dose (164.8 mg/kg/day) group. No adverse histological effects were noted in any organ examined (brain, heart, lungs, liver, spleen, kidneys, eyes, stomach, duodenum, and caecum), with the exception of injection site lesions, at any dose used in the Greener et al. (1987) study.

Sjoberg et al. (1985a)
Although no change in testicular weight was observed in rats administered DEHP intravenously every other day for 10 days, histopathological changes were seen in the testes of rats exposed to the highest dose of DEHP used in this study, 500 mg/kg or 250 mg/kg/day (Sjoberg et al., 1985a). The histopathological effects, including Sertoli cells vacuolization and some spermatocyte degeneration, were only observed in Epon-embedded testicular tissue, not tissue embedded in paraffin. Further, these effects were observed only following electron microscopy examination of

the tissues and were not evident following examination with light microscopy. The NOAEL in this study was 50 mg/kg or 25 mg/kg/day on a time-averaged basis.

Since the study employed a clinically relevant route of exposure; is based on an endpoint assumed to be relevant for humans; involved injection of solubilized (not neat) DEHP; utilized multiple dose levels, appropriate controls and rigorous histopathological examination of the tissues; and detected an endpoint considered to be adverse, the results of the Sjoberg et al. (1985a) study will be used for the derivation of TI values for DEHP. Since the effects seen at the 250 mg/kg/day dose are subtle, the "true" NOAEL for this study is probably closer to 250 mg/kg/day than 25 mg/kg/day. However, rats in this study were 40 days old. It is possible that a higher NOAEL/lower LOAEL would have been detected if neonatal animals were used in the study.

Baxter (2000)

The Baxter Healthcare Corporation (Baxter, 2000) recently made public the results of an unpublished study in which neonatal male rats or rabbits were injected either with DEHP or 4% bovine serum albumin during postnatal days 3-21 (rats) or 14-42 (rabbits). Histopathological examination of the testes and other organs of DEHP-exposed animals revealed no histologic alterations that could be attributed to the test material administered at a dose of 62 mg/kg/day.

AdvaMed (2001)

AdvaMed (2001) recently made available the results of a 21-day repeat dose study of DEHP in neonatal (3- to 5-day old) rats to the FDA. A second group of animals was dosed for 21 days, then held for a recovery period until 90 days of age. At the end of the 21-day dosing period, testicular atrophy and hepatomegaly were observed in neonatal rats following daily intravenous exposure to DEHP at a dose of 300 mg/kg/day. Histopathological examination of the testes of animals in the 300 mg/kg/day dosing group revealed a decrease in the diameter of the seminiferous tubules and a mild depletion of germinal epithelial cells. Although testicular atrophy persisted at the end of the recovery period, histopathological changes were not seen in the recovery group previously exposed to a DEHP dose of 300 mg/kg/day for 21 days. The NOAEL in the study was 60 mg/kg/day; consistent with the results reported previously by Baxter (2000).

In addition to investigating organ weight changes and conducting a histopathological examination of tissues, AdvaMed (2001) also performed a functional assessment of male reproductive capacity (sperm count, sperm motility and sperm morphology) in DEHP-exposed rats at the end of the recovery period. No effect on any of these parameters was observed in the recovery group of animals.

The considerations discussed above regarding the relevance of these studies for TI derivation are summarized in Table 3-3.

Table 3-3. Evaluation of critical toxicity studies (parental route) for DEHP

Study	Route	Effect(s) at LOAEL	Accept or Reject Study for TI Derivation	Rationale
Jacobson et al. (1977)	IV	Histopathological changes in liver, altered BSP clearance kinetics	Reject	Questions about role of confounding factors (e.g., TB outbreak)
Fracasso et al. (1999)	IP	Peritonitis	Reject	Local effect
Nair et al. (1998)	IP	Reduced levels of Vitamin E in the liver	Reject	Not considered to be an adverse effect
Miripol et al. (1975)	IV	Reduced uptake of colloidal carbon	Reject	Not considered to be an adverse effect
Komitowski et al. (1986)	IP	Morphological changes observed in hepatocytes using image analysis	Reject	Not considered to be an adverse effect
Petersen et al. (1975)	IV	Reduced fertility	Reject	Questions about dose
Rubin and Chang (1978)	IV	Pulmonary effects	Reject	Questions about dose; only published in abstract form
Rutter (1973)	IV	Hepatomegaly, increased liver enzyme levels, increased lung weight	Reject	Questions about role of confounding factors (DEHP administered neat)
Rubin and Chang (1976)	IV	Reduced blood pressure	Reject	Only published in abstract form
Curto and Thomas (1982)	IP	Reduced testicular Zn	Reject	Not considered to be an adverse effect
Petersen (1975)	IV	Reduced litter size following exposure of treated males to untreated females	Reject	Questions about dose
Greener et al. (1987)	IV	Reduced body weight gain, hepatomegaly, ↑SGOT	Reject	Questions about the way data were presented and statistical significance of differences. Liver effects assumed to be not relevant for humans
Sjoberg et al. (1985a)	IV	Altered Sertoli cells, degeneration of primary spermatocytes	Accept	Appropriate for use
Baxter (2000)	IV	No adverse effects	Accept	Appropriate for use
AdvaMed (2001)	IV	Testicular atrophy, decrease in diameter of seminiferous tubules and depletion of germinal cells in testes, hepatomegaly	Accept	Appropriate for use

Based on these considerations, the parenteral TI values for DEHP will be based on the NOAEL from the Baxter (2000) and AdvaMed (2001) studies and the LOAEL from the Sjoberg et al. (1985a) study.

Since the toxicity of DEHP following oral administration has been adequately reviewed in other risk assessments (e.g., ATSDR, 2000; CERHR, 2000; KEMI, 2000), no attempt has been made to do so here. The highest NOAEL/lowest LOAEL reported in a valid study for DEHP are 5.8 and 28.9 mg/kg/day, as reported by David et al. (2000). The NOAEL and LOAEL values are consistent with those reported by Poon et al. (1997). Since there is some question about whether the effects seen at this dose in the David et al. (2000) study are dose-related, age-related, or a combination of both, they will not be used as the basis for TI derivation for DEHP. However, the effects seen in the Poon et al. (1997) study are unambiguous and the NOAEL and LOAEL values are essentially the same as those in the David et al. (2000) study, therefore, the oral TI for DEHP will be derived using the NOAEL from the Poon et al. (1997) study.

3.2 Derivation of a Modifying Factor (Step 2)

As defined in ISO/DIS 10993-17, a modifying factor is the product of uncertainty factors selected to account for interindividual variability among humans, interspecies extrapolation, and various deficiencies in the toxicological data available to derive a TI (e.g., lack of a NOAEL, lack of data from appropriate routes or durations of exposure). The value is unitless and is derived as follows:

$$\text{Modifying factor} = UF1 \times UF2 \times UF3,$$

where UF1, UF2, and UF3 are defined in Table 3-4.

Table 3-4. Uncertainty Factors for TI Derivation

Uncertainty Factor Designation	Range	Default	Description
UF1, Interindividual Variability in the Human Population	1-10	10	To account for the variability in response between the mean of the healthy population and the response in some proportion of a sensitive subpopulation.
UF2, Interspecies Extrapolation	1-10	10	To account for the possibility that humans are more sensitive to the adverse effects of a compound than experimental animals are.
UF3, Quality and Relevance of the Experimental Data	1-100	1	To account for limitations in the toxicological data available for TI derivation, including absence of NOAEL value, absence of NOAEL from a long-term study, and lack of data from a clinically relevant route of exposure.

Ideally, the process for selecting values for each of these uncertainty factors is informed by experimental data on the variability in the human response to a compound (UF1) and compound-specific differences in potency between animals and humans (UF2). Some data are available to determine whether the default values proposed for each of these UFs are appropriate or whether an alternative value is justifiable, as discussed below. Also, the conditions under which the experimental study is conducted should be similar to those under which patients are exposed to the compound. Since the conditions used in the Baxter (2000, 2001) and Sjoberg et al. (1985a) studies do not exactly mimic the clinical situation, an additional UF to account for data deficiencies (UF3) was selected, as discussed below.

3.2.1 Interindividual variability in the human population (UF1)

An upper-bound default value of 10 is selected for UF1 to account for the variability in pharmacokinetic behavior of DEHP in the general population and the presumed increased sensitivity of neonates and critically ill patients to the adverse effects of DEHP, compared to adults and healthy individuals, respectively. The rationale for selecting this value is discussed below.

3.2.1.1 Pharmacokinetic variability in the general population and in patients

DEHP is converted to its active metabolite, MEHP, by lipase enzymes (Albro and Thomas, 1973) and MEHP is eliminated following conjugation with glucuronide (Sjoberg et al., 1991). Consequently, individuals with high rates of lipase activity and/or low rates of glucuronidation activity could be at higher risk of DEHP-induced adverse effects than the rest of the population.

Polymorphisms in genes coding for pancreatic (Hegele et al., 2001) and hepatic (Cohen et al., 1999) lipase in humans are known to exist and these polymorphisms can result in lipase deficiency. Low lipase activity would be expected to exert a protective effect in these individuals with regard to DEHP-mediated effects. Conversely, pancreatic lipase activity is increased by heparin administered to patients on hemodialysis (Montalto et al., 1997) and plasma lipoprotein lipase activity is increased by erythropoietin (Goto et al., 1999), which is also administered to patients on hemodialysis. Increased lipase activity would facilitate the conversion of DEHP to its active metabolite. Smoking is also known to increase lipase activity (Kong et al., 2001) and DEHP itself induces lipase activity in rodents (Mocchiutti and Bernal, 1997). Consequently, some individuals in the DEHP-exposed population can convert DEHP to MEHP more efficiently than others. This variability is evidenced, to some extent, by the variability in the rate at which intestinal mucosal cell preparations obtained from two humans hydrolyzed a number of di-n-alkyl phthalates (Lake et al., 1977). The metabolic rates between these two individuals differed by around 3- to 6-fold. Presumably, the degree of variability would increase with a larger sample size.

Polymorphisms have been detected in several human UDP-glucuronyltransferase (UGT) genes resulting in variability in UGT activity in the human population (de Wildt et al., 1999). The polymorphic expression of UGT may be responsible for the large interindividual variation in the conjugation of MEHP in humans (Dirven et al., 1993). Presumably, this variability will result in a reduced capacity of some individuals to conjugate and eliminate MEHP. Reduced ability to glucuronidate exogenous compounds can have clinical consequences, since adverse drug reactions have been observed in patients with deficient UGT activity (Burchell et al., 2000). In addition, various disease states (e.g., cirrhosis) and drugs can impair glucuronidation capacity (Furlan et al., 1999). It is interesting to note that propofol can inhibit UGT activity (Chen et al., 2000) and as discussed in Section 2.0, administration of propofol is also associated with the release of considerable amounts of DEHP from PVC tubing (Loff et al., 2000).

3.2.1.2 Children as a High Risk Population

Based on the results of experimental animal studies, children may be more susceptible than adults to the toxic effects of DEHP following oral exposure; it's not clear whether age-related differences in DEHP-induced testicular toxicity would occur following parenteral exposure.

Supporting this conclusion are data from Gray and Butterworth (1980), Sjoberg et al. (1985a), and Dostal et al. (1988) showing that testicular toxicity is produced following oral exposure of prepubertal rats to DEHP at doses lower than those required to produce this effect in sexually mature rats. However, no age-related differences in the expression of testicular toxicity were seen following intravenous administration of DEHP to rats (Sjoberg et al., 1985c). Nevertheless, there are various factors that may result in increased sensitivity of children to DEHP, compared to adults, even after IV exposure. For example, metabolic differences between children and adults may place children at increased risk of DEHP toxicity. Children have a reduced capacity to metabolize compounds via glucuronidation, compared to adults. Since 60% of an administered dose of DEHP is excreted in humans as the glucuronide conjugate (Albro et al., 1982), a reduced glucuronidation capacity could result in delayed excretion of DEHP or its metabolites. This reduced glucuronidation capacity could play a role in the hepatic effects (e.g., cholestasis) seen in children on ECMO. Bilirubin is excreted as a glucuronide conjugate. The DEHP metabolite, MEHP, also undergoes glucuronidation and has been shown to interfere with bilirubin conjugation (Sjoberg et al., 1991), perhaps as a competitive inhibitor of glucuronidation.

DEHP is converted to the presumed toxic metabolite, MEHP, by lipase enzymes in the gastrointestinal tract. Gastric lipase activity is high in infants to aid in the digestion of fats in milk (Hamosh, 1996). Lee et al. (1993) reported that gastric lipase activity peaks postnatally in children at 28-33 weeks of age. Consequently, these children may be able to convert DEHP to MEHP more efficiently than older children or adults can.

Differences in intestinal permeability between children and adults may also place children at greater risk, due to the greater potential for children to absorb larger amounts of DEHP from the gastrointestinal tract. Similarly, an increased permeability of the blood-testis barrier in children as compared to adults could result in increased exposure of the testes to DEHP or MEHP. The blood-testis barrier forms just before puberty in humans (Furaya, 1978).

DEHP may exert toxic effects on the testes through depletion of zinc or Vitamin E. It is important to note that both zinc and Vitamin E deficiencies are not uncommon in preterm infants (Obladen et al., 1998; Chan et al., 1999). Consequently, DEHP could exacerbate zinc and Vitamin E deficiencies that occur in preterm infants from other causes.

Roth et al. (1988) have suggested that DEHP could contribute to the development of hyaline membrane disease in children undergoing mechanical ventilation. This disease results from insufficient surfactant production in the lungs of newborn infants. Because of its lipophilicity, Roth et al. (1998) speculated that DEHP could either inhibit the formation or promote the degradation of surfactant. This effect is less likely to be seen in the adult lungs because of the increased ability of adults to produce surfactant. DEHP has also been suggested as an etiologic agent for the development of necrotizing enterocolitis in newborns. However, factors such as poor bowel perfusion are more likely contributors to the pathogenesis of this disease than exposure to DEHP.

In addition, children can receive a larger dose of DEHP than adults do when dose is expressed on a mg/kg basis, for example, when the same sized device can be used for both children and adults (e.g., an IV administration set). Further, there are medical procedures that result in DEHP exposure that are almost exclusively done on children, notable among them are ECMO and exchange transfusion.

Since the Sjoberg et al. (1985a) and AdvaMed (2001) studies were conducted using neonatal animals, it is not necessary to apply an additional UF to ensure that the TI is protective for children. Nevertheless, it is prudent to consider the potentially increased sensitivity of children to DEHP in selecting a value for UF1 for DEHP.

3.2.1.3 Critically ill or injured patients as a high risk subpopulation

Critically ill or injured patients may be at increased risk of developing adverse health effects from DEHP, not only by virtue of increased exposure, relative to the general population, but also because

of the physiological and pharmacodynamic changes that occur in these patients, compared to healthy individuals. As mentioned above, factors that increase the lipase-mediated bioactivation of DEHP or the metabolism of MEHP via glucuronidation will increase the potential for DEHP to induce adverse effects in exposed patients. Additional factors that place patients at increased risk include: reduced renal elimination capacity, uremia, protein malnutrition, reduced levels of antioxidants, and impaired cardiovascular status. Two of these factors, protein malnutrition and altered antioxidant status, are especially important for DEHP-induced effects on the testes. Protein malnutrition may place male patients at increased risk for adverse effects of DEHP on the testes since a low protein diet has been shown to exacerbate the toxic effects of DEHP on the testes in rats (Tandon et al., 1992). Unless corrected by nutritional support, critically ill patients can enter a state of protein malnutrition due to increased protein requirements. Accelerated protein breakdown occurs in critically ill patients, such as patients with acute renal failure or sepsis, and patients that have undergone traumatic injuries and burns (Druml, 1998; Ishibashi et al., 1998). Protein-energy malnutrition is a common complication of both hemodialysis and peritoneal dialysis (Kopple, 1999). Patients undergoing peritoneal dialysis experience protein loss through the dialysis effluent (Brewer, 1999), a process that can lead to protein malnutrition. Since a low protein diet can potentiate the testicular toxicity of DEHP in rodents, the potential exists for patients with protein malnutrition to be at increased risk for the development of adverse reproductive effects relative to a healthy, well nourished population.

Ishihara et al. (2000) recently reported that DEHP-induced testicular atrophy can be prevented in rats by administration of ascorbic acid (Vitamin C) and alpha-tocopherol (Vitamin E). If testicular atrophy can be prevented by antioxidant administration, it is interesting to speculate that testicular atrophy may be worsened in antioxidant-deficient animals. This issue may be clinically important since patients undergoing hemodialysis typically have low plasma levels of ascorbate (e.g., Wang et al., 1999; Pereira et al., 2000; Metnitz et al., 2000) and other antioxidants. In addition, patients with ARDS (and, therefore, potentially may be treated with ECMO) have reduced levels of ascorbate and alpha-tocopherol (Metnitz et al., 1999).

Reduction in prostatic and testicular zinc levels in rodents is a hallmark of DEHP exposure and reduced zinc levels could play a role in the etiology of DEHP-induced testicular toxicity, either through a reduction of angiotensin-converting enzyme activity (Rahman et al., 1999) or by failure to inhibit superoxide dismutase (SOD) activity which could lead to increased superoxide anion production (Gavella et al., 1999). As discussed above, a zinc-deficient diet has been shown to produce a range of adverse testicular effects in rats and levels of zinc in seminal fluid are lower in oligospermic men than in normospermic, fertile men in some studies. Plasma zinc levels are reduced in patients undergoing hemodialysis (Lee et al., 2000) and zinc deficiency is not uncommon in preterm infants (Obladen et al., 1998). In addition, chelating agents, such as disodium edetate (EDTA), that are found in preparations of sedative agents, like propofol, can increase the urinary excretion of zinc (Higgins et al., 2000). Since: 1) reduced testicular zinc is seen in DEHP-exposed animals, 2) reduced zinc may play a role in DEHP-mediated testicular damage and is associated with adverse effects on the testis, and 3) low levels of zinc are seen in patients undergoing hemodialysis and some newborns, the potential exists for the low zinc levels seen in patients to exacerbate DEHP-mediated effects.

Altered health status may potentiate DEHP effects on organs other than the testes. Rodents made hypovolemic by withdrawal of blood and held in a hypovolemic state for a given period are more sensitive to the pulmonary effects of DEHP than rodents that had blood withdrawn but received an immediate replacement transfusion (Rubin and Chang, 1978). Therefore, the injured lung may be more susceptible than a healthy lung to adverse effects produced by intravenous administration of DEHP.

3.2.1.4 Conclusions and their impact on the selection of values for UF1

- Variability exists in the general population in the activity of lipase enzymes, which convert DEHP to MEHP, and glucuronosyltransferases, which are responsible for the metabolism and

elimination of MEHP. Individuals with high lipase activity and/or low glucuronidation activity may be at increased risk of DEHP-induced effects, compared to the rest of the population. However, data are unavailable to quantitatively adjust the UF to account for this variability.

- Children are at increased risk following exposure to DEHP because they receive a greater dose of DEHP, relative to adults, and because of various pharmacokinetic differences between children and adults. However, the data used to derive the parenteral TI were obtained using neonatal animals (AdvaMed, 2001) and data from the Sjoberg et al. (1985b) study suggest that age-related differences in DEHP effects in rodents occur only after oral exposure. Nevertheless, it is prudent to consider this factor in deriving the UF1 for parenteral exposure, since the results of one study cannot be taken as conclusive evidence for a lack of age-related effects following parenteral exposure.

- Critically ill or injured patients can be at increased risk for DEHP-induced effects, relative to healthy individuals. However, data are unavailable to quantitatively adjust the UF to account for this increased sensitivity.

Collectively, these factors justify a value for UF1 of 10, since it appears that some individuals in the general population may be more sensitive to DEHP and since some critically ill patients almost certainly are more sensitive to DEHP than healthy individuals.

3.2.2 Interspecies extrapolation (UF2)

Use of the animal-to-human UF assumes that the effects seen in experimental animals are relevant for humans. Selection of values > 1 for this UF also assumes that humans are more sensitive than animals to the compound on a mg/kg/day basis. Based on these assumptions, two questions must be answered in the process of deriving an UF to account for interspecies differences in response to a given dose of DEHP: 1) Are the effects observed in DEHP-exposed experimental animals relevant for humans? and 2) Are humans more sensitive to these effects than experimental animals?

3.2.2.1 Human relevance of effects seen in DEHP-exposed experimental animals

Although hepatic effects seen in rodents have been shown to occur via a PPARα-dependent mechanism and are therefore assumed to be not relevant for humans, Ward et al. (1998) demonstrated that DEHP exerts its effect on the testes in mice via both PPARα-dependent and PPARα-independent mechanisms. Following 8 weeks of exposure to DEHP in the diet, control (+/+) mice developed moderate to severe focal tubular degenerative lesions in the testes. In contrast, PPARα null (-/-) mice developed only mild testicular changes.

Considerable attention has been paid to the potential for DEHP and other phthalate esters to exert biological effects via an estrogenic mechanism. However, it has recently been shown that DEHP (Gray et al., 1999, 2000) and other phthalate esters (Mylchreest et al., 1998) exert an anti-androgenic effect, most likely via reduction of testosterone synthesis (Parks et al., 2000). There are no data to suggest that this effect is limited to rodents. In addition, there are other mechanisms by which DEHP and MEHP could exert adverse effects on the testes in rodents, including inhibition of phospholipase A2, depletion of testicular iron, alteration of antioxidant status, each of which are presumed to be relevant for humans. As a result, there is no mechanistic reason to assume that the adverse testicular effects seen in DEHP-exposed rodents could not also occur in DEHP-exposed patients.

3.2.2.2 Interspecies differences in sensitivity to DEHP

Use of the default UF of 10 to account for interspecies differences in potency is based on the default assumption that humans are more sensitive to the toxic effects of chemical compounds than rodents are. HIMA (1999), Koop (1999) and others have concluded that nonhuman primates are less sensitive to the testicular effects of DEHP than rodents are. If humans are similar to nonhuman primates in their response to DEHP, then it could be argued that a value of 1 or even < 1 would be

appropriate for UF2, if the TI is based on the results of a study conducted in rodents. Data on the comparative response of humans and nonhuman primates to the effects of DEHP are unavailable to answer this question directly, however, information on the similarity and differences between spermatogenesis in humans and nonhuman primates and on the similarity and differences in DEHP metabolism in humans and nonhuman primates will be instructive in addressing this issue. It is also important to examine whether nonhuman primates are less sensitive than rodents to DEHP across all routes of exposure, or if this is a route-specific effect.

Interspecies differences in potency following oral exposure

Data on the relative sensitivity of rodent and nonhuman primates to DEHP have only been obtained following oral exposure to the compound. As shown in Table 3-5, doses of DEHP that produce adverse effects in rodents are without effect in nonhuman primates.

Table 3-5. Comparison of the potency of DEHP in rats and nonhuman primates following oral exposure (based on testicular effects)

Oral Rat				Oral Nonhuman Primate			
Study	**Duration**	**NOAEL**	**LOAEL**	**Study**	**Duration**	**NOAEL**	**LOAEL**
Rhodes et al. (1986)	14 days		2000	Rhodes et al. (1986)	14 days	2000	
Agarwal et al. (1989)	13 days	330	1000	Pugh et al. (2000)	14 days	500	
Parmar et al. (1986)	15 days	1000	2000				
Siddiqui and Srivastava (1992)	15 days	500	1000				
Saxena et al. (1985)	7 days		2000				
Oishi (1985)	14 days		2000				
Gray and Gangolli (1986)	10 days		2800				
Gray and Gangolli (1986)	10 days	2800					
NTP (1982)	13 weeks	320	630	Kurata et al. (1998)	13 weeks	2800	
Poon et al. (1997)	13 weeks	3.7	37.6				

The data shown in Table 3-5 indicate that nonhuman primates are less sensitive than rodents to DEHP following oral administration of the compound.

Spermatogenesis in the marmoset is organizationally similar to the process that occurs in humans, with regard to length of the spermatogenic cycle, duration of spermatogenesis, and number of mitotic divisions (Millar et al., 2000; Weinbauer et al., 2001). Consequently, the marmoset has been described as an appropriate model for experimental studies of human spermatogenesis. By analogy, it can be assumed that DEHP-induced effects on this process seen in marmosets would be applicable for humans. In addition, the pharmacokinetic behavior of DEHP in nonhuman primates is more similar to that in humans than in rodents (Albro et al.,

1982); however, there are metabolic differences observed among primate species. For example, intestinal cell preparations from human mucosal cells may be more efficient in metabolizing a range of phthalate diesters than similar preparations from baboon intestinal cells (Lake et al., 1977), suggesting that humans can metabolize some phthalate esters in the gut more efficiently than at least one species of subhuman primate can. However, caution should be exercised in comparing these data since the metabolic rate in rats and baboons is expressed in units of μmole/hr/mg mucosal cell protein and metabolic rate in human intestinal tissue is expressed in units of μmole/hr/mg total protein. Nevertheless, if humans can metabolize an oral dose of DEHP in the gut more effectively than marmosets can, then humans may be more sensitive to the adverse effects of DEHP than subhuman primates such as the marmoset are.

Table 3-6. *In vitro* hydrolysis of phthalate diesters by intestinal cell preparations (Lake et al., 1977)

Phthalate diester	Rat	Baboon	Human
	Amount of product formed		
	μmole/hr/mg mucosal cell protein		μmole/hr/mg total protein
Dimethyl	1.14	6.67	197.5
Diethyl	0.65	4.33	92.1
Di-n-butyl	0.59	2.19	67.6
Di-n-octyl	0.22	0.19	20.6
DEHP	0.11	0.11	8.1

Since the results obtained with nonhuman primates are assumed to be relevant for humans, 2) nonhuman primates appear to be less sensitive than rodents to the effects of DEHP following oral administration, and 3) the TI is based on effects seen in rodents, then the value selected for UF2 should reflect this difference in potency when deriving the oral TI. However, it is possible for humans to metabolize DEHP more effectively in the gut than some nonhuman primates can, thereby making possibly making humans more sensitive than nonhuman primates to the effects of DEHP. As a result, a value of 3 is selected for UF2 for use in deriving the oral TI.

Interspecies differences in potency following parenteral exposure

If the differences in species sensitivity following oral exposure are solely due to differences in pharmacokinetics, notably, the metabolic conversion of DEHP in the gut and subsequent systemic absorption of MEHP, then it can be assumed that rodents and nonhuman primates (and humans) would be equally sensitive to the effects of DEHP following parenteral exposure. Rhodes et al. (1986) reported that the marmoset excreted only 2% of an orally administered dose of DEHP in the urine, whereas the rat excretes about 50% of a similar dose of DEHP via the urine. In addition, they estimated that the level of DEHP or its metabolites in the tissues of the marmoset would be between one-fifth and one-tenth the levels that would be present in rat tissues following administration of the same dose of DEHP. Consequently, if the pharmacodynamic sensitivity of the marmoset and rodent tissues were similar, then similar effects should be seen in these species if the orally administered dose was five- to ten-fold higher in the marmoset than the rodent. The LOAEL for adverse testicular effects in rats following long-term oral exposure is 37 mg/kg/day (Poon et al., 1997), therefore, the comparable LOAEL expected for this effect in marmosets should be on the order of 185 to 370 mg/kg/day, assuming pharmacodynamic equivalence. However, the LOAEL for these effects in marmosets is much higher, since long-term (13 week) administration of DEHP at doses up to 2500 mg/kg/day had no effect on the testes of exposed animals. These findings suggest that other factors such as differences in the pharmacodynamic sensitivity of the testes between these species could be responsible for the refractoriness of the marmoset to the adverse testicular effects of DEHP. In contrast to Rhodes et al. (1986), Astill et al. (1986) found that a similar percentage of DEHP was

excreted by urinary and fecal routes in rats and cynomolgus monkeys following administration of a relatively low gavage dose (100 mg/kg) of the compound. Consequently, there may be little difference in the rate at which DEHP is hydrolyzed and absorbed in rats and primates following exposure to low doses of DEHP, a finding that further supports pharmacodynamic differences as an underlying reason for species differences in sensitivity to DEHP.

Pugh et al. (2000) reported elevated levels of DEHP and MEHP in the liver of cynomolgus monkeys following oral administration of DEHP, indicating that absorption and metabolism did take place; however, no adverse testicular effects were seen in exposed animals. This finding lends support to the hypothesis that nonhuman primates are less sensitive than rodents to the effects of DEHP on the basis of pharmacodynamic differences in sensitivity.

Data are unavailable on the relative sensitivity of the testes in rodents and nonhuman primates to parenterally administered DEHP. However, many studies indicate that the rat is especially sensitive to the testicular effects of a number of reproductive toxicants, compared to other species. Gray and Beamand (1984) demonstrated that *in vivo* differences in sensitivity between rats and hamsters were in agreement with the results produced *in vitro* on the detachment of germ cells in testicular cell cultures in response to MEHP. Since the hamster and rat cells were exposed to the same concentrations of MEHP, these results suggest that pharmacodynamic differences in sensitivity are at least partially responsible for the differences in response seen *in vivo* between rats and hamsters with regard to testicular toxicity. Rats are also more sensitive that other species to the adverse effects of other testicular toxicants, including 2-methoxyethanol (Ku et al., 1994), gallium arsenide (Omura et al., 1996), perfluoro-n-decanoic acid (Van Rafelghem et al., 1987), carbendazim (Gray et al, 1990), ethane dimethanesulfonate (Gray et al., 1995), 1,3-dinitrobenzene (Obasaju et al., 1991), and 1,2-dibromo-3-chloropropane (Lag et al., 1989). Also, in an *in vitro* assay designed to measure single-strand DNA breaks, Bjorge et al. (1996) found that rat testicular cells were more sensitive to the toxicant than humans cells for 6/15 compounds (either rat cells only responded or rats cells responded at a lower concentration of the toxicant) and equally sensitive for 8/15 (either no response in either species for rats and humans cells responded at same concentration). However, one of the compounds, acrylamide, produced a marginal response in human cells, whereas none was seen in rats cells. Collectively, the results of the studies described above suggest that testicular cells from rats are more sensitive than those from humans or other species to the adverse effects of reproductive toxicants. However, they cannot be used with confidence to specifically state that rodent testicular cells are more sensitive than human cells to the effects of phthalate esters, since the compounds mentioned above may exert their effect on the testes via a different mechanism of action than DEHP does.

The lack of testicular effects observed in nonhuman primates when the dose is corrected for absorption and the weight-of-evidence suggesting that rats are especially sensitive to a number of testicular toxicants, compared to other species (including humans), raises the possibility that pharmacodynamic as well as pharmacokinetic differences serve as the basis for the differences in sensitivity between primates and rodents to the effects of DEHP on the testes. These findings provide suggestive (but not strong) evidence for a departure from the default value for UF2 used to derive a parenteral TI for DEHP. As a result, a value of 3 is selected for this UF. It is important to note, however, that selection of a value > 1 for this parameter still implies that humans are more sensitive than rodents to the testicular effects of DEHP, on a mg/kg/day basis.

The definitive test of DEHP's ability to produce adverse effects in humans is obviously to determine if such effects have been observed in DEHP-exposed humans. HIMA (1999) noted, "Despite some testicular damage to certain rodent species,[x] no similar results have been observed in studies relevant to human exposure to DEHP." Presumably, the phrase, "studies relevant to human exposure to DEHP", refers to studies conducted in nonhuman primates. To our knowledge, male reproductive capacity has not been assessed in any study of humans following exposure to DEHP, with the intent of determining whether DEHP was a causative agent for reproductive problems. Although Ohlson and Hardell (2000) reported a six-fold increase in the

risk for seminoma in men occupationally exposed to PVC, and suggested that the estrogenic effect of DEHP could promote the growth of estrogen sensitive tumor cells in exposed workers, the role of DEHP in producing this effect has not been firmly established. Also, although a strikingly similar pattern of hormonal and histological changes in the testis occurs in male patients on hemodialysis and in experimental animals following exposure to DEHP, it is not possible to determine from the existing data if DEHP plays a role in the etiology of the effects seen in DEHP-exposed patients, since uremia itself can produce these effects. Therefore, human data are unavailable to answer the question of rodent vs. nonhuman primate vs. human sensitivity to the testicular effects of DEHP.

3.2.2.3 Conclusions and their impact on the selection of values for UF2

- The adverse testicular effects seen in DEHP-exposed rodents could theoretically occur in DEHP-exposed humans, since there is no mechanistic reason to assume that the adverse testicular effects are species specific.

- Spermatogenesis in the marmoset is functionally similar to the process that occurs in humans. Therefore, nonhuman primates such as the marmoset are assumed to be appropriate models for humans with regard to the testicular effects of DEHP.

- Since nonhuman primates are less sensitive than rodents to DEHP following oral exposure, and since nonhuman primates serve as an appropriate model for human spermatogenesis, an UF of 1 is selected for UF2 used to derive the oral TI to DEHP. Some evidence suggests (but does not demonstrate) that factors other than species-specific differences in DEHP hydrolysis in the gut and absorption of MEHP may be responsible for the increased sensitivity of rats to the testicular effects of DEHP, compared to nonhuman primates and other species. Based on these factors, a value of 3 is selected for UF2 used to derive the parenteral TI for DEHP. Although this value is a departure from the default for this UF, it is nevertheless consistent with the conservative assumption that humans are more sensitive to the testicular effects of DEHP than rodents are following IV exposure to DEHP.

3.2.3 Data quality and relevance (UF3)

Ideally, the conditions of a toxicity study used to derive the TI should closely mimic exposure conditions in the clinical situation. If there are differences that could result in a greater sensitivity in humans compared to experimental animals, then an additional UF should be applied to account for deficiencies in data quality.

The primary study upon which the parenteral TI is based (AdvaMed, 2001) is indeed an excellent and relevant study. It employed a clinically relevant route duration of exposure and the solubilization of DEHP in a clinically relevant vehicle (Intralipid) minimizes concerns about the influence of the vehicle on DEHP-induced effects. Further, the AdvaMed (2001) study was conducted using a presumably relevant species at a sensitive life-stage. However, there are some differences between the conditions under which rodents were exposed to DEHP in the AdvaMed (2001) study and the conditions under which patients are exposed in the clinical setting (Table 3-6). For example, patients undergoing long-term procedures such as hemodialysis can be exposed to DEHP for much longer periods than were used in the AdvaMed (2001) study. In addition, humans can be exposed to DEHP both prenatally and postnatally, whereas rodents in the AdvaMed (2001) study received DEHP only in the postnatal period. Also, unlike experimental animals in a controlled setting, patients can be exposed to compounds that could potentiate the toxicity of DEHP. Finally, animals in the AdvaMed (2001) study were healthy whereas patients are often quite ill. The potentially increased sensitivity of sick or injured patients to DEHP is taken into account in the value selected for UF1; however, the other issues will be accounted for in UF3. In addition, implications of the reversibility of the lesion in the AdvaMed (2001) for TI derivation will be addressed in this section. Also, modification of UF3 to account for the lack of a NOAEL value in the Sjoberg et al. (1985a) study is explored below.

Table 3-7. Comparison of experimental conditions used in AdvaMed (2001) study and conditions in the clinical setting for neonates in a NICU and adults undergoing hemodialysis.

Exposure Conditions	Experimental Animal Studies	Clinical Setting	
		Neonate in NICU	Adult receiving hemodialysis
IV route of exposure	Yes	Yes	Yes
Short-term duration of exposure	Yes	Yes	No
Similar life-stage of exposure	Yes	Yes	No
Pre- and post-natal exposure	No	Yes	NR
Coexposure to other phthalates	No	Yes	Yes
Compromised health status	No	Yes	Yes

3.2.3.1 Lack of data from a long-term study

Ideally, a TI intended to be protective for long-term exposure to a compound will be based on a NOAEL from a chronic toxicity study (one in which dosing of the animal takes place over a significant proportion of the animal's lifetime). However, studies of sufficient duration are often not available when conducting a safety assessment. Such is the case with the safety assessment of DEHP released from medical device materials, since a valid, long-term toxicity study involving administration of the compound via a parenteral route of exposure is not available. Instead, data from the 12-day study conducted by Sjoberg et al. (1985a), the 14- or 18-day studies conducted by Baxter (2000), and the 21-day study conducted by AdvaMed (2001) will be used to assess the potential for adverse effects to occur following exposure to DEHP in medical procedures, such as hemodialysis, peritoneal dialysis and TPN administration, which could take place repeatedly for extended periods. When short-term data are used to derive a long-term TI, it is commonplace to employ an UF to account for the assumed greater potency of the compound following long-term as compared to short-term exposure. However, it is likely that the LOAEL following long-term parenteral exposure of rodents to DEHP would not be lower than the LOAEL reported in the relatively short-term studies of Sjoberg et al. (1985a) and AdvaMed (2001), since exposure in the short-term studies took place in what is assumed to be a critical and sensitive period for testicular effects and because DEHP has a relatively short half-life and is not expected to accumulate in the body. This conclusion is supported empirically by the similarity in the NOAEL values from the subchronic Poon et al. (1997) study (3.7 mg/kg/day) and the chronic David et al. (2000) study (5.8 mg/kg/day). Therefore, although the parenteral TI is derived using short-term data, it is assumed to be health-protective even for long-term exposure to DEHP, since it is based on the most sensitive endpoint (testicular effects) observed following long- or short-term exposure to DEHP and is also based on data obtained following exposure of what is assumed to be the most sensitive animal species exposed during a sensitive period of development. Therefore, an additional UF to account for the lack of a long-term study will not be applied to the NOAEL and LOAEL from the short-term studies of Sjoberg et al. (1985a), Baxter (2000), and AdvaMed (2001) studies to derive a long-term parenteral TI.

3.2.3.2 Lack of data from a study involving pre- and postnatal exposure

The results of the study conducted by Arcadi et al. (1998) were not used to derive an oral TI for DEHP, because of uncertainty about the dose of the compound that was actually received by maternal animals and their pups; however, this study did illustrate that exposure to DEHP during gestation, followed by postnatal exposure, resulted in the development of adverse testicular effects in the offspring at doses approximately an order of magnitude lower than those that produced adverse effects in rodents exposed only in the postnatal period (based on LOAELs from the Poon et al., 1997 and David et al., 2000 studies). Similarly, the results of the studies by Moore et al. (2001) and Wine et al. (1997) point out that male rats are more sensitive to the

adverse testicular effects of phthalate esters following continuous multigenerational exposure (including *in utero* and lactational exposure) to DEHP and DBP, respectively, than if the animals were only exposed during the postnatal period. However, animals in the studies upon which the parenteral TI is based were exposed to phthalate esters only during the postnatal period. Based on the results of the Arcadi et al. (1998), Moore et al. (2001), and Wine et al (1997) studies, it is possible that the LOAELs in the Sjoberg et al. (1985a) and AdvaMed (2001) studies would have been lower if exposure had taken place both prenatally and postnatally. Exposure during the pre- and postnatal periods more accurately reflect the clinical situation, since neonates exposed to DEHP and MEHP from PVC devices could also have been exposed to phthalate esters *in utero*. In contrast, maternal rats in the laboratory environment are exposed to essentially no phthalate esters during the gestational period (Kessler et al., 2001). Since: 1) prenatal exposure followed by postnatal exposure can increase the sensitivity of rodents to the testicular effects of DEHP, as compared to postnatal exposure only, 2) humans can be exposed to DEHP and other phthalate esters both prenatally and postnatally, and 3) rodents in the studies used to derive the TI were only exposed postnatally, then it is prudent to take this factor into account when deriving a TI for DEHP when dosing occurs during the entire perinatal period.

The potential for adverse effects to occur in humans (or rodents) exposed both pre- and postnatally to DEHP is obviously related to the dose of DEHP received. Adverse testicular effects were seen in rat pups in the Arcadi et al. (1998) study following maternal exposure to DEHP at a dose of about 3 mg/kg/day and the lowest dose in the Moore et al. (2001) study, 375 mg/kg/day, produced these effects (however, no NOAEL was identified in the Moore et al., 2001 study). In contrast, Kohn et al. (2000) estimated the maximum dose of DEHP received by women aged 20-40 years to be 10 μg/kg/day, based on the data reported by Blount et al. (2000) on urinary excretion of phthalates. However, total maximum exposure of women of reproductive age to all phthalate esters is on the order 0.3 mg/kg/day, based on the estimates derived by Kohn et al. (2000). In addition, pregnant women can be exposed to DEHP from medical procedures. For example, women who experience hyperemesis gravidarum are typically rehydrated with IV fluids (Power et al., 2001); however, further nutritional support can be provided either with TPN (Folk and Leslie, 2001; Subramaniam et al., 1998) or enteral feeding (Hsu et al., 1996). As shown previously in Table 2-24, patients receiving nutritional support with TPN or enteral feeding can receive a daily DEHP dose of about 0.14 mg/kg/day. Higher *in utero* exposures could be expected if the mother was exposed to DEHP from hemodialysis, however, female patients with chronic renal failure on hemodialysis experience a much greater incidence of infertility than their counterparts without renal disease. Only about 1-2% of women on hemodialysis become pregnant, and only about 40-50% of those women give birth to live infants (Bagon et al., 1998; Okundaye et al., 1998; Toma et al. 1999). Consequently, the number of infants that experience both high dose prenatal exposure to DEHP (assuming maternal exposure to DEHP from hemodialysis) and high dose postnatal exposure via procedures such as ECMO is likely to be very small.

The results of the above studies suggest that neonates can be prenatally exposed to phthalates from maternal exposure to phthalates in the environment (e.g., use of personal care products) and a certain number of newborns will also receive prenatal exposure to DEHP following maternal exposure to the compound during medical procedures such as enteral or parenteral feeding. The dose of DEHP received by the mother undergoing these procedures may be only about an order of magnitude less than the dose that caused adverse testicular effects in the offspring of rodents treated orally with DEHP. Consequently, a TI should be derived that is sufficiently protective for pre- and post-natal exposure to DEHP.

3.2.3.3 Lack of data from a study involving coexposure to multiple phthalate esters

The implications of coexposure of patients to MEHP and DEHP have been addressed elsewhere (Annex C); however patients are exposed to phthalate esters other than DEHP and MEHP in the hospital environment. Although DEHP is by far the most commonly used plasticizer PVC, dibutyl phthalate (DBP), diethyl phthalate (DEP), dimethyl phthalate (DMP), diisobutyl phthalate (DIP), and butyl 2-ethylhexyl phthalate (BEP) have also been identified in extracts from PVC medical

devices. For example, Khaliq et al. (1992) quantified levels of DEHP, DBP and DMP released from PVC nasogastric tubing. DBP and DEP have been identified as components of PVC used for devices such as microfilters, butterfly catheters, infusion tubing, infusion bags, and intestinal tubing at levels ranging from ≥ 1% to < 20% of the total volatiles extracted from the device (Wahl et al., 1999). DBP has also been shown to leach from denture base material (Lygre et al., 1995). Patients undergoing peritoneal dialysis are exposed to both DEHP and DBP from the dialysate (Sugimura et al., 2001) and multiple phthalates have been identified in food served to hospital patients (Tsumura et al., 2001). Patient exposure to multiple phthalates is also evidenced by data reported by Ching et al. (1981). It is interesting to note in the Ching et al. (1981) study that levels of DBP in the serum of surgical patients exceeded that of DEHP in many cases.

In contrast to the clinical situation, rats in the Sjoberg et al. (1985a), Baxter (2000), and AdvaMed (2001) studies were exposed only to DEHP and there is very little background exposure to other phthalate esters (Kessler et al., 2001). Since the two phthalate esters with the highest exposures (DEHP and DBP) have similar effects on the testes and are thought to exert these effects via an antiandrogenic mechanism, the potential exists for the LOAEL in the Sjoberg et al. (1985a) and AdvaMed (2001) studies to have been lower if the rats had been coexposed to multiple phthalate esters, as occurs in the clinical situation.

3.2.3.4 Lack of a NOAEL value

In cases where a NOAEL is not identified in a study, it is customary to apply an UF of 3 to 10 to the LOAEL to estimate the NOAEL. Although the parenteral TI is derived from the NOAEL in the AdvaMed (2001) study, the TI could also be derived from the LOAEL in the Sjoberg et al. (1985a) study. Since the effects seen at the LOAEL dose in the Sjoberg et al. (1985a) study are fairly subtle, an UF of 3 will be applied to the LOAEL to estimate the NOAEL.

3.2.3.5 Reversibility of DEHP- or MEHP-induced testicular lesions

It has been argued that a smaller UF can be applied when deriving a TI if the effects seen at the LOAEL are reversible (e.g., Gaylor et al., 1999). Recovery of at least some male reproductive capacity (sperm count, sperm motility and sperm morphology) occurred in DEHP-exposed rats at the end of the recovery period in the AdvaMed (2001) study. Although these results are encouraging for neonates exposed to DEHP and MEHP, the following factors should be considered:

- Although recovery was seen in functional parameters, testicular atrophy persisted at the end of the recovery period in rats exposed to DEHP either orally or by IV injection. Consequently, the adverse testicular effects of DEHP were not completely reversible. These findings are consistent with those reported by Oishi (1985), who found that testicular weight did not return to normal in DEHP-treated rats and spermatogenesis continued to be impaired 45 days after cessation of exposure to DEHP. Agarwal et al. (1986) also noted only partial recovery from the testicular effects in rats following cessation of exposure to DEHP.

- Although some functional indices of male reproductive capacity recovered in DEHP-exposed rodents, fertility was not assessed by mating the animals. Therefore, it cannot be said with certainty that functional impairment of reproductive capacity did not occur.

- As discussed above, vitamin deficiency potentiates DEHP-induced aspermatogenesis (Ishihara et al., 2000). Since animals in the AdvaMed (2001) study were presumably not vitamin deficient, it is possible that functional indices of male reproductive capacity would not have returned to normal in vitamin-deficient animals.

Based on these considerations, it is not appropriate to reduce the value for UF3 (and consequently, the value of the TI) to account for the reversibility of the functional deficits following a recovery period; however, the recovery of these indices of male reproductive capacity in the AdvaMed (2001) study is nevertheless encouraging.

3.2.3.6 Conclusions and their impact on the selection of values for UF3

- An additional UF to account for the lack of a long-term study will not be applied to the NOAEL and LOAEL from the short-term studies of Sjoberg et al. (1985a), Baxter (2000), and AdvaMed (2001) to derive a long-term parenteral TI.

- The following factors will be taken into account when selecting a value for UF3: increased sensitivity to DEHP-induced testicular effects during pre- and postnatal exposure and the possibility that humans can be exposed to phthalates other than DEHP and MEHP that exert their effect via a similar mechanism of action.

- The potentially increased sensitivity of sick or injured patients to DEHP was taken into account in the selection of a value for UF1.

- Where a LOAEL is used to derive the TI, an UF of 3 is justified, based on the severity of effects seen at the LOAEL and the relationship of LOAEL to NOAEL values in other studies.

- Some but not all of the adverse testicular effects seen in DEHP-exposed rodents in the AdvaMed (2001) study were reversible following a recovery period. Therefore, the UF will not be adjusted to account for reversibility.

Collectively, these factors justify a value for UF3 of 3 when a NOAEL is used to derive the TI and 10 (approximately 3 x 3) when a LOAEL is used to derive the TI.

3.3 Application of Modifying Factors to Derive Parenteral and Oral TI Values (Step 3)

Based on the considerations discussed above, the following MFs will be used to derive the TI values for DEHP via oral and parenteral routes (Table 3-8).

Table 3-8 Modifying Factors for Derivation of TI Values for DEHP

Route	Endpoint	UF1	UF2	UF3	Modifying Factor
Parenteral	NOAEL from Baxter (2000, 2001)	10	3	3	100
	LOAEL from Sjoberg et al. (1985a)	10	3	10	300
Oral	NOAEL from Poon et al. (1997)	10	3	3	100

Application of these modifying factors to the NOAEL value reported by Baxter (2000, 2001) following parenteral exposure, the LOAEL values reported by Sjoberg et al. (1985a) following IV exposure and the NOAEL reported by Poon et al. (1997) following oral exposure yields the following TI values (Table 3-9).

Table 3-9 TI Values for DEHP

Route	Endpoint	NOAEL or LOAEL value (mg/kg/day)	Modifying Factor	TI (mg/kg/day)
Parenteral	NOAEL from Baxter (2000, 2001)	60	100	0.60
	LOAEL from Sjoberg et al. (1985a)	250	300	0.80
Oral	NOAEL from Poon et al. (1997)	3.7	100	0.04

No parenteral health-based exposure limits have been derived previously for DEHP, however, the TI value derived for parenteral exposure is equivalent to the dose of DEHP received following exposure to this compound at the OSHA 8-hour PEL (OSHA, 1988), assuming 100% absorption (5 mg/m^3 x $10m^3$/day x 1/70 kg = 0.7 mg/kg/day).

Existing health-based exposure limits based on noncancer effects seen after oral exposure have been derived by other regulatory agencies and advisory groups (Table 3-10). Comparison of these values to the TI value derived by CDRH for DEHP reveals that the CDRH-derived value is consistent with the health-based exposure limits derived for DEHP by the Health Canada, the OECD, U.S. EPA, and the EU Scientific Committee on Toxicity, Ecotoxicity and the Environment (CSTEE).

Table 3-10 Existing health-based exposure limits for DEHP based on noncancer effects (oral exposure)

	Agency			
	EU CSTEE	**Health Canada**	**OECD**	**U.S. EPA**
Type of Value	Guidance value for extractable amount	Tolerable Daily Intake (TDI)	Tolerable Daily Intake (TDI)	Reference Dose (RfD)
Risk Value (mg/kg/day)	0.05	0.044[1]	0.04	0.022
Basis	NOAEL 5 mg/kg/day	NOAEL 44 mg/kg/day	NOAEL 37.5 mg/kg/day	LOAEL 19 mg/kg/day
Uncertainty Factor	100	1000	1000	1000
Critical Organ or Effect	Hepatic Peroxisome Proliferation	Maternal and Fetal	Teratogenicity	Liver
Species	Rat	Mouse	Mouse	Guinea pig
Study	RIVM (1992)	Wolkowski-Tyl et al. (1984)	Tyl et al. (1988)	Carpenter et al. (1953)

[1]Currently undergoing review

4.0 Risk Characterization

In the risk characterization step of the safety assessment, exposure information presented in Section 2.0 is compared to the TI values derived in Section 3.0 to assess the likelihood that exposure to DEHP could cause adverse effects in exposed patients.

In Table 4-1, TI values for DEHP are compared to doses of DEHP received by patients undergoing various medical procedures. When assessing the significance of the TI/Dose ratios shown in Table 4-1, it is important to keep in mind that this comparison should not be viewed as a bright-line value, but rather as a general index of the safety. In other words, an TI/Dose ratio > 1 does not necessarily mean that a compound is "safe", nor does a TI/Dose < 1 indicate that adverse effects are likely in humans. Rather, these values should be used in a relative sense to assess the likelihood that exposure to a compound will cause adverse effects in humans. Two other factors should be kept in mind as well when interpreting the significance of these values: 1) the TI is a value with uncertainty that spans perhaps an order of magnitude (Dourson et al., 1996), and 2) TI/Dose ratios based on a comparison between short-term or one-time exposures (e.g., acute transfusion) and a TI based on a repeat-dose toxicity study are likely to be conservative.

This information is being provided to risk managers to assist with regulatory decision-making regarding the safety of PVC medical devices. Factors such as the relevance of the data for humans, uncertainties associated with the toxicity and exposure data, and any benefits conferred by the use of DEHP as a plasticizer for PVC used in medical devices will be considered along with the TI/Dose ratios values in making any regulatory decisions.

The TI/Dose ratios listed in Table 4-1 will allow CDRH to draw conclusions about the risk posed by patient exposure to DEHP in various clinical scenarios. These conclusions are as follows.

4.1 Conclusions Based on TI/Dose Ratios

IV infusion of crystalloid fluids and drugs

Based on the results of the safety assessment, CDRH concludes that there is little to no risk posed by patient exposure to the amount of DEHP released from PVC IV bags following infusion of crystalloid fluids (e.g., normal saline, D5W, Ringers Lactate). Further, there is little risk posed by exposure to the amount of DEHP released from PVC bags used to store and administer drugs that require a pharmaceutical vehicle for solubilization, when label instructions are followed. Administration of propofol for conscious sedation of infants has the potential to result in the administration of large doses of DEHP; however, propofol is not approved for this indication in the US.

Total Parenteral Nutrition (TPN)

The dose of DEHP received by adult patients receiving TPN admixtures is estimated to be less than the TI, suggesting that there is little concern for DEHP-mediated effects in these patients. In addition, non-PVC bags and tubing are typically used to administer TPN, further lessening the concern about DEHP-mediated effects. Although the TI/dose ratio suggests little concern in adult patients receiving TPN, consideration should be given to the use of non-PVC bags and tubing when administering TPN to pregnant women who require nutritional support for the treatment of hyperemesis gravidarum.

The dose of DEHP received by neonates undergoing TPN supplementation is uncertain. The results of one study suggest that neonates can receive a very high dose of DEHP, whereas another suggests that neonates receive doses of DEHP from TPN that are equivalent to the TI.

Therefore, depending on the data used to derive the TI/dose ratio, neonates receiving TPN admixtures with lipid may be at increased risk of DEHP-mediated adverse effects.

Blood transfusion

Relatively high doses of DEHP can be received by patients who are transfused with large volumes of blood and blood products over a short period (e.g., trauma or surgical patients receiving massive transfusions). However, the TI/dose ratio for this procedure is likely to overestimate the actual risk to these patients, since it is intended to be protective of long-term exposure, compared to relatively short-term exposure in acute transfusions. In contrast, a patient undergoing a routine, elective surgical procedure typically receives about two units of packed red blood cells. Transfusion of this volume of blood will result in a DEHP dose equivalent to the TI value, approximately 0.5 mg/kg/day. Long-term transfusion of blood to patients with anemia results in a DEHP dose about an order of magnitude lower. Similarly, infants who receive replacement transfusions in the NICU receive relatively small DEHP doses from the transfusions. Apheresis donors are exposed to relatively little DEHP when the dose is time-averaged over an extended period. Consequently, there is little concern about DEHP-associated adverse effects developing in persons donating platelets or plasma.

Two subpopulations of patients that may be at increased risk from exposure to DEHP following transfusions are infants undergoing exchange transfusion and adults receiving ECMO. However, neither of these procedures is done very often, so the patient population exposed to relatively large doses of DEHP via exchange transfusion or replacement transfusion of adults on ECMO is expected to be small.

Cardiopulmonary bypass and ECMO

The aggregate dose of DEHP received by adults undergoing cardiopulmonary bypass procedures may equal of exceed the TI in some patients. However, heparin-coated tubing is used in about half of “special” or high risk cases and about 17% of “routine” cases (Mejak et al., 2000). Since little DEHP is released from heparin-coated tubing (Karle et al., 1997), the dose of DEHP received by many patients undergoing cardiopulmonary bypass will be less than those undergoing the procedure where uncoated PVC tubing is used.

The dose of DEHP received by neonates undergoing ECMO may exceed the parenteral TI by more than 20-fold, based on the exposure estimate from one study. However, a TI/dose close to 1 for this procedure can be derived using dose information from another study. Therefore, the risk posed by patient exposure to the amount of DEHP released during ECMO is uncertain. It is important to point out that no acute effects were seen in neonates undergoing this procedure in the recent study by Karle et al. (1997); however, it is equally important to point out that testicular toxicity (the assumed most sensitive effect in humans and other species) was not assessed in this study.

Hemodialysis and peritoneal dialysis

Based on recent data on the amount of DEHP retained by patients on hemodialysis, there is little concern regarding exposure to DEHP in patients undergoing this procedure. However, these patients may represent a sensitive subpopulation to the effects of DEHP because of reduced elimination capacity and the potential for uremia and coexposure to other compounds to potentiate the effects of DEHP.

Since very little DEHP is released into peritoneal dialysis fluid, the corresponding risk of systemic effects developing following exposure to this low dose of DEHP is also low.

Enteral nutrition and breastfeeding

Lipid in enteral nutrition solutions can leach out considerable doses of DEHP from PVC bags and tubing. As a result, these patients may be at increased risk of developing DEHP-mediated effects if PVC bags and tubing are used to deliver the enteral nutrition solutions.

Based on theoretical estimates, it is possible for nursing infants of mothers on hemodialysis to receive very high doses of DEHP; however the exact dose received by these babies is highly uncertain. Because of the level of uncertainty in this estimate, a TI/Dose ratio was not derived for this means of exposure to DEHP. Also, because women on hemodialysis are typically infertile, the population of infants exposed in this manner is thought to be very small.

Bags used to store breast milk following the use of a breast pump are typically made from polyethylene or nylon coated with polyethylene. Consequently, it is not expected that infants will be exposed to any DEHP released from a breast pump or milk storage bags.

Aggregate exposure to DEHP from multiple medical devices

DEHP dose estimates typically do not take into account exposure of patients to multiple PVC devices. Consequently, it is important to assess the potential risk of patients in various clinical scenarios by taking into account aggregate exposure to DEHP from multiple devices. For example, neonates in the NICU environment are exposed to DEHP from multiple devices. Based on the dose of DEHP received in such procedures as intravenous administration of sedatives, administration of TPN and replacement transfusion, all common procedures in the NICU, it is possible to estimate that a 4 kg infant could receive a DEHP dose on the order of 3 mg/kg/day for a periods of weeks or months. The resulting TI/dose ratio in this setting is 0.2. In other words, the dose of DEHP received by some infants from device-related sources could be 5-fold greater than the TI. If the neonate is also undergoing ECMO treatment, the TI/dose ratio drops to around 0.05, indicating that the dose of DEHP received by some infants from device-related sources could be 20-fold greater than the dose of DEHP that is not expected to result in adverse effects following intravenous exposure.

Table 4-1. Comparison of Tolerable Intake (TI) Values for DEHP to the dose of DEHP received by adult and neonatal patients undergoing various medical procedures.

	Adult[1]		Neonate[2]	
	DEHP dose (mg/kg/day)	**TI/dose ratio[3]**	**DEHP dose (mg/kg/day)**	**TI/dose ratio[3]**
Infusion of crystalloid IV solutions	0.005	120	0.03	20
IV infusion of drugs requiring pharmaceutical vehicles for solubilization	0.15	4	0.03	20
TPN administration				
Without added lipid	0.03	20	0.03	20
With added lipid	0.13	5	2.5	**0.2**
EVA bag with PVC tubing	0.06	10		
Blood transfusion				
Trauma patient	8.5	**0.1**		
Transfusion/ECMO pts.	3.0	**0.2**		
Exchange transfusion			22.6	**0.02**
Replacement transfusion Neonate in NICU			0.3	2
Replacement transfusion Correction of anemia in Patients receiving Chemotherapy and patients with sickle cell disease	0.09	7		
Replacement transfusion surgical patient undergoing CABG	0.28	2		
Treatment of clotting Disorders with Cryoprecipitate	0.03	20		
Cardiopulmonary bypass				
CABG	1	**0.6**		
Orthotopic heart transplant	0.3	2		
Artificial heart transplant	2.4	**0.3**		
ECMO			14	**0.04**
Apheresis	0.03	20		
Hemodialysis	0.36	2		
Peritoneal dialysis	< 0.01	> 60		
Enteral nutrition	0.14	**0.3**	0.14	**0.3**

[1] 70 kg body weight
[2] 4 kg body weight
[3] Based on TI of 0.6 mg/kg/day for parenteral exposures and 0.04 mg/kg/day for enteral nutrition

4.2 Aggregate Exposure to DEHP and MEHP

In addition to DEHP, patients can be exposed to the DEHP metabolite, MEHP. This compound is formed exogenously by lipases in stored plasma or blood or by hydrolysis in stored and heated IV fluid. As a result, some of the DEHP that is released into stored blood, plasma, or IV fluids will be converted to MEHP before reaching the patient. Exposure to MEHP is important since this compound is thought to be the toxic metabolite of DEHP and because it is more potent than DEHP in producing adverse effects. A method was developed to estimate the aggregate dose of DEHP and MEHP and to express this dose on the basis of DEHP-equivalents (Annex C). However, because of uncertainties associated with the relative potency of DEHP:MEHP and resulting estimates of DEHP equivalent dose, the TI/Dose ratios based on the dose of DEHP-equivalents received by patients will not be used to support regulatory decision making.

4.3 Conclusions Based on Nonsystemic Effects

The conclusions reached in the safety assessment are based solely on the potential for DEHP to cause in adverse systemic effects in exposed patients, based on TI values derived from animal studies. However, the clinical significance of various nonsystemic effects produced by DEHP is explored in Annex D. The ability of DEHP to alter the hemocompatibility of PVC tubing or result in adsorption of drugs to PVC tubing may be the most clinically important endpoints to consider in the risk management phase of the assessment, depending on the device.

5.0 References

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Annex A. Exposure Assessment

Section 2.0 of the main document provides an overview of the doses of DEHP received by patients undergoing various medical procedures. This annex provides more information on how these dose estimates were derived.

DEHP is released from a wide variety of PVC medical devices. A partial list of these devices is provided in Table A-1.

Table A-1. PVC medical devices known to release DEHP

IV storage bags	Ventilator tubing
IV infusion sets	Endotracheal tubes
IV infusion catheters	Nasogastric tubes
Blood storage bags	Enteral and parenteral nutrition storage bags
Blood administration sets	Urinary catheters
PVC exam gloves	Suction catheters
Chest tubes	Nasal cannula tubing
Hemodialysis tubing	Syringes
Extracorporeal membrane oxygenation (ECMO) tubing	Cardiopulmonary bypass (CPB) tubing

In this section, an attempt is made to quantify the dose of DEHP received by patients undergoing various medical procedures. In most cases, exposure is represented as administered dose (mg/kg/day) and is time-averaged over a course of treatment. For example, if an adult patient receives 60 mg of DEHP in a hemodialysis session, and undergoes hemodialysis three times per week, the time-averaged dose of DEHP received by this patient would be 60 mg/session x 3 sessions/week x week/7 days x 1/70 kg = 0.37 mg/kg/day. It is necessary to represent exposure dose in units of mg/kg/day, time-averaged over the exposure period, so a common dose metric exists for comparison of the dose of DEHP received by patients and the dose of DEHP used in toxicity studies. A summary of the estimated DEHP dose received by patients undergoing various procedures is provided at the end of this section (Table A-24).

In addition to DEHP, patients can be exposed to the monoester of this phthalate, MEHP. Since MEHP is thought to be the active metabolite mediating many of the adverse effects of DEHP, it is important to assess exposure to this compound as well.

A.1 Parenteral Exposure to DEHP and MEHP

Parenteral exposure to DEHP and MEHP can occur following intravenous infusion of crystalloid solutions (e.g., normal saline, D5W, Ringers Lactate) and drugs, administration of enteral nutrition and total parenteral nutrition (TPN) solutions, and transfusion of blood or blood products. In addition, patients undergoing cardiopulmonary bypass (CPB), extracorporeal membrane oxygenation (ECMO), hemodialysis or peritoneal dialysis can also be exposed to DEHP. The extent to which DEHP is released from PVC medical devices is largely a function of the lipophilicity of the fluid that comes into contact with the device. Substances like blood, plasma, red blood cell or platelet concentrates; IV lipid emulsion or total parenteral nutrition solution; and formulation aids (e.g., Polysorbate 80) used to solubilize IV medications can readily extract DEHP from PVC tubing and containers. In contrast, nonlipid-containing fluids, like crystalloid IV solutions, saline priming solution

for ECMO and hemodialysis, and peritoneal dialysis solution, extract relatively only small amounts of DEHP from the PVC constituents of the device. Doses of DEHP administered to patients undergoing each of these procedures are estimated below.

A.1.1 Intravenous Solutions

A.1.1.1 DEHP dose following infusion of crystalloid solutions

In the absence of lipid-containing substances, the amount of DEHP that leaches from PVC storage bags into crystalloid IV solutions is generally very small. For example, little or no DEHP was found to leach into crystalloid solution (normal saline, D5W) stored in PVC bags for more than one year (Dine et al., 1991). Similar findings were reported by Moorhatch and Chiu (1974). Corley et al. (1977) quantified levels of DEHP in various crystalloid IV solutions (normal saline, D5W, Ringers Lactate) packaged in PVC bags as a function of administration time and whether the bags were agitated or not. Agitation involved shaking for 24 hours at room temperature. The level of DEHP in nonagitated bags did not increase as a function of administration time and ranged between 0.067 and 0.172 μg/ml, yielding a DEHP dose of 0.134 to 0.344 mg of DEHP/day assuming infusion of 2 L of fluid/day. Agitation increases the concentration DEHP in solution. These levels ranged from 0.43 to 2.87 μg/ml, yielding a DEHP dose to an adult patient receiving 2 L of IV fluid/day of 0.86 to 5.74 mg/day.

Arbin and colleagues (Arbin et al., 1980; 1986) detected lower levels of DEHP in D5W and normal saline than Corley et al. (1977) did. Levels detected by Arbin et al. (1980) ranged from < 0.004 to 0.034 μg/ml. At these concentrations, an adult patient receiving 2 L of IV fluids/day would receive up to 0.068 mg of DEHP.

The upper-bound value of DEHP in crystalloid IV solutions as reported by Corley et al. (1977) for non-agitated bags (0.344 mg/day) was used to develop the adult TI/Dose ratios for this procedure, since non-agitated bags best represent the clinical situation and since this value approximates the upper-bound solubility of DEHP in aqueous media. The time-averaged dose of DEHP delivered to a 70 kg patient receiving 2 L of IV solution/day would be on the order of 0.005 mg/kg/day.

Neonatal patients do not typically receive IV fluid administration via a gravity feed, rather a syringe infusion pump is often used to administer IV fluids to pediatric patients. Although the syringe used is typically made from polypropylene, a small amount of DEHP can be released from the PVC administration tubing. Loff et al. (2000) found that infusion of a crystalloid IV solution through PVC tubing for 24 hours yielded a DEHP dose of 116 μg, equivalent to a dose of 0.06 mg/kg/day for a 2 kg neonate.

It is accepted practice in some facilities to warm IV solutions in a microwave oven. Other facilities will use a blood warmer to increase the temperature of IV fluids. Data are unavailable on the extent to which heating a PVC bag will increase the concentration of DEHP in a crystalloid solution; however, this practice could increase the dose of DEHP to a patient receiving crystalloid solutions intravenously. It should be noted however, that the use of a blood warmer is the more accepted means of warming IV fluids. During this procedure, the infused fluid is heated to about 40^{o}C as it flows through the administration tubing into the patient. As a result, the PVC bag itself is not heated during this procedure and the heated infusate does not enter the PVC bag.

A.1.1.2 DEHP dose following infusion of crystalloid solutions containing lipophilic drugs dissolved in pharmaceutical solvents

The package insert labeling that accompanies a number of drug products, notably antineoplastics, caution against the use of PVC containers for storage and delivery of the drug. If non-PVC containers and non-PVC infusion sets are used to administer the drug, DEHP exposure is expected to be minimal.

Table A-2. Drug Products that Include Labeling Precautions for the Use of PVC Containers

Generic Name	Trade Name
Paclitaxel	Taxol (Bristol-Myers Squibb
Docetaxel	Taxotere (Rhone-Poulenc Rorer)
Tacrolimus	Prograf (Fujisawa)
Teniposide	Vumon (Bristol-Myers Squibb)

Faouzi et al. (1999a) found that 52 mg of DEHP were released into intravenous solution when teniposide was stored in PVC bags for 48 hours at room temperature. A 70 kg patient receiving teniposide stored under these conditions would receive a time-averaged DEHP dose of 0.74 mg/kg/day. When the bags were stored at 19^{o}C, 19 mg of DEHP was released. Since the manufacturer suggests that this drug be reconstituted just prior to administration, and since DEHP concentration in teniposide solution increases as a function of storage time (Faouzi et al., 1999a), considerably less DEHP would be expected to be infused into a patient under standard administration practices. Faouzi et al. (1999a) provided data from a simulated infusion that permit a more accurate estimate of DEHP dose to be made. These investigators prepared teniposide (400 μg/ml) in 250 ml of 5% dextrose solution in PVC bags and conducted a simulated infusion using PVC tubing. Data were then provided on the concentration of DEHP in solution taken from the bag and from the infusion set during a one-hour infusion. Since the data were reported in a figure, the concentration of DEHP infused was obtained by estimating the concentration off the graph and manually integrating the data. Using this approach, it appears that about 2 mg of DEHP could be infused into a patient based on these data. DEHP released from the PVC administration set contributes significantly to the total DEHP dose, especially in the early time periods (i.e., during the first 30 minutes of the infusion). Based on the difference between the concentration of DEHP in solution sampled from the bag and from the administration set, integrated over the duration of the infusion, it appears that the administration set contributed about 0.84 mg of the total 2 mg dose of DEHP that could be administered during the infusion period.

DEHP dose following drug infusion from "low DEHP" bags

The labeling information provided with a number of drugs instructs the user to administer and store the reconstituted drug in PVC bags that release minimal amounts of DEHP, such as Baxter's PL-146 bag. The concentration of DEHP in these bags is assumed to not exceed 5 ppm (5 μg/ml). Table A-3 provides a worst case estimate of the dose of DEHP received by patients receiving these assuming that the drugs are premixed in PL-146 IV bags and the premixed solution is agitated for 24 hours at room temperature before administration to the patient.

Table A-3. Dose of DEHP Received Following Administration of Various Drug Products

Generic Name	Trade Name	DEHP Dose (mg/day)
Ciprofloxacin	Cipro IV (Bayer)	1.0 – 3.0
Cefoperazone sodium	Cefobid Bulk (Pfizer)	0.5
Fluconazole	Diflucan (Pfizer)	1.0
Metronidazole HCl	Flagyl IV (SCS)	0.5
Cimetidine	Tagamet (SmithKline Beecham)	0.75

An explanation of how these estimated doses were derived is provided below.

Ciprofloxacin

The labeling information for Cipro® IV (ciprofloxacin) points out that DEHP can leach from the PVC container used to store and deliver this drug at a concentration up 5 parts per million (ppm). To estimate the dose of DEHP received by patients being administered this drug, information is needed on the volume of solution containing the drug and the frequency with which it is administered. For mild urinary tract infections, the recommended dose of ciprofloxacin is 200 mg every 12 hours (PDR, 1998). The drug comes packaged in a flexible PVC container that contains 200 mg in 100 ml of solution. If the concentration of DEHP in solution is 5 ppm or 5 mg/L, the dose of DEHP received by a patient receiving this drug to treat a urinary tract infection would be:

5 mg DEHP/L x 100 ml/administration x 2 administrations/day x 0.001 L/ml = 1 mg DEHP/day.

More aggressive treatment is required to treat more severe infections. For example, a dose of 400 mg of ciprofloxacin is recommended every 8 hours to treat severe infections of the respiratory tract, bones, joints, or skin. The dose of DEHP received in this dosing regimen would be:

5 mg DEHP/L x 200 ml/administration x 3 administrations/day x 0.001 L/ml = 3 mg DEHP/day.

Cefoperazone Na

Cefoperazone Na (Cefobid Bulk) is available in 1 or 2 g amounts premixed in 50 ml PVC bags to be used as piggyback units. The usual dose is A-4 g/day divided every 12 hours (PDR, 1999). Therefore, administration every 12 hours would yield a DEHP dose of

50 ml/bag x 0.005 mg DEHP/ml x 2 bags/day = 0.5 mg/day.

This dose not include any DEHP released from a PVC administration set. Cefobid Bulk is also available premixed in polyethylene bags (PL-2040). Use of drug stored in PL-2040 bags would result in DEHP exposure from the infusion set only.

Fluconazole

Fluconazole (Diflucan) is available as a premixed solution Viaflex (PL-146) bags. The concentration of Diflucan in the premixed solution is 200 mg in 100 ml or 400 mg in 200 ml (PDR, 1999). The total maximum dose of Diflucan is 400 mg/day. The amount of DEHP expected to be administered with this dose is:

200 ml/day x 0.005 mg DEHP/ml = 1 mg DEHP/day.

Metronidazole HCl

Metronidazole HCl (Flagyl IV) is available premixed in PL-146 bags containing 500 mg of drug. The loading dose of Flagyl IV is 1 g in the first hour, followed by the maintenance dose of 500 mg every 6 hours. Therefore in the first day, a patient could receive six bags of premixed solution. Assuming a DEHP concentration of 5 ppm, the dose of DEHP received by patients treated with Flagyl IV would be:

100 ml/bag x 6 bags/day x 0.005 mg DEHP/ml = 3 mg DEHP/day

Cimetidine

Cimetidine (Tagamet) is available in single dose premixed PVC containers. Each 50-ml bag contains 300 mg of drug. The recommended dosage of Tagamet is 300 mg every four hours. This dosing regimen would result in a maximal DEHP dose of:

50 ml/bag x 4 bags/day x 0.005 mg/ml = 1 mg/day

Again, this estimate does not include the potential contribution of DEHP released from the administration set to the total dose received by the patient.

Concern has been expressed about the dose of DEHP received following infusion of certain lipophilic drugs, notably, several antineoplastic drugs. However, as discussed in Section A.1.1.2 (above), relatively small amounts of DEHP are released from these bags if the drugs are prepared according to the manufacturer's instructions. However, premixing and storage of these drugs in PVC bags at room temperature can result in a considerably higher dose of DEHP being delivered to a patient (e.g. 52 mg/bag as shown by Fauozi et al, 1999). The upper-bound dose DEHP received following administration of drugs prepared in PL-146 bags is on the order of A-3 mg/day or about 0.03 to 0.05 mg/kg/day for a 70 kg adult.

DEHP dose following drug infusion from non-PVC bags

In addition to "low DEHP" PL-146 bags, non-PVC bags are also available for the administration of drugs that require a lipophilic vehicle for solubilization. No DEHP is expected to be released from non-PVC bags (however, some DEHP may be released from a PVC administration set if one is used). Consistent with this expectation, Sautou-Miranda et al. (1999) demonstrated that no DEHP was detected in a solution of paclitaxel stored in a polyethylene container for 15 days.

Drug infusions in pediatric patients

Drug infusions are typically administered to pediatric patients using an infusion pump. Loff et al. (2000) measured the amount of DEHP that could be received by a pediatric patient receiving IV drug therapy (Table A-4).

Table A-4. Dose of DEHP received by neonates undergoing IV drug therapy (Loff et al., 2000)

Drug	Perfusion time (hours)	Concentration of DEHP after perfusion (µg/ml)	Amount in ml	Total Amount of DEHP (µg)	Total Dose of DEHP (mg/kg/day) for a 2 kg neonate
Imipenem	0.5	0.78	8	6.26	0.003
Midazolam	24	1.13	24	26.4	0.013
Fentanyl	24	4.59	29	132.5	0.066
Propofol	24	656	10	6561	3.28

As shown in Table A-4, relatively little DEHP is expected to be received by children undergoing drug therapy with imipenem, midazolam or fentanyl. In contrast, patients receiving propofol can receive a considerable dose of DEHP over a 24 hour period. However, propofol is not approved for sedation in pediatric ICU patients in the US (FDA, 2001), therefore, the upper-bound dose of DEHP received by neonates undergoing conscious sedation is on the order of 0.07 mg/kg/day for a 2 kg infant.

Multiple Drug Infusions

Often, multiple drugs are co-infused in the same IV infusion. One such case is the co-infusion of quinine along with multivitamin preparations. Faouzi et al. (1999b) demonstrated little DEHP is released from PVC bags containing quinine alone in solution; however, the presence of the lipophilic multivitamin cocktail dramatically increased the extent of DEHP release from the bag. Following storage of quinine/multivitamin combinations for 48 hours at 45^{o}C, the concentration of DEHP in the bags reached 21 µg/ml. Consequently, a patient receiving a 500 ml infusion of quinine with a multivitamin cocktail would receive 10.8 mg of DEHP.

A.1.1.3 Exposure to compounds other than DEHP in intravenous infusion solutions

Exposure of patients to MEHP is addressed in Annex C. In addition to MEHP, Arbin et al. (1986) identified a number of contaminants in normal saline solutions stored in PVC bags using GC-MS or gradient liquid chromatography (LC) techniques. Levels of these contaminants in IV solutions stored for about 1 year in 100-ml bags from either ACO Lakemedel AB or Travenol are shown in Table A-5.

Table A-5. Contaminants identified in normal saline stored for 1 year in PVC bags (Arbin et al., 1986)

Contaminant	Concentration (µg/ml)	
	ACO bag	Travenol bag
Phthalic acid	0.026	0.027
Cyclohexanone	-	35.00
Phenol	0.024	0.029
Phthalide	0.016	0.580
Benzoic acid	0.029	-
Benzaldehyde	0.005	0.013
Bisphenol-A	-	0.320
Butyl hydroxyanisol	0.058	-
MEHP	0.454	-
DEHP	0.007	0.005

A number of other compounds (i.e., acrolein, tetrahydrofuran, toluene, xylene) were identified using dynamic headspace GC-MS analysis following heating of the bag to 120^{o}C for 5-20 minutes; however, appearance of these compounds in the infusion solution is dependent on the partition coefficient of the compound between the bag and the solution.

A.1.1.4. Phthalate ester exposure from non-PVC Bags containing drug solutions

Trilaminate bags (outside-polypropylene, middle-nylon, inside-polyethylene) serve as an alternative to PVC bags for the administration of IV drugs that require pharmaceutical vehicles for solubilization. However, Sarbach et al. (1996) found that higher levels of phthalate (presumably, DEHP) were being released from a trilaminate IV bag into aqueous solution containing 0.5% metronidazole than were released from Baxter's Viaflex bag into saline. The trilaminate bag has been marketed under the trade name, Clear-Flex. Levels of phthalate in solution contained in the trilaminate bag ranged from 128 to 149 ug/100 ml. Levels of DEHP in saline contained in the non-agitated Viaflex PVC bag ranged from 0.53 to 0.77 ug/100 ml. By extracting each of the layers of the bag separately, and by analyzing the polyurethane cement used to manufacture the bag, the investigators found that the phthalate came from the polyurethane cement. It is important to point out that the compound identified by Sarbach et al. (1996) may not be DEHP, since a mass spectrum of the chromatogram peak simply indicated a “phthalate structure”. Structural proof by other means (e.g., IR, NMR) was not accomplished to demonstrate that the compound represented by the peak was indeed DEHP. Phthalate anhydride is sometimes used as a curing agent for ester type adhesive which the polyurethane is likely to contain. Phthalate anhydride in water hydrolyzes to phthalic acid, which may be the phthalate structure that Sarbach et al. (1996) observed. Unique identification of the phthalate structure found by Sarbach et al. (1996) is necessary before conclusions can be made about the presence of DEHP in solutions stored in trilaminate bags

A.1.2 Parenteral Nutrition

Total parenteral nutrition (TPN) formulations are often administered to critically ill patients requiring nutritional supplementation. Parenteral administration involves infusion directly into the circulatory system. Typical TPN admixtures contain amino acids, dextrose, electrolytes and lipids. Mazur et al. (1989) have shown that the presence of lipid in the TPN solution increases the concentration of DEHP in the admixture when PVC bags are used. The concentration of DEHP in TPN formulations without added lipid are below the limit of detection. The concentration

of DEHP in the TPN solution increases as a function of time and storage temperature. Table A-6 lists the daily dose (mg/day) received by a patient receiving 3 L of TPN admixture that is either lipid-free or that has a lipid concentration of either 10% or 20%.

Table A-6. Dose of DEHP (mg/day) following administration of 3L of TPN admixture (adapted from Mazur et al., 1989)

Days of storage	Dose of DEHP (mg/day) following administration of 3L of TPN		
	Without addition of lipid emulsion	with addition of 10% lipid emulsion	with addition of 20% lipid emulsion
1	0.3	0	0
2	2.1	9.3	7.8

As shown in Table A-6, the dose of DEHP received by a patient increases as a function of storage time. According to Mazur et al. (1989), TPN solutions are administered within 24 to 36 hours of admixture. During this period, the maximal concentration of DEHP measured in TPN solution by Mazur et al. (1989) was 3.1 µg/ml. The resulting upper-bound dose of DEHP received by a patient following storage of the TPN solution for 48 hours would be 9.3 mg, when all 3 L of TPN solution is infused. However, administration of unrefrigerated TPN solution within 24 hours of admixture is unlikely to deliver more than 3 mg of DEHP.

The results of Mazur et al. (1989) are not consistent with those of Allwood (1986). Following storage of a TPN admixture with 20% Intralipid for 24 hours, the concentration of DEHP in the TPN solution was 40 µg/ml. Infusion of 2.5 L of this admixture into a patient would result in a dose of 100 mg of DEHP. The dose of DEHP received following infusion of 10% or 20% Intralipid alone, 20% Intralipid with TPN or TPN without Intralipid is shown in Table A-7.

Table A-7. Dose of DEHP (mg/day) following administration of 2.5 L of TPN admixture following 24 hours of storage (adapted from Allwood, 1986)

TPN Preparation	Dose of DEHP (mg/day) following administration of 2.5 L of TPN	
	Stored at 4-6^{o}C	Stored at ambient temperature
10% Intralipid	35	80
20% Intralipid	32	72
TPN (2L) with 20% Intralipid (0.5L)		100
TPN without Intralipid		3.75

Allwood (1986) also conducted a simulated infusion without storage to estimate the dose of DEHP received by a patient receiving Intralipid. The results of this study indicate that a patient receiving 500 ml of 10% Intralipid would receive about 2.5 to 2.75 mg of DEHP and a patient receiving 20% Intralipid would receive about 1.5 mg/day.

DEHP dose from PVC administration sets used to administer TPN

Although PVC storage bags are still used for TPN administration, EVA (ethylvinyl acetate) bags are being increasingly used for this application. However, even EVA bags contain PVC components (Kambia et al., 2001), resulting in the release of some DEHP into the TPN solution. In addition, although plasticizer-free tubing can be used gravity infusion of lipid emulsions, the use of PVC tubing is required for pump assisted lipid administration. Pump-assisted administration is necessary to overcome hyperalimentation fluid-lipid density differences and variable central venous back pressures. Further, PVC tubing and infusion pumps are always used to administer lipids to pediatric and neonatal patients. Therefore, it is possible that a significant amount of DEHP could be received by patients receiving TPN even though non-PVC bags are used to store the TPN solution.

The amount of DEHP released into TPN solution stored for 24 hours in EVA bags ranged from 0.2 to 0.7 mg (Kambia et al., 2001); 0.8 to 2 mg was released from the bag and the PVC administration set, following flow of the emulsion through the tubing for 11 hours. Assuming the highest amount of DEHP released from the outlet of the tubing came from emulsions containing the highest concentrations of DEHP, then the amount of DEHP released from the tubing ranged from 0.6 to 1.3 mg/day, based on administration for 11 hours/day. Based on these values, up to 2.8 mg of DEHP could presumably be released from the tubing over a 24-hour infusion and up to 4.4 mg of DEHP total (EVA bag + tubing) could be received over a 24-hour period.

Unlike adults or even older children, neonates typically receive TPN via a syringe infuser. Loff et al. (2000) recently reported that if PVC tubing is used to administer the TPN, an infant could receive over 10 mg of DEHP from the tubing over a 24-hour period (equivalent to 2.5 mg/kg/day for a 4 kg neonate). However, an upper-bound dose of DEHP received by neonates can also be derived from the data reported by Kambia et al. (2001) as follows: 1600 ng/ml (maximum conc. of DEHP measured at outlet of PVC tubing) x 150 ml/kg/day (upper-bound dose rate for administration of TPN to neonates) = 0.24 mg/kg/day.

Wide differences exist in estimated daily dose of DEHP following administration of lipid-containing TPN exist depending on whether data from the Mazur et al. (1989) or Allwood (1986) are used to derive the dose estimate. Also the dose will vary depending on the material used to manufacture the storage bag (DEHP-plasticized PVC, non-DEHP plasticized PVC, or polyolefin) and whether a PVC infusion set is used. In Table A-24, the estimated dose of DEHP received by a 70 kg adult receiving a lipid containing TPN solution (0.08 mg/kg/day) comes from the assumption that 2.8 mg of DEHP can be released from PVC tubing per day (based on data provided by Kambia et al., 2001) and 3.0 mg of DEHP can partition from the PVC bag into TPN solution (based on the data of Mazur et al., 1989, assuming administration of unrefrigerated TPN within 24 hours). However, an estimated DEHP dose of 2.1 mg/kg/day for adults receiving TPN can be derived from the data reported by Allwood (1986) and Easterling et al (1974).

A.1.3 Transfusion of blood and blood products

DEHP migrates from PVC storage bags and into blood and blood products (platelets, plasma, packed red blood cells) because of the lipophilic nature of these biological fluids and cells. The concentration of DEHP reported in blood or blood products is summarized in Table A-8.

Table A-8. Concentration of DEHP in Blood and Blood Products

Blood Product	DEHP concentration Mean (µg/ml)	DEHP concentration Range (µg/ml)	Study
Plasma	44.8	4.3 to 123.1	Plonait et al. (1993)
Plasma	54.6	36.8 to 84.9	Sjoberg et al. (1985)
Plasma	38.0	13.8 to 71.9	Sjoberg et al. (1985)
Plasma		363 to 545	Dine et al. (1991)
Plasma		<110	Vessman and Reitz (1974)
Plasma		100-275	Vessman and Reitz (1974)
Plasma		<890	Vessman and Reitz (1974)
Plasma	72.5		Shintani et al. (1985)
Plasma	172.6		Shintani et al. (1985)
Plasma	266		Cole et al. (1981)
Plasma	145	106 to 209	Marcel (1973)
Plasma		290 to 1230	Contreras et al. (1974)
Platelet- rich plasma	181		Rock et al. (1978)
Platelet-poor plasma	285		Rock et al. (1978)
Leucocyte-poor plasma		25-32	Piechocki and Purdy (1973)
Fresh frozen plasma		11.2 - 339	Loff et al. (2000)
Fresh frozen plasma	26.7		Shintani et al. (1985)
Fresh frozen plasma	12		Cole et al. (1981)
Whole blood	52.5		Jaeger and Rubin (1972)
Whole blood		140 to 620	Contreras et al. (1974)
Whole blood	152.5		Peck et al. (1979)

Whole blood	123.4		Peck et al. (1979)
Platelet concentrate	267.0		Shintani et al. (1985)
Platelet concentrate	491		Rock et al. (1978)
Platelet concentrate		23.4 to 48.8	Loff et al. (2000)
Red cell concentrate	54.6	36.8 to 84.9	Sjoberg et al (1985a,b)
Red cell concentrate	44.8	4.3 to 123.1	Plonait et al. (1993)
Red cell concentrate		7.2 to 30.4	Loff et al. (2000)
Red cell concentrate	152		Peck et al. (1979)

The values listed in Table A-8 illustrate the variability in measurements of DEHP in blood and blood products. The variability can be explained somewhat by factors such as differences in the duration of storage and storage conditions (i.e. temperature), use of various analytical techniques, and differences in levels of lipids in the blood and plasma.

To derive appropriately protective TI/Dose ratios (see Section 4.0), upper-bound concentrations of DEHP will be used to derive administered dose estimates (below). Current clinical practices in transfusion medicine have been taken into account in deriving these administered dose estimates. For example, whole blood is rarely administered clinically. Instead, patients usually receive RBCs, platelets, fresh frozen plasma (FFP) or some combination of these products. Estimates are provided below of levels of DEHP in each type of blood product.

Concentration of DEHP in packed RBC

Levels of DEHP in serum from red cell concentrates prepared for exchange transfusion ranged from 4.3 to 123.1 µg/ml, with a mean of 44.8 µg/ml (Plonait et al., 1993) The upper-bound value from this study is consistent with that reported by Peck et al. (1979). Assuming a volume of about 350 ml/unit of RBCs (McCullough, 1998), each unit of red cell concentrate would be expected to deliver a DEHP dose of 43.1 mg, using the upper-bound concentration (123.1 µg/ml) from the Plonait et al. (1993) study.

Concentration of DEHP in FFP

Another trend that reflects current clinical practice is the use of fresh frozen plasma (FFP) instead of unfrozen, stored plasma. Levels of DEHP in FFP appear to be lower than those measured in unfrozen plasma. Requirements for the preparation of fresh frozen plasma specify that the plasma should be separated from RBCs within 8 hours of storage of the whole blood, then frozen at -18^{o}C. Since amount of DEHP released from PVC changes as a function of temperature, it is not surprising that less DEHP is released into FFP than plasma stored at higher temperatures. To reflect current practice, data on levels of DEHP in FFP will be used to estimate patient exposure to this phthalate ester instead of levels in unfrozen plasma. Also, since platelets are commonly stored in non-PVC bags, it is assumed that exposure to DEHP in patients receiving platelets will occur as a result of DEHP leaching from the blood administration set, if a PVC infusion set is used to administer the platelets.

Dose of DEHP received following the transfusion of blood or blood products

When estimating the dose of DEHP received by patients receiving blood or blood products, it is important to differentiate between two scenarios: 1) infusion of large amounts of blood or blood products over a short period and 2) chronic infusion of smaller volumes of blood over a prolonged period. Acute, large-volume blood transfusion is necessary in the treatment of acute blood loss in trauma patients, some patients undergoing surgery, patients with acute gastrointestinal bleeding and neonates undergoing exchange transfusion. Chronic administration of smaller volumes of blood or blood products is common in the treatment of patients with chemotherapy-associated anemia, blood disorders such as leukemia and aplastic anemia, and in the treatment of patients with clotting disorders.

Short-term blood transfusion

Short-term blood transfusion scenarios include large volume transfusions of blood and blood products to trauma patients, patients with gastrointestinal bleeding, and patients undergoing ECMO, as well replacement transfusions for infants in neonatal intensive care units (NICUs) and adult undergoing surgical procedures.

Large volume replacement in adults

Based on the results reported by other investigators, Sjoberg et al. (1985b) estimated that an adult receiving 2.5 L of blood stored for 21 days would receive a DEHP dose of 1.3 to 2.6 mg/kg. In cases of massive blood loss and transfusion of large amounts of blood, considerably more DEHP could be administered to a patient. For example, Jaeger and Rubin (1972) estimated that a gunshot victim receiving 63 units of blood would receive a DEHP dose of around 8.5 mg/kg. The concentration of DEHP in the blood of this patient was 2.8 µg/ml.

Although it is possible for trauma patients to receive > 50 units of blood or blood products (Hakala et al., 1999), similar to the patient in the scenario described by Jaeger and Rubin (1972), the typical transfusion volume in trauma patients is much less. Farion et al. (1998) reported that a mean of 3.57 units of packed cells was transfused into seriously injured adults and that there has been a decrease in blood product use in the management of these patients. Consequently, use of a DEHP dose derived on the basis of a 63 unit transfusion represents a worst case scenario with regard to DEHP exposure via transfusion. Patients undergoing routine, elective surgical procedures typically receive about two units of blood or blood products (Mallett et al., 2000). Assuming a mean DEHP concentration of 44.8 µg/ml for packed cells (Plonait et al., 1993) and a packed cell volume of 350 ml, transfusion in a typical surgery would result in administration of a DEHP dose of 0.5 mg/kg/day.

As discussed in Section A.1.3.2, patients undergoing ECMO are exposed to relatively large amounts of DEHP. In addition to DEHP released from PVC tubing used in the ECMO device, it is also important to account for DEHP exposure from blood transfusions given to these patients. Patients on ECMO receive RBCs to correct anemia and they receive platelet concentrates, FFP, and cryoprecipitate to treat clotting disorders. As shown in Table A-9, it is possible for adult patients to receive over 600 units of blood products during the course of their ECMO treatment and hospitalization. Daily use of blood components in adult patients undergoing ECMO is shown in Table A-10.

Table A-9. Blood component utilization in adult patients during hospitalization and while undergoing ECMO (Median utilization/patient) (Butch et al., 1996)

Blood product	Median units transfused		
	In hospital	During ECMO	Range
RBCs	45.0	28.5	0-181
Platelet concentrates	112.5	108.0	0-682
FFP	7.0	2.0	0-99
Cryoprecipitate	3.0	2.0	0-240

Table A-10. Daily blood component utilization in adult patients undergoing ECMO (Butch et al., 1996)

Blood product	Units transfused		
	Mean	Median	Range
RBCs	4.6	3.2	0-18
Platelet concentrates	15.0	13.6	0-18
FFP	0.5	0.3	0-2.5
Cryoprecipitate	1.0	0.1	0.8.9

The values listed in Table A-9 and A-10 underscore the massive amounts of blood products required by adult patients undergoing ECMO. The dose of DEHP received during these transfusions is estimated in Table A-11.

Table A-11. Dose of DEHP received from transfusion in adult patients undergoing ECMO

Blood product	Number of units transfused/day (mean)	Volume/unit (ml)	Estimated DEHP concentration (µg/ml)	DEHP dose[1] (mg/kg/day)
RBCs	4.6	350	123.1	2.8
Platelet concentrates	15.0	100	5.6	0.12
FFP	0.5	200	26.7	0.04
Cryoprecipitate	1.0	50	1.0	0.0007

[1]Assumes 70 kg BW

The total dose of DEHP received each day from the blood products used in ECMO for adults is on the order of 3.0 mg/kg/day. The amount of DEHP extracted from blood administration sets should be added to this total. Easterling et al. (1974) found that 4.45 to 10.2 mg of DEHP was extracted from PVC tubing following perfusion of plasma through the tubing for 5 hours. Assuming it takes 30

minutes to hour to infuse one unit of packed RBCs, platelets, or FFP, the tubing would be expected to contribute an additional 1 mg of DEHP to the total administered dose during transfusion of each unit of blood products. Therefore, the total amount of DEHP from the blood products and the infusion set would be 21 mg/day or 0.3 mg/kg/day for a 70 kg adult. This total should be added to the amount of DEHP released from the PVC tubing used in the ECMO device to estimate the total DEHP exposure of adults receiving ECMO. Therefore, the total dose of DEHP received by adult patients being transfused during ECMO treatment is on the order of 3.3 mg/kg/day. Since mean values for the number of units transfused were used to calculate total DEHP dose, the amount of DEHP received by some patients could be considerable greater.

Exchange transfusion in neonates

Infants receiving exchange transfusion could receive a DEHP dose up to 22.6 mg/kg, according to Plonait et al. (1993); however, the DEHP dose received by infants in the Sjoberg et al. (1985a,b) studies ranges from 0.84 to 4.22 mg/kg.

Table A-12 Dose (mg/kg) of DEHP received by neonates at the end of exchange transfusion

DEHP Dose (mg/kg)		MEHP dose (mg/kg)		Study
Mean	Range	Mean	Range	
1.77	0.84 to 3.30	0.10	0.04 to 0.20	Sjoberg et al. (1985a)
2.95	1.71 to 4.22	0.36	0.16 to 0.68	Sjoberg et al. (1985b)
	1.2 to 22.6			Plonait et al. (1993)

Since blood was sampled from the infusion set, there is no need to account to the dose of DEHP leached from the tubing separately.

Sjoberg et al. (1985a,b) and Plonait et al. (1993) also measured levels of DEHP in the postexchange serum of neonates that had been recently transfused. These values are presented in Table A-13.

Table A-13 Concentration (µg/ml) of DEHP and MEHP in serum obtained from neonates at the end of a single exchange transfusion

DEHP concentration (µg/ml)		MEHP concentration (µg/ml)		Study
Mean	Range	Mean	Range	
-	5.8 to 19.6	-	5 (max)	Sjoberg et al. (1985a)
7.8	3.4 to 19.9	6.4	1.5 to 15.6	Sjoberg et al. (1985b)
14.5	6.1 to 21.6	-	-	Plonait et al. (1993)

Slightly higher DEHP concentrations have been measured inpatients receiving platelet concentrates. Rubin and Schiffer (1976) reported plasma DEHP levels from 0.34 to 0.83 mg/dl (34 to 83 µg/ml) at termination of the transfusion platelets that had been stored for up to 26 hours in vinyl plastic bags. Since platelets are no longer stored in PVC bags, the values reported by Rubin and Schiffer (1976) most likely overestimate the DEHP concentration in patients currently receiving platelet transfusions.

Replacement transfusion in neonates in a NICU setting

Critically ill neonates require repeated phlebotomies that may deplete their blood volume. Also, infants are susceptible to anemia of prematurity. As a result, critically ill neonates often require transfusions. Levy et al. (1993) reported that 80% of low birthweight infants in the United States will receive multiple transfusions. Ringer et al. (1998) reported that neonates in one neonatal intensive care unit (NICU) received, on average, 33.6 ml of RBCs and 2.4 ml of FFP in the first 14 days. Infants in this study weighed about 1 kg. The dose of DEHP received by neonates undergoing replacement transfusion with packed RBCs is shown in Table A-14.

Table A-14. Dose of DEHP received from replacement transfusion in neonates

Blood product	Volume[1] (ml)	Estimated DEHP concentration[2] (µg/ml)	DEHP dose[3] (mg/kg/day)
RBCs	33.6	123.1	0.3
FFP	2.4	26.7	0.004

[1]Mean volume infused over 14 days in one of two NICUs
[2]Upper-bound concentration as reported by Plonait et al. (1993) for packed cells and by Shintani et al. (1985) for FFP
[3]Assumes mean body weight of 1.073 kg per Ringer et al. (1998)

The DEHP dose calculated in Table A-14 is based on an upper-bound estimate of DEHP concentration, but a mean estimate of RBC infusion volume. Previously, it was common practice to only use the freshest blood from the blood bank to transfuse neonates. However, it has become increasingly common to transfuse individual neonates repeatedly from one unit of stored packed cells, to reduce the potential for viral transmission. As a result, it is reasonable to use an upper-bound value for DEHP concentration in estimating the dose of DEHP received by these patients. An upper-bound estimate of DEHP dose would take into account upper-bound values for DEHP concentration and the volume infused RBCs. The upper confidence limit of the RBC infusion volume reported by Ringer et al. (1998) for one NICU is 79.6 ml (33.6 +/- 46). Consequently, the upper-bound dose of DEHP that could be received by a 1 kg neonate receiving replacement transfusion over 14 days is 0.7 mg/kg/day.

Since blood used for replacement transfusions is typically drawn up from the storage bag with a syringe and injected into the patient, there is no need to account for DEHP released from infusion sets. However, if blood product are administered via an infusion pump, then the amount of DEHP received by a pediatric patient would be considerably greater. For example, Loff et al. (2000) found that up to 8.1 mg of DEHP was released from PVC infusion tubing following perfusion of 20 ml of fresh frozen plasma through the tubing for 1 hour. This would result in a DEHP dose of around 4 mg/kg/day for a 2 kg child.

Replacement transfusion for adults undergoing surgical procedures

Vamvakas and Carven (2000) recently quantified the number of RBC units transfused into patients undergoing coronary artery bypass graft (CABG) surgery as a function hospital length of stay (LOS). Data are not provided on the concentration of DEHP in each unit of RBCs transfused; however, an estimate of the dose of DEHP received by these patients can be estimated from information on the number of units transfused during their hospital stay and the mean and upper-bound values for DEHP concentration in RBC concentrates, as reported by Plonait et al. (1993). The mean number of units of RBCs transfused into these patients in the Vamvakas and Carven (2000) study was 4.1 over a mean hospital LOS of 9 days. Assuming a mean DEHP concentration in the RBC concentrates of 44.8 µg/ml, the mean dose of DEHP received from transfusion in patients undergoing CABG is:

4.1 units x 44.8 µg/ml x 350 ml/unit x 1/70 kg x 1/9 days = 0.1 mg/kg/day.

The maximum hospital LOS for patients in this study was 63 days. The maximum number of units of RBCs received was 23. Since LOS is highly correlated with the number of units transfused in this study, it is likely that the patients with the longest hospital stays also received the greatest number of RBC transfusions. As a result, an upper-bound estimate of the dose of DEHP received by these patients from transfusion would be:

23 units x 123.1 µg/ml x 350 mg/unit x 1/70 x 1/63 days = 0.2 mg/kg/day.

These estimates do not include any DEHP that may be released from infusion sets or from CPB tubing.

Long-term blood transfusion

Patients with some chronic illnesses and those receiving antineoplastic chemotherapy often become anemic and require blood transfusion. The dose of DEHP received by patients undergoing long-term blood transfusion is estimated below.

Leukemia and aplastic anemia

Jacobson et al. (1977) determined the DEHP dose received by patients with leukemia and aplastic anemia receiving red cells, whole blood, and platelets over the course of one year (Table A-15).

Table A-15. DEHP exposure over a one-year exposure period in patients with aplastic anemia and leukemia (adapted from Jacobson et al., 1977)

	Type and number of units transfused (Range)			DEHP dose (Range)		
Diagnosis	**Red cells**	**Whole blood**	**Platelets**	**Total mg**	**mg/kg**	**mg/kg/day[1]**
Aplastic anemia	4 to 95	6 to 31	19 to 67	56 to 365	2.1 to 14.4	0.006 to 0.04
Leukemia	10 to 95	1 to 36	16 to 146	151 to 1500	3.6 to 27.5	0.01 to 0.08

[1]When time-averaged over one year

Sickle cell disease

Patients with sickle cell disease are typically transfused with 1-2 units of packed cells every 2-4 weeks (McCullough, 1998). Levels of DEHP in packed cells range from 4-123 μg/ml, as reported by Plonait et al. (1993) and 174 μg/ml as reported by Rock et al. (1987). Using the data from Plonait et al. (1993) as an upper-bound value for the concentration of DEHP in packed red cells, the dose of DEHP received by a patient with sickle cell disease would be:

123.1 μg/ml x 350 ml/unit x 2 units/14 days x 0.001 μg/mg x 1/70 kg = 0.09 mg/kg/day.

Chemotherapy-associated anemia

Anemia is a common problem in patients undergoing chemotherapy for cancer treatment. As discussed by Barrett-Lee et al. (2000), 33% of patients receiving chemotherapy will require blood transfusion during their course of treatment. Estrin et al. (1999) reported that an average of 5.1 red blood cell units were infused per patient undergoing chemotherapy.

The data of Veach et al. (1998) allow estimate to be made of the number of transfusions given in each treatment cycle of chemotherapy. For example, Taxol is administered in a regimen that involves 3-week cycles with 3 cycles given in a typical course of treatment. Patients receiving Taxol in the Veach et al. (1998) study received about 3 transfusions during the course of therapy, or about 1 transfusion (presumably packed red cells) every 3 weeks. Therefore, the upper-bound estimate of DEHP exposure in this scenario is:

123.1 μg/ml x 350 ml/unit x 1 unit/21 days x 0.001 μg/mg x 1/70 kg = 0.03 mg/kg/day.

Maintenance treatment of clotting disorders

Cryoprecipitates containing clotting factors are administered to patients with clotting disorders. Marcel (1973) found that cryoprecipitate packs contained from 0.8 to 1.9 mg of DEHP each. Since patients with clotting disorders can receive up to 400 bags of cryoprecipitate in one year, the total DEHP dose received by these patients is on the order of 0.03 mg/kg/day.

A.1.4 Cardiopulmonary bypass and ECMO

Cardiopulmonary bypass is used in a number of cardiac surgical procedures (e.g., heart valve replacement, CABG surgery, heart transplantation, correction of congenital defects) and is also used as a means to oxygenate the blood during cardiac or pulmonary failure. Cardiopulmonary bypass used as a means to supplement blood oxygenation is termed extracorporeal membrane oxygenation (ECMO). Since considerable lengths of PVC tubing is typically used in heart-lung bypass circuits (i.e., 600 cm of PVC tubing can be used in ECMO circuits) the potential exists for patients undergoing these procedures to be exposed to DEHP.

Barry et al. (1989) showed that levels of DEHP and MEHP increased dramatically in patients who had undergone cardiopulmonary bypass during cardiac surgery. Although the dose of DEHP or MEHP received by these patients only from the CPB device and PVC tubing was not calculated, the total dose of these phthalate esters from all sources (i.e., tubing, transfusions) was estimated (Table A-16).

Table A-16. Dose of DEHP received during cardiac surgery (Barry et al., 1989)

Procedure	DEHP dose (mg/kg/day)[1]	MEHP dose (mg/kg/day)[1]
Coronary artery bypass graft (CABG)	15.4 to 72.9	2.2 to 8.0
Orthotopic heart transplantation	2.3 to 21	0.45 to 2.5
Artificial heart transplantation	3.8 to 167.9	0.25 to 18.8

[1]in the first 24 hours following surgery

The concentration of DEHP and MEHP measured in the blood of children undergoing cardiopulmonary bypass during corrective surgery for congenital heart defects ranged from 1.1 to 5.06 µg/ml for DEHP at the end of CPB and 0.06 to 2.66 µg/ml for MEHP at the end of CPB (Barry et al., 1989).

Two groups of investigators, Shneider et al. (1989) and Karle et al (1997), have estimated the dose of DEHP received by infants undergoing ECMO (Table A-17).

Table A-17. Dose of DEHP received by infants undergoing ECMO

DEHP dose range (mg/kg)	DEHP concentration in blood during ECMO (µg/ml)	Study
4.7 to 34.9	0 to 34.9[1]	Karle et al. (1997)
42 to 140[2]	26.8[3] 33.5[4]	Shneider et al. (1989)

[1]Depending on circuit, normalized to a 4 kg infant
[2]3 to 10 day course of treatment
[3]Following 14 days of ECMO
[4]Following 24 days of ECMO

Information is unavailable to accurately estimate the dose of DEHP received by these patients on a mg/kg/day basis, since the exposure period is represented as a range (3-10 days). However, if we assume that the larger DEHP doses were received by patients undergoing this procedure for 10 days, the time averaged dose of DEHP received by these neonates is expected to be 3.5 to 14 mg/kg/day.

Estimates of DEHP dose derived by Karle et al. (1997) are based on the rate at which DEHP is extracted from ECMO tubing by circulating blood *in vitro*. It is interesting to note that Karle et al. (1997) demonstrated that little or no DEHP was released from heparinized PVC tubing. Although data are not available on the dose of DEHP received by patients undergoing ECMO using a heparin-coated circuit, it is anticipated, based on the results of the Karle et al. (1997) study, that many patients currently undergoing this procedure will receive little or no DEHP from the ECMO tubing. Although heparin-coated tubing is available in the US, the FDA has not approved the use of heparinized ECMO circuits.

To reduce circuit preparation time, many ECMO centers preprime the ECMO circuits with normal saline and hold them in a preprimed state for as long as 30 days. As might be expected, Riley et al. (1997) found no DEHP (level of detection 120 ng/ml) in normal saline used to preprime ECMO circuits, even after being preprimed for as long as 4 weeks.

Based on the data collected by Roy et al (2000), it is assumed that fewer than 1000 infants undergo this procedure annually in the US.

A.1.5 Hemodialysis and peritoneal dialysis

A.1.5.1 Hemodialysis

Hemodialysis represents a medical procedure that has the potential to deliver considerable doses of DEHP to a patient. For example, Faouzi et al. (1999) recently reported that, on average, 75.2 mg of DEHP was extracted during a single dialysis session, with a range of 44.3 to 197.1. Assuming a patient receives hemodialysis three times per week, the time-averaged dose of DEHP received on a daily basis ranges from 19 to 84.5 mg/day. This value is consistent with that reported by other investigators (Table A-18).

Table A-18. Dose of DEHP Delivered During Hemodialysis

DEHP Dose (mg/day)[1]	Study
19 to 84.5	Faouzi et al. (1999)
10.2 to 154.3	Pollack et al. (1985b)
3.9 to 64.2	Gibson et al. (1976)
13.7 to 38.5	Kevy et al (1981)
19.7	Flaminio et al. (1988)
6.4	Fayz et al. (1977)
4.3	Easterling et al. (1974)

[1]Assuming hemodialysis 3 times/week

Faouzi et al. (1999) point out that not all infused DEHP is retained by the patient. These investigators have estimated that 3.6 to 59.6 mg of DEHP is retained in a single dialysis session. Assuming 3 dialysis sessions per week, this dose is equivalent to a time-averaged dose of 0.02 to 0.36 mg/kg/day for a 70 kg patient.

Data are also available on the concentration of DEHP and MEHP in the blood of patients undergoing hemodialysis (Table A-19).

Table A-19. Concentration of DEHP and MEHP in the blood of patients undergoing hemodialysis.

Study	DEHP Concentration (μg/ml)	MEHP Concentration (μg/ml)
Faouzi et al. (1999)	2 to 3 (approx.)	
Pollack et al. (1985b)	0.3 to 7.6	0.9 to 2.83
Nassberger et al. (1987)	0.8 to 4.2	
Malik et al. (1983)	0.4 to 1.0	
Lewis et al (1978)	0.3 to 1.9	

A.1.5.2 Peritoneal dialysis

Since peritoneal dialysis fluids are crystalloid in nature, it is not surprising that little DEHP is delivered to a patient in this procedure. Nassburger et al. (1987) measured levels of DEHP in peritoneal dialysis solution ranging from 4 to 11 μg/L. Similarly, DEHP concentrations in peritoneal dialysis fluid ranged from 1.1 to 3.7 μg/L, as measured by Sugimura et al. (2001). However, Mettang et al. (1996) found DEHP levels in dialysis fluid that ranged from 21 to 130 μg/L (Table A-20). Assuming a patient undergoing continuous ambulatory peritoneal dialysis (CAPD) is dialyzed with 8 L of fluid/day, the upper-bound estimate of the daily dose of DEHP infused into the peritoneum would be on the order of 1 mg/day (0.13 μg/ml x 8,000 ml/day x 0.001 mg/μg). Since the majority of an intraperitoneally injected dose of DEHP is not be absorbed (Rhodes et al., 1983) the administered dose of 1 mg/day is likely to overestimate the absorbed dose. Furthermore, a considerable amount of the infused DEHP will be returned upon drainage of the perfusate from the peritoneum.

It is interesting to note that both Nassburger et al. (1987) and Mettang et al. (1996) observed that the concentration of MEHP in dialysis fluid was considerably greater than levels of DEHP (Table A-20).

Table A-20. Levels of DEHP and MEHP in peritoneal dialysis solution

Study	DEHP Concentration (μg/ml)	MEHP Concentration (μg/ml)
Nassberger et al. (1987)	0.004 to 0.011	0.315 to 0.396
Mettang et al. (1996)	0.021 to 0.13	0.137 to 0.239

Although it is unlikely that all of the DEHP or MEHP that is infused into the peritoneum in CAPD patients is systemically absorbed, Nassberger et al. (1987) and Mettang et al. (1996, 2000) measured dramatic increases in levels of DEHP and MEHP in the serum of patients undergoing peritoneal dialysis, therefore, some percentage of the compound in the dialysate is undoubtedly absorbed. Unfortunately, data (e.g. AUC data) are unavailable to estimate absorbed dose of phthalates in patients undergoing this procedure. Phthalic acid is the major metabolite identified in the serum of patients undergoing CAPD (Mettang et al., 1999, 2000). The use of a plasticizer-free peritoneal dialysis system had little effect on levels of DEHP or MEHP measured in patients undergoing CAPD, as compared to serum levels found in patients using a conventional peritoneal dialysis, however, serum levels of phthalic acid were significantly lower in patients using the phthalate-free device.

Although the dose of DEHP or MEHP absorbed across the peritoneum by patients undergoing CAPD is likely to be low, as compared to other procedures, the endpoint of concern in patients exposed to DEHP and MEHP from CAPD may be a "local" one - peritoneal sclerosis - an endpoint that is not affected by the systemically absorbed dose.

A.1.6 Apheresis

Data are unavailable on the dose of DEHP received by donors undergoing apheresis. However, Doull et al. (1999) used two assumptions to derive an estimate of the DEHP dose received by individuals undergoing this procedure: 1) that data on the amount of DEHP released during hemodialysis provide an upper-bound estimate of DEHP dose for this procedure and 2) that leaching of DEHP from PVC apheresis tubing is linear over time. If 74 mg of DEHP are released during a hemodialysis procedure lasting 5 hours (a value consistent with that reported by Fauozi et al., 1999b), it was assumed by Doull et al. (1999) that 14.8 mg of DEHP could be released during one apheresis procedure lasting one hour. Further assuming that platelet/plasma donation occurs once/month, the time averaged dose of DEHP received by a donor would be around 0.5 mg/day. FDA regulations stipulate that patients cannot donate platelets more than twice per month. Also, 2 hours is a more realistic estimate for the duration of an apheresis procedure. Therefore, assuming the dose of DEHP received by an apheresis donor is probably more on the order of:

74 mg/5 hours x 2 hours x 2 procedures/month x month/30 days = 1.97 mg/day.

This dose is equivalent to 0.03 mg/kg/day for a 70 kg donor; however, it should be pointed out that there is considerable uncertainty associated with this estimate.

A.2 Oral Exposure

In the medical device context, oral exposure to DEHP can occur following release of this phthalate from enteral feeding bags and tubing or from nasogastric tubing used for aspiration of stomach contents and decompression of the stomach. In addition, a means of oral exposure to DEHP that has largely been ignored is lactational transfer of DEHP to nursing infants. As discussed below, nursing infants of women receiving hemodialysis can theoretically receive a very large daily dose of DEHP. An additional source of oral exposure to phthalate esters, release from denture material, is possible. Although DEHP has been detected in leachates from dental composites (Lee et al., 1998), phthalates other than DEHP are typically used as plasticizers for this application.

A.2.1 Enteral nutrition

The enteral feeding is becoming preferred over parenteral nutrition as a means to provide nutrition to critically ill patients (Sigurdsson, 1997). Some patients, especially those receiving care at home or in nursing facilities, will receive nutritional support enterally (via the gastrointestinal tract) rather than parenterally. Exposure to DEHP can come from the PVC bag used to store the enteral nutrition solution and the nasogastric tube, if one is used to administer the solution.

No data are available on the extent to which DEHP is released from enteral nutrition storage bags; however, the assumption can be made that these bags release DEHP at the same rate as bags used to store TPN admixtures.

An estimate of the amount of DEHP released from PVC nasogastric tubes can be derived from the data of Khaliq et al. (1992). In this study, the rate of DEHP release from PVC tubing was quantified using different solvents and under various extraction conditions (temperature, duration). Extraction of a 1 cm^2 section of tubing for one day in various solvents resulted in

DEHP release ranging from 14A-204 µg/200 ml. Since the extraction was actually conducted in 1 ml of solvent, the release rate for a piece of tubing with a surface area of 1 cm^2 is around 1 µg. A 16 Fr nasogastric tube has an internal diameter of 5.3 mm and is typically 100 cm in length. Therefore, the surface area of a nasogastric tube exposed to enteral feeding solution would be:

$$SA = 2\Pi rh$$

$$SA= (2)(3.14)(0.265\ cm)(100\ cm) = 166.4\ cm^2$$

Assuming a release rate of around 1 µg DEHP/cm^2/day from the tubing, based on the data obtained by Khaliq et al. (1992), a typical adult nasogastric tube would be expected to release DEHP at a rate of:

$$166.4\ cm^2 \times 1\ \mu g\ DEHP/cm^2/day \times 0.001\ mg/\mu g = 0.17\ mg/day$$

on the first day of use. After 15 days of extraction, the tubing sections extracted by Khaliq et al. (1992) yielded 625-1008 µg of DEHP/200 ml of solvent, equivalent to a rate of 0.2 to 0.34 µg/cm^2/day for a 1 cm^2 section of tubing extracted into 1 ml. An upper-bound estimate of the rate at which DEHP is released from a 100 cm, 16 Fr nasogastric tube kept in place for 15 days would be:

$$166.4\ cm^2 \times 0.34\ \mu g/cm^2/day \times 0.001\ mg/\mu g = 0.057\ mg/day.$$

This value does not take into account any DEHP that is released from the nonlumenal side of the tubing, although some release from this surface undoubtedly occurs.

Long-term (> 30 days) enteral nutrition is typically administered via a gastrostomy tube. These tubes are almost always made from polyurethane or silicone, thereby minimizing exposure to DEHP.

The total amount of DEHP received by a patient receiving enteral nutrition can be estimated from is the sum of the amount released from the bag and from the tubing. Using the data from Mazur et al. (1989), and assuming that that the enteral nutrition admixture contains a similar amount of lipid as the parenteral admixture, an upper-bound estimate of this dose is:

$$9.3\ mg/day\ (bag) + 0.17\ mg/day\ tubing = 9.47\ mg/day.$$

A more typical daily dose from enteral nutrition would probably be on the order of:

$$3\ mg/day\ (bag) + 0.057\ mg/day\ (tubing) = 3.057\ mg/day.$$

If the data of Allwood (1986) are used, the total dose of DEHP would be:

$$100\ mg/day\ (bag) + 0.17\ mg/day\ (tubing) = 100.17\ mg/day.$$

By comparison, estimates of the amount of DEHP received by the general population via food range from around 0.3 mg/day for typical individuals to around 2 mg/day for highly exposed individuals.

A.2.2 DEHP exposure to breastfeeding infants of nursing mothers receiving hemodialysis

One means of exposure to DEHP and MEHP that seems to have been largely overlooked is lactational transfer from a nursing mother to her offspring. The rodent studies that demonstrate adverse effects in offspring following ingestion of milk from DEHP-exposed dams (e.g., Parmar et

al, 1985; Dabholkar, 1988; Cimini et al., 1994; Stefanini et al., 1997) suggest that transfer of enough DEHP or MEHP can take place to cause adverse effects.

Levels of DEHP in human milk have been reported in two German studies. Gruber et al. (1998) reported DEHP concentrations of 71-160 µg/kg milk from 5 subjects (mean 93.2 +/- 37.5, median 76). In a comprehensive review of DEHP exposures, Pfordt and Bruns-Weller (1999) reported DEHP levels in human milk of 0-110 µg/kg milk from 5 subjects (mean 0.034 +/- 0.043, median 0.02). Presumably, none of the subjects included in each of these studies had recently undergone medical procedures that would have exposed them to relatively large doses of DEHP. Unfortunately, experimental data are unavailable on levels of DEHP in milk from mothers who have undergone or are undergoing medical procedures such as hemodialysis. In the absence of data from these patients, it's possible to derive preliminary estimates the concentration of DEHP and MEHP in human milk either from the experimentally derived milk:plasma partition coefficients for rats reported by Dostal et al. (1987) or by using theoretical partitioning models, such as those developed by Begg and Atkinson (1993). Dostal and colleagues (1987) report that the milk:plasma partition coefficient for DEHP is < 200, which is not surprising given the lipophilic nature of this compound. Conversely, the milk:plasma partition coefficient for MEHP is 0.33, largely because of it's acidic nature and because it is highly bound to plasma proteins (F_u about 1-2%). Use of the Phase Distribution Model of Begg and Atkinson (1993) results in an estimated milk:plasma partition coefficient for MEHP in humans of 0.26, a value that closely corresponds to the experimentally derived value reported by Dostal et al. (1987).

To estimate the dose of DEHP or MEHP received by a nursing infant, data are needed on the concentration of these phthalate esters in maternal plasma, the milk:plasma partition coefficient (which is estimated above) and an estimate of daily milk consumption by infants. A value of 150 ml/kg/day is typically used in risk assessments involving lactational transfer.

Although the incidence of pregnancy in women on hemodialysis is low (about 1-7%), these patients do give birth and some presumably some would breastfeed their children. Levels of DEHP in these patients range from about 0.4 to 8 µg/ml, however, the latest data from Faouzi et al. (1999) suggests that levels of about 3 µg/ml are reached after 4 hours of dialysis. Levels of MEHP in these patients range from 0.885 to 2.83 µg/ml, according to Pollack et al. (1985). Therefore, the dose of DEHP received by a nursing infant from a mother on hemodialysis could be on the order of:

3 µg/ml x 200 x 150 ml/kg/day = 90 mg/kg/day

The dose of MEHP is estimated to be approximately:

1 µg/ml x 0.33 x 150 ml/kg/day = 0.05 mg/kg/day

The actual dose of DEHP received by infants could be higher, since Dostal et al. (1987) noted that the milk:plasma partition coefficient for DEHP in rats was > 200, and since upper bound values of DEHP in the plasma of hemodialysis patients were not used. However, the actual dose of DEHP received by these infants could be lower as well. Based on the concentration of DEHP in human milk (around 0.1 µg/ml) and the concentration of DEHP in plasma (also around 0.1 µg/ml), the milk:plasma partition coefficient in humans in the general population exposed to low doses of DEHP is probably around 1. Consequently, dose of DEHP received by nursing infants of mothers exposed to DEHP via hemodialysis could be much less than the 90 mg/kg/day estimate that is based on rodent data. Because of the level of uncertainty in these estimates, TI/Dose ratios will not be derived for this means of exposure to DEHP. Furthermore, due to

infertility in women on hemodialysis, the number of infants exposed to these very high levels of DEHP via nursing is likely to be very small (perhaps on the order of 100).

A.3 Inhalation Exposure

Since PVC tubing is used in respirators, it is theoretically possible for some amount of this plasticizer to be released from the tubing into the respiratory air stream and administered to the patient. Based on levels of DEHP measured in the condensate collected from the water traps of respirators, Roth et al (1988) estimated that a patient could receive an inhalation dose of DEHP ranging from 1 to 4200 µg/hour. Although patients are probably exposed to some DEHP via this method since the water vapor in the air circulating in the PVC tubing may solubilize some of the DEHP on the surface of the tubing, use of data on the concentration of DEHP in the water from the respirator water trap does not provide an accurate means to estimate DEHP dose, since this fluid is not transferred to the patient.

A worst case scenario would involve breathing air saturated with DEHP continuously for 24 hours/day. The vapor saturation concentration of DEHP in air at 25°C is 5.3 $\mu g/m^3$. Oie et al. (1997) found that DEHP is associated with the particulate phase as well as the vapor phase, and up to 3 times more DEHP may be associated with the vapor phase. Consequently, the worst case concentration of DEHP in the air would be 5.3 $\mu g/m^3$ + 15.9 $\mu g/m^3$ = 21.2 $\mu g/m^3$. The default inhalation rate for an adult is 20 m^3/day and 9.3 m^3/day for an 8 kg child. Therefore, the upper-bound estimate of the dose of DEHP received by a patient via inhalation would be:

$$21.2\ \mu g/m^3 \times 20\ m^3/day/70\ kg \times 0.001\ \mu g/mg = 0.006\ mg/kg/day\ (adult)$$

$$21.2\ \mu g/m^3 \times 9.3\ m^3/day/8\ kg \times 0.001\ \mu g/mg = 0.02\ mg/kg/day\ (child)$$

Based on the concentration of DEHP measured in the air stream passed through PVC respiratory tubing, Hill (1997) it is estimated that a patient undergoing respiratory therapy would receive a daily DEHP dose ranging from 28.4 to 94.6 µg, which is equivalent to a dose of 0.0004 to 0.001 mg/kg/day for a 70 kg adult.

Because of the uncertainties associated with this estimate, a TI value for inhalation exposure to DEHP will not be derived.

Partitioning of DEHP from an Endotracheal Tube into Respiratory Mucus

Instead of being volatilized and delivered to the patient via the respiratory air stream, DEHP could partition from a PVC endotracheal tube into the respiratory tract mucus, where it could subsequently be taken up by a patient. Latini and Avery (1999) observed stiffening and color changes in PVC endotracheal tubes used for only a few hours and thought that these changes may be due to a release of the plasticizer from the material. Overnight extraction in chloroform:methanol solution produced a loss of DEHP from the tubing ranging from 0.06-0.12 mg per mg of tubing (Latini, 2000), equivalent to a loss of 120 mg of DEHP from a typical pediatric endotracheal tube (Hinberg, 2000). However, the dose of DEHP received by intubated patients from an endotracheal tube cannot be estimated with certainty from these data for two reasons: 1) the extraction conditions used by Latini and Avery (1999) do not necessarily mimic the extraction conditions present *in vivo* and 2) if DEHP does partition to respiratory mucus, a great deal of this mucus is suctioned from intubated patients, therefore, not all of the DEHP-containing mucus will be absorbed.

Alternately, if we assume that an endotracheal tube will release DEHP at approximately the same rate as a nasogastric tube, then the data from Khaliq et al. (1992) can be used to derive a rough of

the amount of DEHP released from an ET tube. Presumably, DEHP will be released from the outside and the lumenal side of the tube. A typical pediatric ET tube has an ID of 7.5 mm and an OD of 10 mm and a length of 32 cm, therefore, the inner and outer surface areas of the tube are approximately 75 and 100 cm^2, respectively. Only about one-half of the outer surface of the tube will be in contact with the tracheal mucosa and perhaps only one-half of the DEHP released from the lumenal side will be absorbed, because of suctioning. Therefore, the total dose of DEHP released by the tube is approximately:

$$175\ cm^2/2 \times 0.34\ \mu g/cm^2/day = 0.03\ mg/day.$$

A.4 Dermal/Mucosal Exposure

The potential exists for DEHP to be released from skin surface- or mucosal membrane-contacting PVC devices such as urinary catheters, drug delivery patches, occlusive dressings, oxygen masks, and endotracheal tubes. However, there are insufficient data to accurately characterize the amount of DEHP that would be released from these devices and taken up by the body. Although nasogastric tubes contact the esophageal mucosa, it is assumed that the majority of the DEHP released from these devices is extracted from the lumenal side of the tubing and is subsequently absorbed in the gastrointestinal tract.

Patients are assumed to have only incidental contact with PVC gloves worn by health care workers. Since this risk assessment deals only with potential health risks to patients, the potential risk to health care workers from dermal exposure to DEHP will not be assessed. However, it is useful to note that KEMI (1999) has estimated that a health care worker wearing gloves for 2 hours/day will receive a DEHP dose of 0.007 mg/kg/day.

A.5 Aggregate Exposure to DEHP from Multiple Medical Devices

A.5.1 Neonates in NICU setting

Patients in various clinical scenarios are often exposed to multiple PVC devices. For example, neonates in the NICU environment are exposed to DEHP from multiple devices. Based on the dose of DEHP received in such procedures as intravenous administration of sedatives, administration of TPN and replacement transfusion, all common procedures in the NICU, it is possible to estimate that a 4 kg infant could receive a DEHP dose on the order of 3 mg/kg/day for a periods of weeks or months (Table A-21)

Table A-21 Aggregate exposure of neonates to DEHP in the NICU environment.

Procedure	DEHP dose (mg/kg/day)[1]
IV administration of sedative	0.03
IV administration of TPN	2.5
Replacement transfusion	0.3
Total[2]	2.83

[1] 4 kg infant

[2] Doesn't include DEHP does from endotracheal intubation, nasogastric tube or ECMO

A.5.2 Adult patients undergoing ECMO

The total dose of DEHP received by patients undergoing ECMO can be grossly underestimated if this dose is estimated simply from data on the extent to which DEHP is released from PVC tubing used in the device. Since these patients are multiply transfused and can receive over 600 transfused units (RBCs, platelet concentrates, FFP, cryoprecipitate) during their course of ECMO and hospitalization, a considerable amount of DEHP can also be received from transfused blood products as well as the PVC used in the ECMO device. Patients undergoing ECMO are also multiply transfused and may receive drugs (e.g., antibiotics, vitamins) solubilized in pharmaceutical surfactants that promote DEHP release from PVC bags. For example, an adult undergoing ECMO could receive a DEHP dose on the order of 4 mg/kg/day, if aggregate exposure from multiple devices is considered. The principle contribution to the total dose of DEHP received by these patients comes from the multiple transfusions needed by these patients, not the PVC tubing used in the ECMO device.

A.5.3 Adult patients undergoing surgical procedures

Adult patients receiving a coronary artery bypass graft surgery are can receive DEHP from a during a number of medical devices, including an endotracheal tube, IV bags and tubing (especially if a multivitamin solution is infused), chest tubes, hemodynamic monitoring catheters, nasal cannula, nasogastric tube, and blood bags and administration sets. The dose of DEHP received by these patients, as estimated by Barry et al. (1988), is based on the concentration of DEHP in the blood, and therefore, takes into account aggregate exposure.

A.6 Coexposure to Other Phthalate Esters

In addition to DEHP and MEHP, patients may also be exposed to other phthalate esters used as plasticizers for medical grade PVC. Although DEHP is by far the most commonly used plasticizer PVC, dibutyl phthalate (DBP), diethyl phthalate (DEP), dimethyl phthalate (DMP), diisobutyl phthalate (DIP), and butyl A-ethylhexyl phthalate (BEP) have also been identified in extracts from PVC medical devices. For example, Khaliq et al. (1992) quantified levels of DEHP, DBP and DMP released from PVC nasogastric tubing. DBP and DEP have been identified as components of PVC used for devices such as microfilters, butterfly catheters, infusion tubing, infusion bags, and intestinal tubing at levels ranging from $\geq$ 1% to < 20% of the total volatiles extracted from the device (Wahl et al., 1999). Other phthalates, such as DIP and BEP were also identified by Wahl et al. (1999) as constituting a fraction of the volatiles extracted from some devices (Table A-22).

Table A-22. Phthalate esters identified in extracts from various medical devices (adapted from Wahl et al., 1999)

Device	DEP	DIBP	DBP	BEP	DEHP
Syringe 60 ml	A		A		A
Insulin syringe	A		A		
Heparin syringe	A		A		B
Microfilter 40 µl	B		B	A	B
Serum monovette	A		A		
Butterfly	B			B	B
Luerlock obturator	A		A		B
Infusion tubing	A		B	B	C[3]
Infusion bag	A		B	A	C
Blood storage bag					C
Blood infusion tubing	A	B	A	B	C
Intestinal tubing	B		B		B
Dialysis tubing	A		A		C

A <1% total volatiles; B < 20% total volatiles; C < 85% total volatiles

While the data of Wahl et al. (1999) do not enable a quantitative estimate of the dose of each of these phthalate ester to be derived, they do indicate that patient exposure to multiple phthalate esters is possible following the use of PVC medical devices.

Patient exposure to multiple phthalates is also evidenced by data reported by Ching et al. (1981). It is interesting to note that levels of DBP in the serum of surgical patients exceeded that of DEHP in many cases (Table A-23).

Table A-23. Serum plasticizers levels measured in surgical patients (Ching et al., 1981)

Patient	DBP (µg/ml)	DEHP (µg/ml)
Control	37	3
1	35	8
2	0.2	4
3	41	14
4	0.3	7
5	0	6

It's not clear, however, that exposure to DBP occurred following patient exposure to PVC devices, since levels of this compound were higher than those of DEHP in the single control patient enrolled in the study. Ching et al. (1981) speculate that the measured DBP may have come from alcohol wipes used in the blood collection process.

In addition, the general population is exposed to multiple phthalates (Blount et al., 2000), in particular, DBP, DEP and BBP. Presumably, patients can be exposed to these phthalates esters from environmental sources and to DEHP from medical devices. Since phthalate esters can produce similar adverse effects in exposed experimental animals, it may be reasonable to develop an approach to account for co-exposure to these compounds. If DBP, DEHP and other phthalate esters that patients are exposed to exert their effects via a common toxicological mechanism of action, it may be prudent to develop such an approach for phthalate esters. This approach is discussed in greater detail in Section 4.0, Risk Characterization.

A.7 Conclusions

Patients undergoing procedures such as IV therapy and IV administration of drugs, transfusion of blood products, hemodialysis, peritoneal dialysis, artificial ventilation, enteral and parenteral nutrition support, cardiopulmonary bypass and ECMO can be exposed to DEHP released from PVC medical devices. The estimated dose of DEHP received by adult and neonatal patients undergoing various medical procedures is summarized in Table A-24. These values will be used to derive TI/Dose ratios in Section 4.0.

Table A-24. Estimated dose of DEHP received by adult and neonatal patients undergoing various medical procedures.

Procedure	DEHP dose (mg/kg/day)	
	Adult (70 kg)	Neonate (4 kg)
Infusion of crystalloid IV solutions	0.005	0.05
IV infusion of drugs requiring pharmaceutical vehicles for solubilization		
When administered according to manufacturer's instructions	0.05	0.03
When stored mixed and stored at room temperature for 48 hr	0.74	
TPN administration		
Without added lipid	0.03	0.03
With added lipid	0.18	2.5
Lipid alone	0.04	
Blood transfusion		
Trauma patient	8.5	
Transfusion/ECMO in adult patient	3.0	
Exchange transfusion/neonate		22.6
Replacement transfusion/neonate in NICU		0.65
Replacement transfusion/correction of anemia in patients receiving chemotherapy and in patients with sickle cell disease	0.12	
Replacement transfusion/surgical patient undergoing CABG	0.28	
Treatment of clotting disorders with cryoprecipitate	0.03	
Cardiopulmonary bypass		
CABG	1	
Orthotopic heart transplant	0.3	
Artificial heart transplant	2.4	
ECMO		14
Apheresis	0.03	
Hemodialysis	0.36	
Peritoneal dialysis	< 0.01	
Enteral nutrition	0.14	0.14

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Annex B: Summary of Results of Parenteral Toxicity Studies of DEHP

Hepatic effects observed following parenteral administration of DEHP to experimental animals

Study	Species	Route	Frequency/ Duration	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Effect
Pollack et al. (1989)	Rat	IP	Daily for 7 days		3906	Hepatomegaly
Srivastava et al. (1975)	Rat	IP	21 days		714	Altered liver enzymes
Seth et al. (1979)	Rat	IP	10 days		976	Mild hepatic congestion and bile duct proliferation
Nair et al. (1998)	Rat	IP	Up to 7.5 mg/kg as a single administration or every other day for 12 days	3.8		No adverse effect, but decreased level of Vitamin E in the liver at doses ≥ 0.75 mg/kg/day
Leber et al. (1979)	Rat	IP	Single administration	2000		No adverse effect
Leber et al. (1979)	Rat	IP	2000 mg/kg every other day for 14 days		1000	Hepatomegaly, ↑ MFO activity, ↓ GST activity
Leber et al. (1979)	Rat	IP	56 x 500 mg/kg over 19 weeks		210.5	Hepatomegaly, ↑ MFO activity, ↓ GST activity
Rathinam et al. (1990)	Rat	IP	Once daily for 7 days		1000	↓ Liver weight, ↓ MFO activity, ↑ GST activity
Komitowski et al. (1986)	Hamster	IP	30 mg/kg once with sacrifice after 7 days		4.3	Morphological changes to hepatocytes using image analysis, no effects seen histopathologically
Schultz et al. (1975)	Mouse	IP	6 weeks		250	Hepatomegaly
Calley et al. (1966)	Mouse	IP	Daily for 6 weeks		250	Hepatomegaly
Rhodes et al. (1986)	Marmoset	IP	Once daily for 14 days		1000	No increased liver weight
Lawerence (unpublished)	Rat	SC	1x/week for 12 weeks		714	No effect on liver weight or BSP clearance
Greener et al. (1987)	Rat	IV	18 days	91.7	164.8	Hepatomegaly, ↑SGOT
Sjoberg et al. (1985a)	Rat	IV	50 or 500 mg/kg every other day for 12 days	25	250	Increased liver weight, no change in liver enzymes or BSP clearance
Baxter (2000)	Rat	IV	18 days postnatally	62		No adverse effects
Baxter (2000)	Rabbit	IV	28 days postnatally	62		No adverse effects
AdvaMed (2001)	Rat	IV	21 days	60	300	Hepatomegaly
Garvin et al. (1976)	Rat	IV	2x/week for 26 or 63 days			No significant difference in total billirubin, SGOT levels or BSP clearance
Rutter (1973)	Dog	IV	Daily injection for 21 consecutive days		21.4	Hepatomegaly, altered liver enzymes
Rutter (1975)	Dog	IV	6 day/week for 4 weeks	1		No adverse effects
Jacobson et al. (1977)	Rhesus monkey	IV	1 year		0.021	Histopathological changes in the liver, decreased BSP clearance

Pulmonary effects observed following parenteral administration of DEHP to experimental animals

Study	Species	Vehicle	Frequency/ Duration	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Effect
Schulz et al. (1975)	Rat	Tween-DMSO	Single dose		50	Histopathological changes in lung without respiratory distress
Schulz et al. (1975)	Rat	Tween-DMSO or Tween	Single dose		250	Respiratory distress, increased lung weight, signs of hemorrhagic congestion
Rubin and Chang (1978)	Rat	Plasma	Single dose		200 (LD50)	Dose-related increase in lung edema and lethality during exchange transfusion
Rubin and Chang (1978)	Rat	Plasma	Single dose		7.7 to 13	Increased lethality and presence of hemorrhagic lungs following replacement transfusion
Garvin et al. (1976)	Rat	DEHP-containing plasma extract	Twice a week for 63 days	1.05		No pulmonary effects
Greener et al. (1987)	Rat	4% BSA	Daily for 18 days	164.8		No pulmonary effects
Petersen (1975)	Dog	Neat	Once daily for up to 22 days	10		No gross postmortem findings, no abnormal clinical signs
Rutter (1973)	Dog	Neat	Single dose	100	300	Increased respiratory rate
Rutter (1973)	Dog	Neat	Once daily for 14 days		50	Red/dark blue areas over lung surface
Rutter (1973)	Dog	Neat	Once daily for 4 weeks		21.4	Increased relative lung weight, histopathological changes
Rutter (1975)	Dog	Neat	Once daily for 21 days	1.4		No pulmonary effects

Testicular effects observed following parenteral administration of DEHP to experimental animals

Species	Route	NOAEL	LOAEL	Effect	Duration	Study
Mouse	IP		250	Testicular atrophy	6 weeks	Calley et al. (1966)
Rat	IP		700	Focal degeneration of seminiferous tubules, edema of testicular interstitium	22 days	Seth et al. (1976)
Mouse	IP	100		No adverse effects	5 days	Curto and Thomas (1982)
Mouse	IP	50		No adverse effects	20 days	Curto and Thomas (1982)
Rat	IP		50	↓ testicular Zn	20 days	Curto and Thomas (1982)
Rat	IP		282	↓ testicular ATPase, (higher doses) Testicular atrophy, oligospermia, seminiferous tubule degeneration,	21 days	Agarwal et al. (1989)
Mouse	IP	3000	6000	↓ sperm count, testicular atrophy	5 days administration, 12 weeks observation	Douglas et al. (1986)
Rat	IP	5200		No adverse effects	5 days administration, 12 weeks observation	Douglas et al. (1986)
Mouse	IP		250	Testicular atrophy	6 weeks	Schultz et al. (1975)
Rat	IP	3.5		No adverse effects	Single injection or every other day for 12 days	Nair et al. (1998)
Marmoset	IP	1000		No adverse effects	14 days	Rhodes et al. (1986)
Rat	IV	62		No adverse effects	18 days	Baxter (2000)
Rabbit	IV	62		No adverse effects	28 days	Baxter (2000)
Rat	IV	60	300	Testicular atrophy, decrease in diameter of seminiferous tubules and depletion of germinal cells in testes	21 days	AdvaMed (2001)
Rat	IV	25	250	Sertoli cells vacuolization and spermatocyte degeneration	10 days	Sjoberg et al. (1985a,b)
Dog	IV	100		No adverse effects	28 days	Rutter (1973)

Developmental effects observed following parenteral administration of DEHP to experimental animals

Species	Route	NOAEL[1]	LOAEL[2]	Effect	Experimental Design	Study
Rat	IP		1000	Reduced fetal weight	Administered on GD 5, 10 and 15	Singh et al. (1972)
Rat	IP	1000	2000	Increased incidence of gross fetal abnormalities	Administered on GD 5, 10, and 15	Singh et al. (1972)
Mice	IP		50	Increased incidence of mid-ventral white spot	Administered once on GD 10.5	Tomita et al. (1986)
Mice	IV	1.25		No adverse effects	Administered once either on GD2 or GD7	Petersen et al. (1975)
Rat	IV	1.25		No teratogenic effects	Administered once eight days following breeding	Petersen et al. (1975)
Rat	IV	3.5		No teratogenic effects	Administered on GD 6-15	Lewandowski et al. (1980)
Rat	IV	91.7	164.8	Reduced body weight gain and increased liver weight	Postnatal exposure to 3-day-old rat pups for 18 consecutive days	Greener et al. (1987)

Cardiovascular effects observed following parenteral administration of DEHP to experimental animals

Study	Species	Route	Frequency	Dose (mg/kg/day)	Effect
Rubin and Chang (1978)	Rat	IV	Single dose	40	Fall in arterial blood pressure
Calley et al. (1966)	Rabbit	IV	Single dose	300	Fall in arterial blood pressure
Miyahara et al. (1973)	Rabbit	IV	Single dose	500	Fall in arterial blood pressure and heart rate

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Annex C. Aggregate Safety Assessment for Coexposure to DEHP and MEHP

In addition to conversion of DEHP to MEHP in the body, DEHP can be converted to MEHP exogenously by lipases in stored plasma or blood or by hydrolysis in stored and heated IV fluid. As a result, some of the DEHP that is released into stored blood, plasma, or IV fluids will be converted to MEHP before reaching the patient. Previous safety assessments have only explicitly accounted for exposure to DEHP; however, it is important to also account for exposure to MEHP, especially since MEHP is more potent than DEHP in producing adverse reproductive effects.

C.1 Mixtures Risk Assessment Approaches

In risk assessment, two approaches have been developed to assess the combined potency of constituents of chemical mixtures: the Hazard Index Approach and the Relative Potency Approach.

C.1.1 Hazard index approach

The Hazard Index approach is described in ISO/DIS 10993-17 as follows:

> If the compounds being leached from a device exert their effects via a common toxicological mechanism of action or are structurally similar to one another (e.g., phthalate esters, acrylates, methacrylates), and the dose of these compounds received by a patient is well below the respective TI value for each compound, it can be assumed that any effects will occur in an additive fashion, that is, the combined effects of two or more agents is equal to the sum of the effects of each agent given alone. As a result, a Hazard Index (HI) approach can be used to estimate the likelihood that adverse effects will occur following exposure to the mixture. A HI can be calculated as follows:
>
> $$HI = \sum_{i=1}^{n} \frac{dose_i}{TI_i}$$
>
> Where n is the number of components of the mixture and dose of each constituent received by the patient.

Use of the HI approach would be appropriate for estimating the combined potency of MEHP and DEHP since they exert their effect via a common mechanism of action; however, there are insufficient toxicity data to derive a TI for MEHP. As a result, use of the HI approach for combined exposures to DEHP and MEHP is impractical.

C.1.2 Relative Potency Approach

The relative potency approach is typically used to estimate the combined potency of complex mixtures of dioxins and dioxin-like compounds, polycyclic aromatic hydrocarbons, and cholinesterase-inhibiting pesticides, but has also recently been proposed as a means to estimate the combined potency of complex mixtures of phthalate esters (Gray et al., 2000). To estimate the potency of the mixture from it's individual chemical components using this approach, it is necessary to define the potency of each of the components relative to an index compound,

typically the constituent for which we have the largest body of scientific data of acceptable quality. The total concentration the mixture components, expressed relative to an index compound, can be derived as follows:

$$C_{mixture} = C_{index} + \Sigma \ [RPF_i \ x \ C_i]$$

where $C_{mixture}$ = total mixture concentration expressed in terms of the index compound, C_{index} = concentration of the index compound in mixture, C_i = concentration of the mixture component$_i$, and RPF_i = the proportionality constant relative to the index compound for the mixture component$_i$. With regard to DEHP and MEHP, DEHP will serve as the index compound and the concentration of MEHP will be expressed in terms of DEHP equivalents.

The relative potency values are also known as Toxic Equivalency Factors or TEFs. In their guidance for conducting health risk assessment of chemical mixtures, the EPA (1999) has differentiated TEFs from RPFs, based on the criteria described in Table C-1.

Table C-1. Differences Between TEF and RPF

TEF	RPF
TEF apply to all heath endpoints	RPF may be limited to specific health endpoints
TEF apply to all exposure routes	RPF may be limited to specific routes
Implies greater precision due to higher quality/more abundant data	Implies less precision due to lower quality/fewer data

As discussed below, the relative potency factors for MEHP and DEHP are primarily based on a specific health endpoint (testicular toxicity), are limited to specific routes (parenteral) and are associated with some uncertainty. As a result, it may be more appropriate to refer to the MEHP:DEHP relative potency value as an RPF, using the EPA criteria.

C.2 Derivation of an RPF for MEHP in Terms of DEHP Equivalents

C.2.1 Do MEHP and DEHP meet the criteria for RPF derivation?

Specific criteria must be met before an RPF can be derived for any set of compounds. The chemical constituents of the mixture should produce similar toxicologic effects and the mechanism by which they produce these effects should be the same. Also, the compounds should occur as a mixture in the exposure media. Finally, RPF approach assumes additivity of dose. With regard to MEHP and DEHP, it is well known that they produce similar effects on the testes and do so via the same mechanism. As discussed in Section 2.0, both compounds are found in stored blood and plasma and stored IV solutions. The dose additivity assumption has not been explicitly validated for MEHP and DEHP; however, since MEHP has been shown to be the active metabolite of DEHP in the testes (Gray et al., 1982; Gray and Gangolli, 1986; Oishi, 1993), it can safety be assumed that doses of DEHP and MEHP will be additive, since DEHP is thought to exert its effects following conversion to MEHP.

C.2.2 Selection of an RPF value for MEHP

Although it has been demonstrated in numerous studies that MEHP is more potent than DEHP, a challenge exists in selecting an RPF to quantitatively (or semi-quantitatively) represent this potency difference. Ideally, the RPF for MEHP would be derived from a study in which dose-response curves for testicular effects were derived following IV administration of both compounds individually. Unfortunately, such a study has not been conducted. Alternately, an RPF for MEHP can be derived using data in the published literature on the relative potency of MEHP and DEHP following oral and IP administration and in *in vitro* studies.

Relative potency of MEHP and DEHP in in vitro studies

The relative potency of MEHP:DEHP in *in vitro* studies without a metabolic activating system may not accurately reflect the relative potency of these compounds *in vivo* following parenteral administration; however, these studies do provide an opportunity to compare the relative pharmacodynamic potency of the compounds without considering the bioactivation of one and the detoxification of the other. As shown in Table C-2, the relative *in vitro* potency of these compounds ranges from > 10 to >1000, depending on the endpoint and study.

There are numerous other studies in the literature that underscore the increased potency of MEHP compared to DEHP in producing effects in testicular cells in vitro, however, the results of these studies do not lend themselves to quantitative determination of an RPF for MEHP. For example, Grasso et al. (1983) found that 100 µM MEHP inhibited FSH binding to cultured rat Sertoli cells, whereas incubation with 100 µM DEHP had no effect on FSH binding. Also, Gangolli (1982) showed that 200 µM MEHP produced dissociation of germ cells from Sertoli cells in culture, while the same concentration of DEHP did not. Finally, Moss et al. (1988) reported that MEHP stimulated lactate production in Sertoli cell cultures but DEHP had no such effect.

Relative potency of MEHP and DEHP following oral administration

As shown in Table C-2, the relative potency of MEHP:DEHP for testicular effects ranges from about 3 to 10 following oral administration of the compounds. Relative potency values derived from oral studies are likely to underestimate the relative potency of MEHP and DEHP following parenteral exposure, since DEHP will be more potent following oral vs. parenteral exposure, because it is bioactivated in the gut, and the potency of MEHP will be less following oral exposure, compared to parenteral, because it is detoxified in the gut. Consequently, in oral studies, the value for the denominator (DEHP potency) goes up and the value for the numerator (MEHP potency) goes down.

Table C-2. Relative MEHP/DEHP potency for testicular effects

Relative potency MEHP/DEHP	Route	Comments	Study
>10	In Vitro	MEHP inhibited state 3 oxygen consumption in testicular mitochondria at doses as low as 0.065 mumole/ml, whereas DEHP doses up to 0.65 mumole/ml did not	Oishi et al. (1990)
> 100	In Vitro	0.1 μM MEHP suppressed basal Sertoli cell proliferation, whereas 10 μM DEHP did not	Li et al. (1998)
> 1000	In Vitro	MEHP conc. As low as 1 μM caused germ cell detachment after 48 hours, whereas DEHP conc. as high as 1000 μM did not.	Sjoberg et al. 1986
3.5	Oral	Reduction in relative testes weight, tubular diameter, and testicular zinc, along with histopath scores, was similar following administration of a single dose of 2.8 g/kg DEHP or 0.8 g MEHP	Teirlynck et al. (1988)
10	Oral	DEHP caused an increased chromosomal aberration rate at 3750 mg/kg, whereas MEHP caused same effect at 375 mg/kg	Tomita et al. (1982)
2	IP	DEHP administration resulted in reduced zinc in anterior prostate at 50 mg/kg, whereas MEHP produced same effect following injection of 25 mg/kg	Curto and Thomas (1982)

The relative potency of MEHP:DEHP for other endpoints may inform the process of developing a RPF for these compounds with regard to reproductive effects. The results of Shiota and Mima (1985) suggest that MEHP is 20-fold more potent than DEHP in producing maternal toxicity in pregnant ICR mice following gavage administration and 80-fold more potent following IP administration (Table C-3).

Table C-3. Relative potency of DEHP and MEHP in producing maternal effects in pregnant ICR mice (from Shiota and Mima, 1985)

Route	Dose (mg/kg/day)		Relative Potency MEHP/DEHP
	MEHP	DEHP	
Gavage			
NOAEL	50	1000	20
LOAEL	100	2000	20
Intraperitoneal			
NOAEL	50	4000	80
LOAEL	100	8000	80

The results of Yagi et al. (1980) and Tomita et al. (1982) suggest that MEHP is approximately an order of magnitude more potent than DEHP in producing fetal malformations, increased fetal death and decreased fetal weight following administration by gavage to ddY-Slc mice on gestational day 7 (LOAEL of 104 mg/kg/day for MEHP vs. 984 mg/kg/day for DEHP).

Relative potency of MEHP and DEHP following parenteral administration

Few studies are available to assess the relative potency of parenterally administered MEHP and DEHP, especially for testicular effects. Curto and Thomas (1982) reported that the relative potency of DEHP and MEHP depends on the endpoint being examined. For example, rats injected IP with 50 mg/kg MEHP experienced a 37% decrease in zinc levels in the anterior prostate, an effect produced following administration of 100 mg/kg DEHP, suggesting a 2-fold difference in potency. However, the same dose of DEHP resulted in reduced levels of zinc in the testes, whereas the 50 mg/kg dose of MEHP did not, suggesting that DEHP is more potent in producing this effect.

The only other results available for determining the relative potency of MEHP and DEHP following parenteral exposure are those of Shiota and Mima (1985) and are described in Table C-2.

C.3 Selection of an RPF for MEHP

The results of *in vitro* studies suggest that MEHP could be as much as 1000-fold more potent than DEHP in producing adverse effects on testicular cells; however, it's not clear how relevant the *in vitro* relative potency values are for the *in vivo* state, since DEHP can be bioactivated in the body and MEHP can be detoxified. In contrast, MEHP is about 3- to 10-fold more potent than DEHP in producing adverse testicular effects following oral administration, and 20-fold more potent in producing developmental effects (in one study). Similarly, it's not clear how these

values reflect the relative potency following parenteral administration, due to bioactivation of DEHP and detoxification of MEHP in the gut. Based on the results of the few parenteral studies of MEHP:DEHP relative potency, MEHP could be slightly more potent than DEHP, less potent than DEHP (for some endpoints) or could be as much as 80-fold more potent (for developmental effects). The wide range of the relative potency values for MEHP and DEHP underscore the difficulty in selecting an RPF for MEHP to use in a cumulative risk assessment of these compounds. Since the weight of evidence suggests that MEHP is at least an order of magnitude more potent than DEHP to testicular cells, it is reasonable to assign a provisional RPF value of 10 to MEHP until better data are available on the relative potency of MEHP and DEHP following parenteral exposure. Consequently, it will be assumed that a 1 mg/kg dose of DEHP will produce the same effects in the testes as a 10 mg/kg dose of MEHP, for the purpose of deriving DEHP-equivalents. Designation of an RPF for MEHP suggesting that the relative potency of this compound is "about an order of magnitude" greater than DEHP following parenteral exposure is also intended to emphasize the lack of precision in the value and the uncertainty selecting the value.

C.4 Total MEHP and DEHP Dose in terms of DEHP equivalents

Using the data on the dose of DEHP and MEHP received by patients undergoing various procedures (Section 2.0), it is possible to derive a total dose of DEHP and MEHP in terms of DEHP equivalents (Table C-4).

Table C-4. Total dose of DEHP and MEHP in terms of DEHP equivalents

Procedure	DEHP dose (mg/kg/day)	MEHP dose (mg/kg/day)	DEHP equivalent dose (mg/kg/day)
Infusion of IV crystalloid solutions	0.005	0.013	0.135
Blood transfusion			
Trauma patient	8.5		
Transfusion/ECMO (adult)	3.0	2.0	23
Exchange transfusion (neonate)	22.6	0.68	29.4
Replacement Transfusion (neonate)	0.3	0.0043	0.34
Cardiopulmonary bypass			
CABG	1	0.1	2
Orthotopic heart transplant	0.3	0.03	0.6
Artificial heart transplant	2.4	0.26	5

It is not known whether DEHP is converted exogenously to MEHP in stored TPN or enteral nutrition solutions.

Although both DEHP and MEHP have been detected and quantified in patients undergoing hemodialysis, it is not clear how much of the MEHP was formed *in vivo* and how much, if any, was formed exogenously in the hemodialysis circuit.

The values for DEHP equivalent dose were used to derive TI/Dose ratios for aggregate exposure to DEHP and MEHP (Table C-5).

Table C-5. Total dose of DEHP and MEHP in terms of DEHP equivalents

Procedure	TI/Dose ratio	
	DEHP alone	DEHP + MEHP
Infusion of IV crystalloid solutions	120	4
Blood transfusion		
Transfusion/ECMO (adult)	0.2	0.03
Exchange transfusion (neonate)	0.02	0.02
Replacement Transfusion (neonate)	2	2
Cardiopulmonary bypass		
CABG	0.6	0.3
Orthotopic heart transplant	2	1
Artificial heart transplant	0.3	0.1

As shown in Table C-5, the procedures with TI/Dose ratios >1 when only DEHP was taken into account continued to have TI/Dose ratios >1 when exposure to both DEHP and MEHP was accounted for.

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Annex D. Nonsystemic Effects

Systemic effects (effects seen at a organ or tissue site distant from the portal of exposure or injection site) serve as the basis for derivation of TI values; however, DEHP produces other effects, either locally upon administration or *ex vivo* that may be clinically important as well. Although these effects cannot serve as the basis for derivation of a TI value, they may be important to consider during the risk management phase of the assessment.

D.1 Role of DEHP in mediating the poor hemocompatibility of DEHP-plasticized PVC

The thrombogenic nature of PVC materials is well known (Yianni, 1995). As discussed below, there is substantial evidence that the extent of platelet aggregation is due to the presence of DEHP in the material and not the PVC itself. In addition, complement activation, a process associated with adverse hematological effects, is greater following exposure of blood to DEHP-plasticized PVC than to other polymers. Each of these effects, increased platelet aggregation and complement activation, can have adverse clinical consequences in patients undergoing various medical procedures.

Kim et al. (1976) found that the absorption of γ-globulin and fibrinogen was greater on phthalate-contaminated PVC surfaces than surfaces that had been cleaned by methanol. The presence of these proteins on the surface of PVC induces platelet adhesion to the surface. Jones et al. (1989) found that platelet adhesion was greater on PVC plasticized with DEHP than PVC plasticized with either trioctyl trimellitate or polymeric adipate. Zhao and Courtney (1999) recently confirmed the findings of Jones et al. (1989). These investigators found greater fibrinogen adsorption onto DEHP-plasticized PVC than onto unplasticized PVC. Notable are their findings that the extent of fibrinogen adsorption increases as a function of the level of DEHP on the surface of the polymer. These results lead the authors to conclude that: "…reduction in the amount of plasticizer at the surface [of the polymer] improves the blood compatibility of plasticized polyvinyl chloride, and the influence of blood is due primarily to the plasticizer rather than the polyvinyl chloride."

It is interesting to note that the adhesion of fungus to PVC was also enhanced by the presence of plasticizers (DEHP or dioctyl adipate) in the polymer (Webb et al., 1999).

Reduced platelet adhesion has been observed on some alternatives to DEHP-plasticized PVC. For example, Lee et al. (1999) found that the adhesion of platelets on PVC film was significantly reduced by the incorporation of polyethylene oxide (PEO)-containing amphiphilic block copolymer additives to the PVC. Coating the blood contact surface of PVC materials with various substances also improves the hemocompatibility of the tubing (Kicheva et al., 1995).

Platelet adhering to polymer surfaces may initiate a sequence of events leading to thrombus development on the polymer surface. Release of thrombi into the blood stream can have clinical consequences. For example, microemboli released from ECMO circuits are thought to be responsible for infarcts in the brain, lung and kidney of patients undergoing ECMO therapy (Fink et al., 1989). Also, neurological complications following cardiopulmonary bypass are thought to be due to the release of microemboli (Taylor et al., 1999), although many of these emboli may be air bubbles, not thrombi released from a PVC surface. The use of in-line filters will obviously reduce the risk of clinical sequelae associated with the release of microemboli from PVC surfaces.

Complement activation on the surface of polymeric materials is associated with adverse hematological effects. Higher levels of complement (C3a) and FXII-like activity were observed on DEHP-plasticized PVC than on regenerated cellulose (Cuprophan) or an acrylonitrile-allyl sulphonate copolymer (AN69S) (Lamba et al., 2000). To put these results into perspective, the authors of this study note:

> The complement generating capacity of PVC/DEHP is greater than that of Cuprophan, a membrane that is regarded as a high complement activator. Therefore, the role of the blood tubing in determining the biocompatibility of extracorporeal procedures must be acknowledged. … There is evidence that the surface of medical grade PVC is rich in plasticizer [28,29], and thus, one may expect that plasticizer has the potential to influence the blood response.

Complement activation sets up a complex cascade of events involving chemotaxis of leukocytes which can release cytokines and induce platelet activation. These events are thought to play a role in the inflammatory response seen in patients on CPB. As a result, DEHP is able to promote complement activation on the surface of plasticized PVC, an event that may have adverse clinical consequences.

Significantly less complement activation and platelet adherence occur on heparin-coated PVC tubing (Wendel and Ziemer, 1999). Karle et al. (1997) found that heparin coating of PVC tubing dramatically reduces the amount of DEHP released from the tubing. Therefore, improved hemocompatibility of heparin–coated tubing may be due, in part, to reduced DEHP on the surface of the material. Consequently, heparin coating could be explored as a means to block the ability of DEHP to promote the deposition of protein, adhesion of platelets, and activation of complement on PVC.

D.2 Role of DEHP in Mediating Drug Adsorption onto PVC Surfaces

Recommendations for the use of non-PVC tubing for the intravenous administration of some drugs are intended to limit the amount of drug adhering to the surface of the tubing, not to limit the dose of DEHP received by the patient. Drug loss by binding to the surface of PVC tubing or bags will limit the dose of the drug that will reach the patient. Although drug loss is typically greater in PVC bags and tubing, compared to bags and tubing made from alternate materials (e.g., polyethylene), it was only recently shown that the amount of drug loss is correlated with the amount of leaching of DEHP from the tubing, at least for cyclosporine (Yano et al., 2001). Consequently, the presence of DEHP in PVC tubing may have important clinical consequences separate from those associated with patient exposure to DEHP.

D.3 Possible Role of DEHP in Producing Peritoneal Sclerosis

Peritoneal sclerosis is a serious complication of peritoneal dialysis therapy. Although factors such as the osmolarity, pH and lactate content of the dialysis solution may contribute to the pathogenesis of peritoneal sclerosis (Carozzi et al., 1993), several investigators have postulated a role for DEHP in the pathogenesis of this condition (Gandhi et al., 1980; Fracasso et al., 1993, 1999; Solary et al., 1986; Nassburger and Arbin, 1987; Calo et al., 1993; Carozzi et al., 1993).

A recent study (Fracasso et al., 1999) demonstrated that peritoneal sclerosis was produced in rats following intraperitoneal injection of a DEHP dose of 0.05 mg/kg/day for 7 days. Since DEHP was injected neat, the possibility exists that similar effects would not occur following infusion of DEHP-containing dialysate. Dialysate stored in DEHP-containing bags stimulated the proliferative capacity of peritoneal fibroblasts, whereas dialysate stored in DEHP-free bags (Clear-Flex, Bieffe) did not (Carozzi et al., 1993). It is reasonable to assume that proliferation of peritoneal fibroblasts is an initial step in the process leading to thickening or sclerosis of the

peritoneal membrane. The results of Carozzi et al. (1993) suggest that levels of DEHP in dialysate stored in DEHP bags are sufficient to initiate the process of peritoneal sclerosis.

Solary et al. (1986) described a case report in which a patient undergoing peritoneal dialysis developed a culture-negative peritonitis with a high eosinophil count following infusion of dialysate that had been stored in PVC bags. The white blood cell count in the peritoneal dialysis fluid fell dramatically following infusion of dialysate stored in glass bottles, then increased again when PVC-stored dialysate was used. The influx of eosinophils into the peritoneum could be in response to an inflammatory reaction.

Mechanistic support exists for a role for DEHP in the pathogenesis of peritoneal sclerosis in patients receiving peritoneal dialysis. Carozzi et al. (1993) have shown that *in vitro* exposure of peritoneal T lymphocytes and macrophages to peritoneal dialysis solution contained in DEHP-containing PVC bags resulted in increased release of IL-1 and interferon gamma and a decrease in release of prostaglandin E2, a cytokine that inhibits collagen synthesis, as compared to exposure of these cells to dialysis solution stored in DEHP-free bags (Clear-Flex, Bieffe).

The work of Stabellini et al. (1998) further supports the ability of DEHP to stimulate fibroblasts and produce fibrosis. These investigators introduced either undiluted or diluted DEHP (10 µmol/ml) into a previously created air pouch in rat subcutaneous tissue. Exposure to DEHP produced hyperplastic changes and alterations to fibroblasts in the subcutaneous tissue. It is also interesting to note that repeated intraperitoneal injection of DEHP in rats results in a reduction in the rate and extent of absorption of this compound from the peritoneal cavity (Pollack et al., 1985). Reduced absorption could be caused by thickening of the peritoneal membrane. Further, repeated IP injections of DEHP in rats resulted in a diminished effect on microsomal activity in the liver, as compared with a single IP injection (Agarwal et al., 1982). This finding could also be explained by fibrosis of the peritoneal membrane and reduced peritoneal absorption of the compound.

While the results of the above studies do not confirm a role for DEHP in the etiology of peritoneal sclerosis in patients undergoing peritoneal dialysis, they do nevertheless provide supporting evidence for a contributory role for DEHP in this process. Although osmolarity, pH, and lactate and glucose content of the dialysis solution are all factors that have been associated with the pathogenesis of peritoneal sclerosis, the results of the above studies suggest a possible contributory role for DEHP.

The clinical significance of peritoneal sclerosis cannot be underestimated, because patients with reduced dialytic capacity of the peritoneal membrane must be switched to hemodialysis. As a result, any role for DEHP in the etiology of this condition should be explored further.

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