Summary of the 2002 Report of the Health Canada Expert Advisory Panel on DEHP in Medical Devices

In January 2002, Health Canada released the Final Report of the Expert Advisory Panel on DEHP in Medical Devices.[1] Below is a summary of the Expert Panel's findings.

The Panel made recommendations based on a 2001 Health Canada review entitled "DEHP in Medical Devices: An Exposure and Toxicity Assessment,"[2] and external studies, including the most recent findings of the US National Toxicology Program's Center for the Evaluation of Risks to Human Reproduction (NTP-CERHR)[3] and the US Food and Drug Administration (FDA).[4]

Overall Findings

The Health Canada Expert Advisory Panel made 12 recommendations. Key among them are:

Protect vulnerable populations.

DEHP-containing devices should not be used in the following circumstances (i.e., only devices containing an alternative to DEHP should be used in these situations):

- In all newborns and in pre-pubertal males, for high exposure procedures such as ECMO (except where the kits are heparin coated to prevent leaching), during cardiac surgery, during TPN, and for double volume exchange transfusions;
- In some adults such as heart transplant patients, those undergoing cardiac bypass, hemodialysis patients, and pregnant and lactating women;
- When administering lipophilic drug formulations;
- In adult trauma patients who fall into a potentially sensitive population (heart transplant recipients, pregnant or lactating women.)[5]

Label products containing DEHP.

The Panel recommends that labeling of products always indicate that DEHP is present in a particular product. To supplement the use of disclosure labeling, the Panel recommends that the indications of use (risk communications) should be captured in the clinical practice guidelines recommended below.[6]

Adopt some DEHP-free alternatives immediately.

As alternative products are already available (albeit at significantly elevated cost), the Panel recommends that total parenteral nutrition solutions be administered to newborns and infants only via products which do not contain DEHP.[7]

Adopt other DEHP-free alternatives as quickly as possible.

Alternate 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 transfusions, ECMO, cardiopulmonary bypass, exchange transfusion, hemodialysis, TPN and lipophilic drug formulations.[8]

Research into further methods for reducing release of DEHP from products containing this plasticizer as well as into alternatives to DEHP-containing products should be urgently encouraged.[9]

The Expert Advisory Panel describes its conclusions as "contrary to the June 1999 review and consensus statement of the American Council on Science and Health, which states that 'DEHP…is not harmful to humans….'" Conversely, the findings are "very similar to those of the October 2000 NTP-CERHR Expert Panel Report...(which concluded)...the risk to infants, toddlers, critically ill children and during pregnancy and lactation may be more significant."[10]

The complete list of Expert Panel recommendations is included at the end of this summary document.

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Health Canada's Responsibility

Health Canada has ultimate responsibility for decision-making on DEHP in medical devices – it has responsibility for approving DEHP as an additive, product labeling and for approving products containing DEHP.

The Expert Panel concluded "In the presence of certain or possible risks, Health Canada (HC), in its capacity as regulator, will err on the side of caution. HC will also balance decisions according to the known risks, and the consequences of proceeding with or without regulations."[11]

Background

Health Canada's Exposure and Toxicity Assessment of DEHP provides relevant background for the Expert Panel's recommendations.

DEHP: Preferred Plasticizer for Medical Devices

Di(2-ethylhexyl) phthalate, commonly referred to as "DEHP," is used as a plasticizer of polyvinyl chloride (PVC) in the manufacture of a wide variety of consumer products. Plasticizers provide PVC with characteristics such as flexibility, strength and bondability. Plasticizers allow PVC to be softened and shaped into many designs without cracking or leaking, "which is of great importance in many medical device applications."[12]

DEHP is currently the only phthalate plasticizer used in PVC medical devices. DEHP is the "plasticizer of choice"[13] for medical devices because it provides the "desired mechanical properties."[14] By weight, PVC-based medical devices contain, on average, 20%-40% DEHP[15] with some products containing as much as 80% DEHP.[16]

Medical Procedures Where PVC is Most Commonly Used

A variety of medical devices use PVC, including: blood and blood-component storage bags, intravenous (IV) solution containers and administration sets, respiratory tubing, extracorporeal membrane oxygenation (ECMO) therapy tubing sets, continuous ambulatory peritoneal dialysis (CAPD), hemodialysis sets, autopheresis sets, nasogastric feeding tubes and oxygen tents.[17]

Mechanisms of Action of DEHP

There are essentially no data to confirm cause-effect relationships between DEHP exposure and toxicity in humans.[18] Evaluation of risks to humans can only be extrapolated from animal data. Certain mechanisms by which toxicity occurs in rodents have been found to be relevant to humans, and consequently rodent data are considered "relevant to predicting that DEHP has the potential to produce adverse reproductive effects in humans."[19] The Expert Panel concluded "the animal data must be taken to indicate at least the theoretical possibility of developmental and testicular toxicity, particularly in the young human with high exposure levels."[20]

Absorption and Metabolism of DEHP

Patients are exposed to DEHP via the intravenous route, the inhalation route or by digestion.[21] DEHP administered via the gastrointestinal tract is substantially converted to the monoester, MEHP, by intestinal lipases before absorption into the systemic circulation. "In primates, including humans and marmosets, a smaller proportion of DEHP is hydrolyzed and absorbed as the monoester (than in rats) apparently because of less lipase activity in primate intestines."[22] DEHP administered orally is converted more rapidly to MEHP than if administered intravenously.[23] The degree of biotransformation of DEHP to MEHP is important since MEHP is generally agreed to be the testicular toxicant that has led NTP-CERHR to raise a "serious concern" for neonates exposed to DEHP.[24]

Adult humans and other primates excrete MEHP as a glucuronide, while rodents metabolize it further.[25] Children, however, lack mature glucuronidation pathways until they are 3 months old – this important clearance mechanism is therefore not fully available to neonates and young infants.[26] Similarly, individuals with kidney disease and other health problems may be compromised by the inability to metabolize DEHP.[27]

Developmental and Reproductive Effects of DEHP

Health Canada participated on the NTP-CERHR review of DEHP, which only looked at the risks of DEHP exposure to human reproduction and development. "The report's review of reproductive and developmental toxicity generally reflects the position of the NTP-CERHR review, although Health Canada did conduct an independent review."[28]

"Studies have provided a consistent picture of the toxic effects on the reproductive system that are produced by exposure of rodents to DEHP during development in utero and the nursing period, after weaning, and during the adult phase."[29]

Males show testicular damage, and at higher doses, lower sperm counts and reduced fertility, while adult female rats show decreased hormone production, suppressed and delayed ovulation, ovarian dysfunction and infertility.[30]

The Sertoli cells, which orchestrate spermatogenesis in the testes, are the primary target for testicular toxicity of DEHP and other phthalates.[31] Exposure to DEHP causes "significant changes" in the morphology and function of the Sertoli cells, and the effects differ with age and between species.[32]

Exposure to DEHP can be Increased Under Certain Circumstances

Health Canada reports that DEHP leaches out of medical devices:

"Since the DEHP in PVC is not chemically bound to PVC, it can leach out when a PVC-containing medical device comes in contact with fluids such as blood, plasma, and drug solutions, or it can be released when the device is heated. The rate at which DEHP and other plasticizers migrate from the medical device depends on the storage conditions: temperature of the fluid in contact with the device; the amount of fluid in contact with the PVC; the contact time; the extent of shaking or flow rate of the fluid; and the lipophilicity of the fluid."[33]

DEHP leaches into many IV and enteral formulas/solutions, including whole blood, plasma, total parenteral and enteral nutrition solution, and solutions containing Polysorbate 80 and other formulation aids used to solubilize some IV medications.[34] The conditions under which medical devices are stored or treated can increase the migration of DEHP. Hence, "(l)ong storage or time of use, increased temperature, and agitation all increase the leaching of DEHP from medical devices. Leaching is also enhanced by increased lipid content or by the lipophilic nature of liquids that contact DEHP in medical devices."[35]

Multiple Exposures to DEHP

Multiple sources of DEHP exposure must be considered when evaluating the aggregate risk to an individual patient in a medical setting.

"For many patients, particularly critically ill neonates, examining single sources of exposure (e.g., ECMO or ventilation) may significantly underestimate the total exposure. For example, neonates who require ECMO also require multiple replacement blood transfusions, parenteral feeding, medications, and IV fluids. Many of these other medical procedures may substantially increase DEHP exposure."[36]

DEHP and Blood Products

There are three types of PVC blood bags on the Canadian market, plasticized with either DEHP, tri-2(ethylhexyl)trimellitate (TEHTM) or butyltri-n-hexyl-citrate (BTHC). Non-PVC bags, made of polyolefin and ethylene vinyl acetate (EVA), both of which have no added plasticizer, are currently used for the storage of blood components (platelets).[37] Canadian Blood Services and Hema Quebec use blood bags and plasmapheresis bags made of PVC-DEHP. The current practice in Canada is to store only platelets in DEHP-free bags.[38]

DEHP is known to stabilize red blood cell membranes and allow for storage of up to 42 days.[39] The Expert Panel identifies the need for additional research on blood storage time and alternative products.

"For susceptible populations, the Panel encourages an exploration of special systems and procedures to reduce exposure to DEHP and its metabolites from use in blood products"[40]

Restricting the Use of DEHP – Populations at Greatest Risk

The Expert Panel believes that the concerns about adverse effects warrant restricting use of DEHP-containing products for certain populations and uses:[41]

- **(T)he most susceptible populations.** For example, animal and in-vitro studies suggest the possibility of testicular effects (in males) and cardiac effects. Newborns have increased susceptibility to a broad range of substances so would be expected to be at greatest risk of DEHP-related toxicity if this were to occur in humans. These concerns are also relevant to potential exposure of the fetus via the placenta in pregnancy or newborns through lactation. Pre-pubertal males would be potentially susceptible to the testicular effects beyond the newborn period. Even certain adults might have increased susceptibility, e.g., heart transplant recipients to the potential cardiac effect.[42]
- **(F)or uses where exposure is high or long-term.** Thus, even a population with presumed lower susceptibility such as adults might be considered at theoretical risk of the above toxicities demonstrated in animal/in vitro models if exposure may be either very high, e.g. during cardiac procedures or during multiple transfusions for trauma, or long-term, e.g., during hemodialysis (where impaired renal function may also impede clearance of metabolites.)[43]

The panel also expressed concern that "pregnant women undergoing certain medical procedures may adversely affect the development of their offspring," due to factors such as MEHP passing across the placenta and into breast milk, and the special vulnerability of the fetus.[44]

Accelerate Exploration of Alternatives to DEHP

Alternatives to DEHP-plasticized PVC currently include PVC softened with citrates, trimellitates and adipates, or alternate plastics to PVC.[45] The vast majority of alternative plastics to DEHP-plasticized PVC are inherently flexible, including silicone, EVA (ethylene vinyl acetate) and polypropylene, therefore do not require any plasticizer.

The Panel recommends immediate measures to protect vulnerable populations from exposure to DEHP from certain treatments and products, and the exploration of the safety and availability of additional alternative products.

The Panel considered the difference in costs of some DEHP-free materials and the availability of these alternatives in Canada. The limited use of ECMO in Canada led the Panel to feel that the cost of alternative materials in ECMO should not be a major consideration.[46] Similarly, DEHP-free tubing was recommended for total parenteral nutrition solutions (which can be high in lipids, which increases extraction of DEHP[47]), despite higher costs.[48]

In terms of availability of alternatives, the Panel noted that new alternative plastics already approved for medical uses in the US and in Europe could be considered for use in Canada, and could be approved "fairly quickly."[49] The Panel felt strongly that "(P)lasticizers intended to be used as alternatives to DEHP should be shown to have a safety profile at least as good as DEHP before adoption for use in medical devices."[50]

The Panel recommends the adoption of Clinical Practice Guidelines "to reduce DEHP exposure for high susceptibility high exposure populations...and to reduce exposure to DEHP from use of DEHP-containing devices for certain intermediate-risk populations as a supplementary approach to disclosure labeling..."[51]

Adopt the Precautionary Principle

In assessing the potential risks of DEHP, the Expert Panel noted the value of animal data, and acknowledged the absence of human data. They consider, therefore, what kind of evidence Health Canada may wish to include in order to make decisions about medical devices.

The Panel "would support (Health Canada) in enunciating a clear precautionary principle regarding the regulation of all medical devices, even where human data are incomplete or inconclusive."[52]

The Panel considered the following description of the Precautionary Principle: "When an activity raises threats of harm in human health or environment, precautionary measures should be taken even if some cause and effect relationships are not fully established scientifically. In this context the proponent of an activity, rather than the public, should bear the burden of proof. The process of applying the Precautionary Principle should be open, informed, and democratic and must include potentially affected parties. It must also involve and examination of the full range of alternatives, including no action."[53]

Expert Panel Recommendations

1. While it is not within the Panel's mandate to determine whether or not ECMO is an effective treatment, it does recommend that alternate products that are already available, (i.e., heparin coated tubing,) should be utilized for all ECMO procedures in newborns and infants.

2. Tubing and storage bags used for administration of lipophilic drugs or drugs which contain surfactants (i.e., 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. (Also see later recommendations on labeling.)

3. As alternative products are already available (albeit at significantly elevated cost), the Panel recommends that total parenteral nutrition solutions be administered to newborns and infants only via products which do not contain DEHP.

4. Research into further methods for reducing release of DEHP from products containing this plasticizer as well as into alternatives to DEHP-containing products should be urgently encouraged.

5. The sub-populations to be considered at greatest risk should include the following:
   - Newborns including premature
   - Infants and young children
   - ECMO patients
   - Cardiopulmonary bypass patients
   - Exchange transfusion patients (infants & children)
   - Patients receiving certain IV therapies, particularly those on TPN and those receiving lipophilic drug formulations, etc.

   Sub-populations that should be considered to be at possible but presently undetermined risk include:
   - Trauma patients receiving multiple blood transfusions
   - Hemodialysis patients
   - Oxygen therapy patients
   - Children of breast-feeding (lactating) females
   - The fetus (i.e., pregnant women)
   - Pre-pubescent males

6. The highest priorities for further study in the Panel's opinion include: ECMO, hemodialysis, intrauterine transfusions, TPN, oxygen therapy, IV therapy, particularly using blood products, IVIg, etc., and enteral feeding. In view of the limited data available for many of the above applications, the Panel's further recommendations are limited to IV delivery products, preparatory or storage products.

7. Alternate 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 transfusions, ECMO, cardiopulmonary bypass, exchange transfusion, hemodialysis, TPN and lipophilic drug formulations.

8. 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, the Panel encourages an exploration of special systems and procedures to reduce exposure to DEHP and its metabolites from use in blood products.

9. DEHP-containing devices should not be used in the following circumstances (i.e., only devices containing an alternative to DEHP should be used in these situations):
   - In all newborns and in prepubertal males, for high exposure procedures such as ECMO (except where the kits are heparin coated to prevent leaching), during cardiac surgery, during TPN, and for double volume exchange transfusions;
   - In some adults such as heart transplant patients, those undergoing cardiac bypass, hemodialysis patients, and pregnant and lactating women;
   - When administering lipophilic drug formulations;
   - In adult trauma patients who fall into a potentially sensitive population (heart transplant recipients, pregnant or lactating women.)

10. The Panel recommends that labeling of products always indicate that DEHP is present in a particular product. To supplement the use of disclosure labeling, the Panel recommends that the indications of use (risk communications) should be captured in the clinical practice guidelines recommended below.

11. Health Canada should encourage national professional organizations to develop clinical practice guidelines to reduce DEHP exposure for potentially sensitive populations (Recommendation 5) and high exposure uses.

12. The Panel recommends that Health Canada support and facilitate by any means possible the conduct of research to define the real level of risk to humans from DEHP exposure, as well as the safety and efficacy of alternative products. The Panel further recommends that HC develop clear guidelines governing the approval for human use of products where human data are lacking.

Endnotes

1. Source document: Health Canada Expert Advisory Panel on DEHP in Medical Devices: Final Report 2002 January 11. http://www.hc-sc.gc.ca/hpb-dgps/therapeut/zfiles/english/advcomm/eap/dehp/eap-dehp-final-report-2002-jan-11_e.pdf . (Hereafter cited as "Expert Panel, Page _")
2. "DEHP in Medical Devices: An Exposure and Toxicity Assessment." Ottawa: Medical Devices Bureau, Therapeutic Products Directorate, Health Products and Foods Branch, Health Canada, (Revised February 2002). (Hereafter cited as "Health Canada, page_")
3. NTP-CERHR Expert Panel Report on Di(2-ethylhexyl)phthalate, National Toxicology Program, US Department of Health and Human Services, Center for the Evaluation of Risks to Human Reproduction. October 2000. (Hereafter cited as "NTP-CERHR, page_")
4. United States Food and Drug Administration (FDA), Center for Devices and Radiological Health. 2001. Safety Assessment of Di(2-ethylhexyl)phthalate (DEHP) Released from PVC Medical Devices. Rockville, MD: US FDA.
5. Expert Panel, Page 16.
6. Expert Panel, Page 16.
7. Expert Panel Page 8. It should be noted that for some product lines, cost-competitive DEHP-free products are on the market. See: Leaversuch, Robert D. 1999. "Specialty polyolefins challenge PVC in medical fluid systems." Modern Plastics, July: 92-96.
8. Expert Panel, Page 13.
9. Expert Panel, Page 10.
10. Expert Panel, Page 5.
11. Expert Panel, Page 4.
12. Health Canada, Page 1.
13. Health Canada, Page 1.
14. Health Canada, Page 1.
15. Health Canada, Page 3.
16. Expert Panel, Page 9.
17. Health Canada, Page 3.
18. Expert Panel, Page 5.
19. Health Canada, Page i.
20. Expert Panel, Page 5.
21. Health Canada, Page 4.
22. Health Canada, Page 32.
23. Health Canada, Page 31.
24. NTP-CERHR, page 101.
25. Health Canada, Page 38.
26. Health Canada, Page 38.
27. Health Canada, Page 38.
28. Health Canada, Page iii. In addition to the effects on the developing male reproductive tract, studies have indicated DEHP toxicity in the lungs, heart, kidneys and liver (Rossi, 2001. Neonatal Exposure to DEHP (di-2-ehtylhexyl phthalate) and Opportunities for Prevention. Health Care Without Harm)
29. Health Canada, Page 55.
30. Health Canada, Page 55.
31. Health Canada, Page 56.
32. Health Canada, Page 56.
33. Health Canada, Page 3.
34. Health Canada, Page 3.
35. Health Canada, Page 19.
36. Health Canada, Page 31.
37. Health Canada, Page 4.
38. Health Canada, Page 7.
39. Expert Panel, Page 13. Note – DEHP is not regulated by Health Canada as an additive.

40. Expert Panel, Page 14. Note: A citrate-plasticized PVC blood bag is on the market (Baxter) with a shelf-life equivalent to that of the DEHP bag (42 days).
41. Expert Panel, Page 15.
42. Expert Panel, Page 15.
43. Expert Panel, Page 15.
44. Expert Panel. Page 82.
45. Health Canada, Page 83.
46. Expert Panel, Page 6.
47. Health Canada, Page 9.
48. Expert Panel, Page 8.
49. Expert Panel, Page 10.
50. Expert Panel, Page 13. Health Care Without Harm challenges the Expert Panel's assertion that human data are required to justify the safety of non-DEHP alternatives (Expert Panel, page 14 and 17). Animal data were determined relevant to assessing the risk from DEHP and should be acceptable to justify alternatives. Furthermore, the Panel should acknowledge the difficulty of studying the impacts of fetal or infant exposures on testicular development.
51. Expert Panel, Page 17.
52. Expert Panel, Page 19.
53. Raffensberger C, Tickner T, eds. Protecting Public Health and the Environment: Implicating the Precautionary Principle. Washington: Island Press, 1999:353-4.

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