The Weight of the Evidence on DEHP:

Exposures are a Cause for Concern, Especially During Medical Care

Assessments conducted for the governments of the United States, Canada, and the European Union have all concluded that exposures to di-2-ethylhexyl phthalate (DEHP) are of concern to some patient populations and subsets of the general public. Especially vulnerable are infants and toddlers, pregnant and lactating women, and patients undergoing certain medical procedures. All of the government-sponsored assessments point to the need for action, with the Canadian and Swedish studies recommending specific action to reduce DEHP exposure in health care and other vulnerable populations. The FDA has recommended that medical device manufacturers reformulate products to remove DEHP and that hospitals use alternatives to DEHP-containing products, whenever possible, for high risk populations.

Listed below are summaries of the major conclusions from reports by the U.S. National Toxicology Program's Center for Evaluation of Risks to Human Reproduction, U.S. Food and Drug Administration, Health Canada Expert Advisory Panel, the Swedish National Chemicals Inspectorate (for the European Union), the European Chemicals Agency, and California's Office of Environmental Health Hazard Assessment.

United States — National Toxicology Program (NTP) — Expert Panel (2000, 2005, 2006)

The NTP's Center for Evaluation of Risks to Human Reproduction (CERHR) convened an expert panel in 2000 to review available data pertaining to exposures and effects of DEHP and convened a second expert panel in 2005 to update their first report, based on newly published data. In 2006, the NTP reviewed these findings and released its final assessments and recommendations.

The NTP concluded that DEHP is a reproductive and developmental toxicant in animals, animal studies are relevant to humans, and current exposure levels are of particular concern for three distinct human populations: critically ill infants, healthy infants and toddlers, and pregnant and lactating women.

Critically ill infants

The 2000 panel concluded: "The available reproductive and developmental toxicity data and the limited but suggestive human exposure data indicate that exposures of intensively-treated infants/children can approach toxic doses in rodents, which causes the Panel serious concern that exposure may adversely affect male reproductive tract development [in humans]." The 2005 panel affirmed the 2000 panel and concluded: "Parenteral medical exposure to DEHP of critically ill infants can exceed general population exposure by several orders of magnitude." The expert panel estimated the upper range of DEHP/MEHP exposure from medical procedures in infants to be 6000µg/kg body weight/day. The expert panel has serious concern that such exposures may adversely affect male reproductive tract development and function. The panel believes that the benefits of medical procedures can be significant, but that minimizing exposure to DEHP should be a goal. This conclusion concurs with that of the first expert panel. The final 2006 NTP report reaffirmed these findings and the conclusion citing serious concern for potential harm. DEHP exposures were again estimated to be as high as 6000µg/kg body weight/day. The report concludes: "There is serious concern that certain intensive medical treatments of male infants may result in DEHP exposures levels that affect development of the male reproductive tract."

Pub 3-11 This publication is part of *Going Green: A Resource Kit for Pollution Prevention in Health Care.* For additional copies of this or other publications included in the kit, or to find out how to get a complete kit, visit Health Care Without Harm on the Web at www.noharm.org/goinggreen.
This version: March 16, 2009

Healthy infants and toddlers

The 2000 panel concluded: "If healthy human infant/toddler exposure is several-fold higher than adults [it will approach levels found to be toxic in rodents, therefore], the Panel has concern that exposure may adversely affect male reproductive tract development [in humans]." The 2005 panel concluded: If the level of exposure is at the high end of the estimated exposure range for the general population, the expert panel has **some concern** that exposure to DEHP can adversely impact reproductive development in male children older than one year. The expert panel has **concern** that DEHP exposure can adversely affect reproductive development in infants less than one year old. These conclusions are a refinement of the first panel's conclusion of concern for the entire healthy infant/toddler population. The 2006 final NTP report reaffirmed these conclusions of the 2005 panel regarding healthy infants and toddlers.

Pregnancy and lactation

The 2000 panel concluded: "[T]he panel has concern that ambient oral DEHP exposures to pregnant or lactating women may adversely affect the development of their offspring." The 2005 panel concluded: Estimates of exposure to DEHP for the adult human population range from 1–30 µg/kg body weight/day. Based upon this exposure estimate, the expert panel has **some concern** for the effects of DEHP on male offspring of humans exposed during pregnancy. This is a reduction in the level of concern from the first expert panel due to greater confidence in exposure levels in the general population and to greater confidence in the effect level in experimental animals. Further, this expert panel expressed **concern** for possible effects on male fetuses of women undergoing certain medical treatments where additional exposure to DEHP could occur. The 2006 final NTP report reaffirmed the findings of the 2005 panel for adult human exposures, and for male offspring of pregnant and lactating women undergoing medical treatment. The panel noted that for male infants "although DEHP exposures are assumed to be the same as for the general population, the developing male reproductive tract is sensitive to the adverse effects of DEHP."

*Note: Levels of concern expressed by expert panels include negligible concern, minimal concern, some concern, concern, and serious concern. The NTP Panel was only charged with assessing the reproductive and developmental toxicity of DEHP. It did not consider other potential toxicological effects of DEHP.

United States — Food and Drug Administration (FDA) — Safety Assessment (2001)

The FDA, which assessed the safety of DEHP use in polyvinyl chloride PVC medical devices, concluded that exposures to patients during the following medical procedures may exceed the Agency's tolerable intake level for DEHP:

- All patients receiving enteral nutrition;
- Infants receiving total parenteral nutrition (TPN) with lipids;
- Infants undergoing exchange transfusions;
- Adults and infants undergoing extracorporeal membrane oxygenation (ECMO) therapy;
- Adults undergoing cardiopulmonary bypass; and
- Nursing infants or fetuses of mothers on hemodialysis.
    - Infants undergoing multiple procedures (high cumulative exposure)
    - Hemodialysis in peripubertal males

United States — Food and Drug Administration (FDA) — Public Health Notification (2002)

In 2002, the FDA issued a public health notification pointing out that, for some of the above procedures, PVC devices that do not contain DEHP can be substituted, or devices made of other materials (such as ethylene vinyl acetate (EVA), silicone, polyethylene or polyurethane) can be used, if available. The FDA notification recommends "considering such alternatives when these high-risk procedures are to be performed on male neonates, pregnant women who are carrying male fetuses, and peripubertal males."

Canada — Health Canada — Expert Advisory Panel on DEHP (2002)

The Expert Advisory Panel proposed a risk management strategy to Health Canada to address the hazards posed by DEHP to human health in medical devices. The Panel recommended that "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)."

Therefore:

- "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 ...clinical practice guidelines..."
- "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."
- "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, cardio-pulmonary by-pass, exchange transfusion, hemodialysis, TPN and lipophilic drug formulations."

RESTRICTIONS ON DEHP USE IN THE EUROPEAN UNION

European Union Directives Restricting the Use of DEHP in Products (2001)

DEHP is classified as toxic to reproduction according to the EU Directive 67/548/EEC on Classification and Labeling of Dangerous Substances. This means that it "may impair fertility" and "may cause harm to the unborn child." The EU directive is limited to chemical preparations and does not restrict the use of DEHP in products such as medical devices. In the EU, DEHP has been banned in cosmetics and certain toys and children's products.[1]

European Union — Draft Risk Assessment, 2004

(prepared by the Swedish Chemicals Inspectorate)

The Swedish Chemicals Inspectorate (KemI) in its report for the European Union assessed the toxicity of DEHP for all human populations. It concluded that DEHP poses risks to many sub-populations. "Due to the wide spread use and exposure to humans of DEHP and the ability of the substance to cause effects on fertility and foetal development,"there is need for limiting the risks from DEHP exposure for human health for:

- Patients:
  - Neonates receiving transfusions
  - Children receiving long-term blood transfusion or extracorporeal oxygenation
  - Adults receiving long term hemodialysis
- Children:
  - from toys and baby equipment, from indoor air and from car interiors
  - living near plastic manufacturing facilities
  - living near non-polymer formulation facilities
  - living near municipal sewage treatment plants and paper recycling facilities
- Workers during the:
  - manufacture of DEHP
  - industrial use of DEHP
  - industrial end-use of products containing DEHP

European Union — Draft Risk Reduction Strategy, 2005

(prepared by the Swedish Chemicals Inspectorate)

The draft Risk Reduction Strategy proposes a set of legislative actions to limit the risks of DEHP exposure to all vulnerable populations. The recommended actions include:

- "the use of DEHP should be restricted in medical devices giving rise to exposure of neonates and groups identified to be of concern in the RAR [risk assessment report] assuming availability of safe alternatives;"
- "the use of DEHP should be restricted in toys and child care articles (*decision finalised*);"
- "the use of DEHP should be restricted in packaging materials (*action under discussion that would add to reduced exposure from multiple pathways*);"
- "The use of DEHP should be restricted in products with high production volume and giving rise to outdoor exposure, e.g. roofing, coil coating, cables, coated fabric, hoses, profiles, car undercoating, shoe soles;" and

- "Concentrations of DEHP in sewage sludge, in cow's milk and in human breast milk should be periodically followed on community level as additional important markers for environmental emissions and continuous exposure to DEHP. A comprehensive community follow up of the outcome of actions taken should be initiated. It should include workplace exposure, environmental emissions and concentrations in sewage sludge, in cow's milk as well as in human breast milk. If by 2010 this community follow up indicates an insufficient reduction of direct and indirect exposure of humans, a ban on all remaining uses of DEHP should be activated. (*further action, to be taken after having monitored achieved results*)."

European Parliament's Resolution on DEHP (2001, 2005)

In 2001, the European Parliament adopted a resolution in response to the Commission Green Paper on environmental issues of PVC and called for the Commission and the PVC industry to examine how targets might be set to reduce the use of phthalates, including DEHP, particularly in medical equipment. The resolution also asked the Commission to examine alternatives to the uses of phthalates as plasticizers.

In February 2005, the European Parliament brought this issue again to the forefront by adopting a resolution on the European Environment & Health Action Plan 2004-2010. The resolution called for restricting the market and/or use of dangerous substances, including DEHP, in domestic products for indoor use and in medical devices, specifically for vulnerable groups, particularly new-born babies, children, pregnant women, elderly persons, workers and other high-risk sections of the population that are heavily exposed.

European Chemicals Agency, (2008)

In 2008, the European Chemical Agency (ECHA), Member State Committee released the Support Document for Identification of Bis (2-ethylhexyl) Phthalate (DEHP) as a Substance of Very High Concern. The ECHA included DEHP among the first group of 15 "very high concern' chemicals identified as part of the EU chemical regulation Registration, Evaluation and Authorization of Chemicals (REACH). The evaluation of DEHP classifies the chemical as a substance toxic to reproduction, noting that it may impair fertility and may cause harm to the unborn child. The European Commission will evaluate substances placed on the 'Candidate List' and will make recommendations for which substances to advance to an Authorisation List, with action anticipated in June, 2009.

German Federal Institute for Drugs and Medical Devices (BfArM) (2004)

In 2004, the German Federal Institute for Drugs and Medical Devices (BfArM) issued a warning to health care professionals in order to minimize exposure to DEHP primarily for high-risk patient groups. These include fetuses, premature infants and newborns, as well as children in pre-puberty age. It was recommended that:

- medical devices manufacturers actively engage and strive for further development of safer DEHP-free alternative products;
- manufacturers consequently provide users with a comprehensive explanation on the risks of DEHP in medical devices as well as label correspondingly their products;
- neonatal intensive care units use alternative products if available and suitable for the relevant procedure in order to act with precaution and therefore avoid DEHP exposure for premature infants and newborns.

California — Office of Environmental Health Hazard Assessment (OEHHA) (2003)

In 2003, the state of California's OEHHA listed DEHP as a reproductive toxicant under the Safe Drinking Water and Toxic Enforcement Act of 1986. In California, manufacturers and others who make or use products containing DEHP are now required to provide warnings to consumers that their products contain a chemical known by the state of California to cause reproductive toxicity.

The American Medical Association (2006)

Responding to the science regarding adverse health impacts related to DEHP exposures, the American Medical Association (AMA) approved in December, 2006, a resolution encouraging hospitals and physicians to phase out of PVC medical devices, especially those containing DEHP, and urged adoption of safe, cost-effective, alternative products where available. The resolution also urges expanded manufacturer development of safe, cost-effective alternative products to PVC medical device products, especially those containing DEHP.

Phthalates and US Federal Regulatory Policy Consumer Product Safety Improvement Act of 2008 (2008)

In 2008, the U.S. Congress passed the **Consumer Product Safety Improvement Act of 2008**, which includes a federal ban on phthalates in toys and children's products, taking action to reduce exposures and protect

children's health. DEHP is one of six phthalates banned from children's products through this federal legislation. (See Section SEC. 108. PROHIBITION ON SALE OF CERTAIN PRODUCTS CONTAINING SPECIFIED PHTHALATES).

The National Academy of Sciences

The National Academy of Sciences in their report, *Phthalates and Cumulative Risk Assessment: The Task Ahead*, recommends that risks associated with phthalate exposure should be considered in the context of cumulative exposures to all phthalates and other anti-androgens. When infants, toddlers, fetuses/ pregnant women are exposed to DEHP from medical devices it adds to the already existing burden of chemicals that may also interfere with normal development of the reproductive tract. This highlights the concern for risk of harm from exposures to DEHP, placing added importance on the FDA public health notification and the NTP findings, and the need to phase out DEHP to protect health.

Endnotes

1. Toys: DIRECTIVE 2005/84/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 14 December 2005 amending for the 22nd time Council Directive 76/769/EEC on the approximation of the laws, regulations and administrative provisions of the Member States relating to restrictions on the marketing and use of certain dangerous substances and preparations (phthalates in toys and childcare articles) Official Journal of the European Union, L 344/40, 27. December 2005. Cosmetics: COUNCIL AND EUROPEAN PARLIAMENT DIRECTIVE 2003/15/EC of 27 February 2003 amending Council Directive 76/768/ EEC on the approximation of the laws of the Member States relating to cosmetic products. Official Journal of the European Union, L 66/26, 11.March 2003

Further Information and Bibliography

For detailed summaries of the government studies see the Health Care Without Harm website at www. noharm.org. For the complete reports, see the citations below.

California Environmental Protection Agency Office of Environmental Health Hazard Assessment, Safe Drinking Water and Toxic Enforcement Act of 1986 (Proposition 65) — Notice to Interested Parties, October 24, 2003. *Chemical Listed October 24, 2003 as Known to the State of California to Cause Reproductive Toxicity*. Cal EPA.

COMMISSION DIRECTIVE 2001/59/EC of 6 August 2001 adapting to technical progress for the 28th time Council Directive 67/548/EEC on the approximation of the laws, regulations and administrative provisions relating to the classification, packaging and labeling of dangerous substances. Official Journal of European Union, L 225/1 21.AUG 2001.

Consumer Product Safety Improvement Act of 2008; U.S. Consumer Product Safety Commission. http://www.cpsc.gov/ cpsia.pdf

European Chemicals Agency; Candidate List for Chemicals of Very High Concern for Authorisation. http://echa.europa.eu/ chem_data/candidate_list_table_en.asp Support Document: For Identification of Bis (2-Ethylhexyl) Phthalate (DEHP) as a Substance if Very High Concern. http:// echa.europa.eu/doc/candidate_list/svhc_ supdoc_dehp_publication.pdf

European Parliament resolution on the Commission Green Paper on environmental issues of PVC (COM(2000) 469 - C5-0633/2000 - 2000/2297(COS)). Texts Adopted by Parliament: 03.April 2001, also available at http://www.europarl.eu.int/omk/ omnsapir.so/pv2?PRG=CALDOC&FILE= 010403&LANGUE=EN&TPV=PROV&S DOCTA=8&TXTLST=1&Type_ Doc=FIRST&POS=1

European Parliament resolution on the European Environment & Health Action Plan 2004-2010 (2004/2132(INI)), P6_ TA(2005)0045. A6-0008/2005. Texts adopted by Parliament Wednesday 23 February 2005. More at http://www. europarl.eu.int/omk/sipade3?PUBREF=-// EP//TEXT+TA+20050223+ITEMS+DOC +XML+V0//EN&LEVEL=3&NAV= X#sdocta10

German Federal Institute for Drugs and Medical Devices - Bundesinstitut für Arzneimittel und Medizinprodukte.: DEHP als Weichmacher in Medizinprodukten aus PVC (DEHP as a softener in PVC Medical Devices). Referenz-Nr.: 923/0604. 24. June 2004. Recommendations available at http://www.bfarm.de/cln_042/nn_424524/ DE/Medizinprodukte/riskinfo/recommend/ dehp__Weichmacher__Medizinprod.html

Health Canada – Medical Devices Bureau, Therapeutic Products Directorate, Health Products and Foods Branch. 2001. *DEHP in Medical Devices: An Exposure and Toxicity Assessment*. Ottawa: Health Canada.

Health Canada – Medical Devices Bureau, Therapeutic Products Directorate, Health Products and Foods Branch. 2002. *Health Canada Expert Advisory Panel on DEHP in Medical Devices: Final Report 2002 January 11*. Ottawa: Health Canada.

The National Academy of Sciences; Phthalates and Cumulative Risk Assessment: The Task Ahead. 2008. Committee on the Health Risks of Phthalates; Board on Environmental Studies and Toxicology; Division on Earth and Life Studies. National Research Council *of The National Academies;* The National Academies Press. Washington, D.C.

National Toxicology Program (NTP), Center for the Evaluation of Risks to Human Reproduction (CERHR). 2000. *NTP CERHR Expert Panel Report on Di (2-ethylhexyl) Phthalate*. Alexandria, VA: NTP CERHR.

National Toxicology Program (NTP), Center for the Evaluation of Risks to Human Reproduction (CERHR). November 2005. *NTP CERHR Expert Panel Update on Reproductive and Developmental Toxicity of Di (2-ethylhexyl) Phthalate*. Alexandria, VA: NTP CERHR

National Toxicology Program, Center for the Evaluation of Risks to Human Reproduction, DEHP Monograph (pdf), November 2006

>>

Swedish National Chemicals Inspectorate. 2005. *Risk Assessment: bis(2-ethylhexyl) phthalate* (Final Draft). CAS-No.: 117-81-7, EINECS-No.: 204-211-0. Solna, Sweden: KemI.

Swedish National Chemicals Inspectorate (KemI). 2005. Risk Reduction Strategy DEHP Human Health: Bis(2-ethylhexyl) phthalate (Draft: October 2005). CAS-No.: 117-81-7, EINECS-No.: 204-211-0. Solna, Sweden: KemI.

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: U.S. FDA.

United States Food and Drug Administration (FDA), Center for Devices and Radiological Health. 2002. *FDA Public Health Notification: PVC Devices Containing the Plasticizer DEHP*. Rockville, MD: U.S. FDA.

Health Care Without Harm

1901 North Moore St.
Suite 509
Arlington, VA 22209
Phone: 703.243.0056
Fax: 703.243.4008
www.noharm.org
info@hcwh.org

This publication is part of *Going Green: A Resource Kit for Pollution Prevention in Health Care*. For additional copies of this or other publications included in the kit, or to find out how to get a complete kit, visit Health Care Without Harm on the Web at www.noharm.org/goinggreen.