



## **DRAFT POSITION STATEMENT ON DEHP IN MEDICAL DEVICES FOR STAKEHOLDER CONSULTATION**

### **BACKGROUND**

The Medical Devices Bureau of Health Canada has completed a review of the scientific and medical literature that forms the basis for concerns that Di(2-ethylhexyl) phthalate (DEHP) leached from medical devices may pose health hazards to patients. As part of the study, the Medical Devices Bureau prepared an internal report, *DEHP in Medical Devices: An Exposure and Toxicity Assessment*.

In April 2001, Health Canada convened an Expert Advisory Panel on DEHP in Medical Devices (EAP-DEHP) to review the report prepared by the Medical Devices Bureau and provide specific advice on managing the risks associated with the use of medical devices containing DEHP. Members of the advisory panel represented a broad range of expertise on use, science, clinical practice and toxicology of substances in medical devices. The Advisory Panel presented its report including recommendations in February 2002, at which time stakeholders were given the opportunity to submit written comments. A variety of stakeholders, representing health care professionals, public interest groups, members of the public, and the vinyl and medical devices industry provided written comments.

Health Canada has reviewed the comments and has developed this draft position paper on DEHP in medical devices. This draft position is based on knowledge of the current science, recommendations of the Expert Advisory Panel, and comments from stakeholders.

### **CONSIDERATIONS**

**1. Medical Exposure to DEHP.** Di(2-ethylhexyl) phthalate (DEHP) is a chemical additive used to soften a wide variety of medical devices made of polyvinyl chloride (PVC) plastic, including catheters, tubing and bags used to administer blood, plasma, drugs, and other fluids. DEHP can leach from the PVC plastic into the fluids that come into contact with it. DEHP exposure levels depend of the nature of the medical device and the medical procedure used, its frequency and duration. These parameters determine the volume of fluid in contact with the PVC, its lipid content and temperature, and the length of time the fluid is in contact with the plastic.

**2. Toxicity of DEHP.** Exposure to DEHP results in a wide range of adverse effects in rodents and other animals, including adverse reproductive and developmental effects. DEHP is thought to have the potential to produce similar adverse reproductive and developmental effects in humans. Of greatest concern, are the adverse effects on the developing testes of young animals. Not all species are equally susceptible to the toxic effects of DEHP. In particular, primates are thought to be less susceptible than rodents.

There is no reliable data on the toxicity of DEHP or its metabolites in humans. There are reports in the medical literature of a variety of adverse effects seen in patients exposed to DEHP from medical devices. However, these studies were not properly designed to demonstrate any cause-effect relationship between human exposure to DEHP and toxicity. Consequently, evaluation of risk to humans can only be extrapolated from animal data. Such extrapolations are questionable due to significant species differences in metabolism and pharmacokinetics that may completely alter the effect of a substance between experimental animal models and the human. Only good quality and extensive human data can reliably confirm or refute a concern about toxicity.

Health Canada has reviewed recent studies which reassess certain aspects of the toxicity of DEHP in rodents and refine the no-observed-adverse-effect-levels (NOAEL). The studies provide some reassurance that the rodent NOAEL for both parenteral and oral exposures are somewhat higher than previously thought and also fill in some important data gaps. Health Canada is also aware of plans for additional studies intended to fill other data gaps. Nevertheless, there currently is no published data concerning male primates exposed orally and intravenously to DEHP during the neonatal, pre-adolescent and peri-adolescent periods, which are believed to be the most sensitive periods for testicular toxicity. The possibility of adverse effects from high exposures in potentially sensitive humans can therefore not be conclusively ruled out at this time.

**3. Risk Management.** Although there is no data on the reproductive and developmental toxicity of DEHP or its metabolites in humans, the mechanism by which developmental and testicular toxicity in particular occur in rodents appears relevant to humans. The animal data indicate a theoretical possibility of developmental and testicular toxicity, particularly in young human males exposed to high levels of DEHP, and support risk management measures to limit exposure to DEHP. Protection of susceptible populations from DEHP exposures at levels that may pose significant risks based on the animal data is warranted. A viable option is a balanced risk reduction strategy, in which the theoretical risk of adverse reproductive and developmental effects from exposure to DEHP are balanced against the benefits of DEHP-containing medical devices as well as the medical advantages and drawbacks of the substitute materials and their availability.

The greatest concern is in humans where the susceptibility of the patient and exposure are both high. In these situations, the use of alternative products is justified as a prudent cautionary measure even without clear evidence of human toxicity. Individuals who are not as susceptible are less of a concern, but may also merit consideration for the need for alternative procedures in cases of high DEHP exposure. Alternatives to DEHP-containing devices must be shown to have a safety profile at least as good as those with DEHP before adoption for use.

The ability of DEHP to alter the hemocompatibility of PVC tubing or result in adsorption of drugs to PVC tubing is another important consideration in selecting the appropriate risk management option, depending on the device.

**4. Most Susceptible Subgroups.** The subgroups which are believed to be the most susceptible to adverse effects of DEHP exposure are male newborns (particularly prematures) and fetuses, male infants and young children, and (possibly) peripubertal males.

**5. Medical Procedures that may Result in Relatively High DEHP Exposures**

The use of DEHP-containing medical devices for the following medical procedures, may expose patients to relatively high concentrations of DEHP.

- exchange transfusion in newborns and infants
- extracorporeal membrane oxygenation (ECMO) in newborns and infants
- administration of lipid-containing total parenteral nutrition therapy (TPN) solutions to newborns and infants
- enteral nutrition (lipid-containing solutions) in newborns and infants
- multiple intensive care unit (ICU) procedures in sick newborns
- intravenous (IV) infusion of lipophilic drugs or drugs which contain surfactants
- cardiac surgery in newborns and infants
- ECMO and associated blood transfusions in adults
- cardiopulmonary bypass in adults
- artificial heart transplant in adults
- coronary artery bypass in adults
- enteral nutrition in adults
- trauma patients receiving multiple blood transfusions

**6. Procedures of Greatest Concern (High Exposure of the Most Susceptible Subgroups)**

The use of DEHP in the following subgroups may put these individuals at higher risk:

- volume exchange transfusion in newborns and infants
- ECMO in newborns and infants
- cardiac surgery in newborns and infants
- administration of TPN solutions that contain lipids to newborns and infants
- enteral nutrition in newborns and infants
- multiple ICU procedures in sick newborns
- IV infusion of lipophilic drugs or drugs which contain surfactants

**7. Health Canada's mandate**

The implementation of an effective risk management strategy must involve all the partners in the healthcare sector. Health Canada's jurisdiction is limited to the regulation of the sell, import or distribution of medical devices. All stakeholders will need to be involved in the risk management strategy in order for any option to be successful.

## RECOMMENDATIONS

Based on the current understanding of the science and the needs of the medical system, Health Canada believes that the following recommendations represent the most prudent approach. The Department will review all new data on the toxicity of DEHP as it becomes available.

### General Recommendations

1. Precautions should be taken to limit medical exposure to DEHP in certain groups of patients who, based on the animal data, may be at risk. These are male newborns, infants and young children, pregnant women carrying a male foetus, and peripubertal males.
2. Steps should be taken to allow healthcare professionals to identify medical devices that contain DEHP so that they can make informed decisions about the use of these devices in the treatment of their patients.
3. Alternatives to DEHP should not be introduced unless there is adequate data on their safety and efficacy.
4. Medical procedures should not be avoided because of the possible health risk associated with DEHP exposure as the benefits of these procedures outweigh any possible health risk associated with DEHP exposure.

### Specific Recommendations

- 1. Blood Bags.** DEHP should continue to be used in blood bags until an alternative which allows acceptable storage times becomes available or failing this, until human data confirms harm from this practice. For susceptible populations, consider special strategies and procedures, such as the use of the freshest blood stored at the lowest possible temperature, to reduce exposure to DEHP and its metabolites from blood products.
- 2. Alternative Measures.** Alternative measures are immediately justifiable and should be introduced as quickly as possible to protect those sub-populations at greatest risk, namely the fetus, newborns, infants and young children receiving volume exchange transfusions, extracorporeal membrane oxygenation (ECMO), cardiopulmonary bypass, cardiac surgery, TPN, enteral nutrition, and lipophilic drug formulations.
- 3. Use of Alternatives for ECMO.** Alternative products that are already available (i.e., heparin-coated tubing) should be utilized for all ECMO procedures in newborns and infants.

**4. Administration of Lipophilic Drugs.** Tubing and storage bags used for the administration of lipophilic drug formulations should not contain DEHP, or strategies to decrease DEHP exposure should be employed, particularly when administering these drugs to infants and children. Many manufacturers of lipophilic drugs already recommend the use of non-DEHP plasticised materials for drug administration. Specialty administration sets, bags, and tubing manufactured with non-DEHP materials are currently available for use with lipophilic drugs.

**5. Administration of TPN Solutions.** As suitable alternative products are already available, (e.g., EVA containers, silicone and polyurethane tubing), total parenteral nutrition solutions that contain lipids should be administered to newborns and infants only via DEHP-free products. Administration of lipid-free TPN solutions, such as dextrose and amino acid mixtures, can be safely done using DEHP-containing products, as there is little concern about DEHP exposure in patients undergoing these procedures.

**6. Administration of Other IV Solutions.** The IV administration of crystalloids fluids such as normal saline, dextrose, and Ringer's lactate can continue to be done via DEHP-containing products as there is little concern about DEHP exposure in patients undergoing these procedures.

**7. Clinical Practice Guidelines.** National professional health care organizations should develop clinical practice guidelines to reduce DEHP exposure for potentially sensitive populations.

**8. Disclosure of the Presence of DEHP.** Manufacturers of a medical device made of PVC that may be used in the procedures listed in Consideration 5, should take steps to inform users through labelling if the device contains DEHP, since health care professionals need this information to make informed risks management decisions.

**9. Research.** Manufacturers should conduct research into methods for reducing release of DEHP from products containing this plasticizer as well as into alternatives to DEHP-containing products. Priority should be given to studies that define the real level of risk to humans from DEHP exposure, including research into other possible adverse health effects of DEHP exposure, as well as the safety and efficacy of alternative products.