Summary of the FDA Safety Assessment of DEHP Released from PVC Medical Devices: What it Says, What's Next

On September 5, 2001, the U.S. Food and Drug Administration (FDA) warned that some medical products made from polyvinyl chloride (PVC) may expose patients to unsafe amounts of the plasticizer di(2-ethylhexyl) phthalate (DEHP). The FDA warning came in the agency's long-awaited safety assessment on DEHP. DEHP is used to soften PVC medical devices such as bags and tubing. DEHP has been shown to produce a wide range of adverse effects in experimental animals.

The FDA concluded that exposures to patients during the following medical procedures may exceed the tolerable intake of DEHP:

- Adults and infants undergoing extracorporeal membrane oxygenation (ECMO) therapy;
- Infants undergoing exchange transfusions;
- All patients receiving enteral nutrition; infants receiving total parenteral nutrition (TPN);
- Adults undergoing cardiopulmonary bypass; and
- Nursing infants of mothers on hemodialysis.

While the FDA document does not attempt to quantitatively assess the risk posed by exposure of patients to DEHP, it does note that aggregate exposures to DEHP from multiple devices can result in doses that exceed the tolerable intake. For example, the FDA calculates that infants receiving multiple treatments in neonatal intensive care units may be receiving 20 times more DEHP from medical device related sources than what the agency considers tolerable.

The FDA further recommended that health care practitioners take action to reduce exposures. The FDA's safety assessment supports an Expert Panel convened by the National Toxicology Program in October 2000 that raised concerns about DEHP for some patient populations.

How did the FDA review the safety of medical devices containing DEHP?

The FDA chose to conduct a safety assessment rather than a risk assessment. A safety assessment does not assess the risk of a particular exposure, but instead develops a general index of safety or risk for patients by comparing the doses received while undergoing various medical procedures to a calculated Tolerable Intake (TI) value. The TI value is the dose of a compound that is not expected to result in adverse effects after exposure to the compound. The TI is considered conservative and is intended to be protective even for sensitive individuals in a population.

What did the FDA consider in its safety assessment?

The FDA considered species differences in the metabolism and toxicity of DEHP, pharmokinetics, and routes of exposure in their safety assessment. By doing so, the FDA addressed concerns that might be raised about the relevance of animal studies to humans and the importance of exposure routes to toxicity. The FDA derived a TI for both oral and parenteral exposure. A comprehensive review of the literature informed both estimates of the dose received by patients undergoing various procedures and the identification of critical health effects of DEHP in experimental animals. The exposure assessments were based on direct measurements in patients and estimates based on the rate of leaching of DEHP from medical devices.

The TI values for DEHP were based on the most sensitive endpoint identified in the scientific literature - the immature male testes. The TI values were based on the LOAEL (lowest-observed-adverse-effect-level) and the

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This version: June 20, 2002

NOAEL (No-Observable-Adverse Effect-Level) derived from several significant DEHP studies. Uncertainty factors were applied to the NOAEL and LOAEL from key studies to account for interspecies differences, variability in the human response, and deficiencies in the data.

Based on this approach, a parenteral TI value of 0.6 mg/kg/day and an oral TI value of 0.04 mg/kg/day were derived. The oral TI value is consistent with the health-based exposure limit values for DEHP developed by the US EPA, Health Canada, the Organization for Economic Cooperation and Development (OECD), and the European Union Scientific Committee on Toxicity, Ecotoxicity, and the Environment (CSTEE).

A TI/dose ratio was calculated for medical procedures believed to expose patients to DEHP. A TI/dose ratio of less than 1 means that the individual procedure exposes the patient to DEHP in excess of the TI. (See abbreviated table below. More TI/dose ratios can be found in Table 4.1 within the FDA safety assessment.) Hence, the last column illustrates that neonates are exposed to DEHP above the TI for TPN, enteral nutrition, ECMO, and exchange transfusions.

What did the FDA find?

Based on the safety assessment, the FDA found that DEHP exposure through medical devices and procedures does raise concerns for providers and their patients. There were several groups of patients at risk for exceeding the Tolerable Intake of DEHP based on exposures from medical devices and/or procedures. These groups include:

- Adults and infants undergoing Extracorporeal Membrane Oxygenation (ECMO);
- Infants undergoing exchange transfusions;
- All patients receiving enteral nutrition;
- Infants receiving total parenteral nutrition (TPN);
- Infants receiving medical therapy in neonatal intensive care units where exposures to DEHP may come from multiple sources simultaneously;
- Adults undergoing cardiopulmonary bypass; and
- Nursing infants of mothers on hemodialysis.

Table 1. Selected FDA Comparisons of Tolerable Intake (TI) Values for DEHP to the Dose of DEHP Received During Certain Medical Procedures

	Adult DEHP dose (mg/kg/day)	Adult TI/dose ratio	Neonate DEHP dose (mg/kg/day)	Neonate TI/dose ratio
IV: crystalline solutions	0.005	120	0.03	20
IV drugs with vehicles	0.15	4	0.03	20
Total Parenteral Nutrition (lipid solution)	0.13	5	2.5	0.2
Enteral nutrition	0.14	0.3	0.14	0.3
ECMO	3.0	0.2	14	0.04
Exchange Transfusions			22.6	0.02

What are the next steps in the FDA process?

The next phase of the FDA process is the development of a risk management strategy. The strategy could include a range of actions including provider and consumer education, provider and consumer alerts, and requirements for labeling medical devices containing DEHP. The FDA stated that it will consider the availability and safety of alternatives to DEHP and PVC in developing a risk management strategy.

Are there additional and emerging issues of importance to patients, health care providers, and the general population?

According to the FDA safety assessment, "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." But the Tolerable Intake values are all based on single exposures to DEHP. Moreover, the FDA notes that some DEHP is converted to MEHP in blood or crystalloid solutions before the product is administered to the patient. For infusion of crystalloid IV solutions, for example, considering the increased potency of MEHP as a testicular toxicant, the FDA estimates that the TI/dose ratio would drop from 120 to 4.

The Tolerable Intake values calculated by the FDA are based solely on the effects of DEHP on the immature male testes and do not consider potential non-systemic effects. The FDA notes

their importance however, and suggests non-systemic effects for which there are significant supporting literature will be considered in the risk management phase of their work. The safety assessment also does not discuss concerns about the effects of DEHP on the liver and lungs, nor does it discuss the clinical implications of background levels of DEHP in the general population to which exposures from medical procedures are added.[1]

Non-systemic effects of DEHP highlighted in the FDA safety assessment

Non-systemic effects of DEHP on patients can be clinically significant. The safety assessment points out that DEHP causes platelet aggregation and complement activation, likely to result in clinically important microemboli. The safety assessment notes that brain infarcts and dysfunction have been attributed to DEHP leaching from PVC tubing, as well as infarcts of lungs and kidneys. Thus, DEHP can alter hemocompatibility of PVC tubing. DEHP can also result in adsorption of drugs to PVC tubing and may have a role in the development of peritoneal sclerosis in patients undergoing peritoneal dialysis.

Emerging issue of background exposures not highlighted in the FDA assessment

It remains important to recognize that, beyond the specifically identified groups, the entire population is exposed to background levels of phthalates from other sources. For example, background levels of DEHP are estimated at approximately 3-30 micrograms/kg/ day, largely from dietary sources. This raises a concern for additional populations, in particular women of childbearing age. Women of reproductive age in the general population are routinely exposed to background levels of DEHP that constitute 25% (and perhaps as much as 75%) of the FDA's oral tolerable intake, prior to receiving any medical treatment. Recent data from the Centers for Disease Control show that women of reproductive age are also among the most highly exposed to another phthalate, DBP, that has very similar toxic effects. Consequently, when considering all sources of exposure, pregnant women undergoing medical procedures will more readily be exposed to levels of DEHP that will put their developing fetuses at risk.

Emerging issue of effects on the liver and lungs not highlighted in the FDA assessment

In addition to effects on the developing male reproductive tract, questions have been raised about the effects of DEHP exposure on the liver and lungs. One prospective study found cholestasis in infants supported by ECMO.[2] The authors hypothesize that hemolysis during ECMO produces a large bilirubin load, the excretion of which is inhibited by inspissated bile and/or DEHP. Another study, however, did not find cholestasis after ECMO, but DEHP plasma concentrations in the second study were substantially lower than in the first (estimated aggregate exposure levels 4.7-35 mg/kg vs. 42-140 mg/kg)[3] Recently, renewed concerns have surfaced about a contributory role of DEHP in the genesis of hepatotoxicity frequently observed in infants receiving TPN.[4] Although this potential hazard has not been studied, the science does show that larger quantities of DEHP leach from PVC tubing when TPN solution passes through than were previously estimated. The authors of this study estimate that infant exposures from TPN may reach 10 mg/kg/day, which is more than one order of magnitude higher per kg than adult exposures from hemodialysis and are experienced daily.

DEHP also leaches from PVC endotracheal tubes during use. One study documents a direct relationship between time of endotracheal tube use and DEHP leaching.[5] The authors hypothesize a link between DEHP exposure and the risk of bronchopulmonary dysplasia in premature newborns. This potential hazard has never been studied in infants. DEHP deposition in the infant lung, however, has been documented after ventilation with PVC tubing.[6]

Is the FDA safety assessment consistent with the findings of other governmental bodies?

The FDA joins other governmental agencies in the United States and abroad in expressing concern about the risks posed by PVC medical devices that leach DEHP. In October 2000, the National Toxicology Program's Center for the Evaluation of Risk to Human Reproduction's expert panel report expressed "serious concern" that exposure to DEHP may adversely affect male reproductive tract development in critically ill infants and "concern" over the levels of DEHP exposure to pregnant women, breast-feeding mothers, and healthy infants and toddlers.

In July 2001, the Swedish National Chemicals Inspectorate, acting on behalf of the European Union, reported that people "are exposed to DEHP during their entire lifetime, via the environment, consumer products and medical equipment" and that there is a need to institute additional risk reduction measures now.

For the full FDA report, go to **http://www.fda.gov/cdrh/ost/dehp-pvc.pdf**

Notes

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