



Center For The Evaluation Of Risks To Human Reproduction

**DRAFT
May 2006**

**NTP Brief on the
Potential Human Reproductive and
Developmental Effects of
Di(2-ethylhexyl) Phthalate (DEHP)**

INTRODUCTION

DEHP (di(2-ethylhexyl) phthalate; CAS RN 117-81-7) is a high production volume chemical used as a plasticizer of polyvinyl chloride in the manufacture of a wide variety of consumer products, such as building products, car products, clothing, food packaging, and children's products (but not in toys intended for mouthing), and in medical devices made of polyvinyl chloride.

In 1999–2000, the CERHR Phthalates Expert Panel evaluated DEHP and six other phthalates for reproductive and developmental toxicities. Since release of the CERHR Expert Panel Report on DEHP in 2000, approximately 70 papers relevant to human exposure and reproductive and/or developmental toxicity of DEHP have been published. Because most people in the United States are exposed to DEHP and it is known to cause adverse effects on reproduction and development in laboratory animals, there is considerable interest in its possible health effects on people. For these reasons, the CERHR convened an expert panel to conduct an updated evaluation of the potential reproductive and developmental toxicities of DEHP.

The NTP-CERHR Monograph on DEHP includes the NTP Brief on DEHP, a list of the expert panel members (Appendix I), the expert panel's report on DEHP (Appendix II), and all public comments received on the expert panel's report on DEHP (Appendix III). The NTP-CERHR monograph is intended to serve as a single, collective source of information on the potential for DEHP to adversely affect human reproduction or development. Those interested in reading this report may include individuals, members of public interest groups, and staff of health and regulatory agencies.

The NTP Brief on DEHP presents the NTP's interpretation of the potential for exposure to DEHP to cause adverse reproductive or developmental effects in people. The NTP brief is intended to provide clear, balanced, scientifically sound information. It is based on information about DEHP provided in the expert panel report, public comments on the expert panel report, comments from peer reviewers on the NTP Brief, and additional scientific information available since the expert panel meeting.

DEVELOPMENTAL TOXICITY AND REPRODUCTIVE TOXICITY

The CERHR evaluation process addresses effects on both development and reproduction. While there are biological and practical reasons for considering developmental toxicity and reproductive toxicity as two separate issues, a clear separation of the two is not always possible. It is important to keep in mind that life in mammals, including humans, is a cycle. In brief, the cycle includes the production of sperm and eggs, fertilization, prenatal development of the offspring, birth, postnatal development, sexual maturity, and, again, production of sperm and eggs.

Toxic effects are often studied in a “life stage specific” manner. Thus, developmental toxicity is typically studied by exposing pregnant laboratory animals to the substance of interest and looking for adverse effects on development of the resulting offspring. Developmental toxicity can be detected as death, structural malformations, or reduced weights of the fetuses just prior to birth or abnormal structural or functional development after birth. Reproductive toxicity is often studied by exposing sexually mature animals to the substance of interest and effects are detected as impaired capacity to reproduce.

Over the years, toxicologists realized that exposure during one part of the life cycle may lead to adverse effects that are apparent only at a different stage of the life cycle. For example, exposure of a sexually mature animal to a substance capable of inducing genetic damage in eggs or sperm might have no apparent effect on the exposed individual. How-

ever, if a genetically damaged egg or sperm from that individual is involved in fertilization, the genetic damage might lead to death of offspring before they are born or a genetic disorder in the surviving offspring. In this example, chemical-induced damage in the germ cells is observed as a developmental disorder in the next generation.

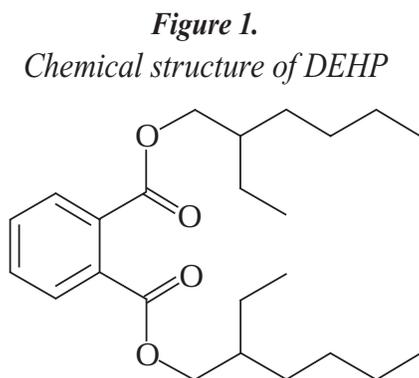
In contrast, development of both the male and female the reproductive systems begins well before birth and continues until sexual maturity is attained. Thus, the exposure of sexually immature animals, either before or following birth, to agents that adversely affect development of the reproductive system can result in structural or functional reproductive disorders. These effects may become apparent only when reproductive studies are conducted after the exposed individual reaches sexual maturity.

Thus, in the case of genetic damage induced in eggs or sperm, damage to reproductive cells gives rise to developmental disorders. Conversely, in the case of adverse effects on development of the reproductive tract, developmental toxicity results in reproductive disorders. In both of these examples it is difficult to make a clear distinction between developmental and reproductive toxicity. This issue is important in the present evaluation because laboratory animal studies provide evidence that DEHP exposure before or soon after birth can cause developmental toxicity affecting reproductive capacity in later stages of the life cycle.

NTP BRIEF ON DEHP

What is DEHP?

DEHP is an oily liquid with the chemical formula $C_{24}H_{38}O_4$ and the structure is shown in Figure 1.



It is one of a group of industrially important chemicals known as phthalates. Phthalates are used primarily as plasticizers to add flexibility to plastics. DEHP is used in a wide variety of products including flooring, wallpaper, auto upholstery, raincoats, toys, and food packaging. It is not used in toys intended for mouthing, such as nipples or teething rings. DEHP is currently the only phthalate plasticizer used in polyvinyl chloride (PVC) medical devices such as blood bags and tubing.

DEHP is produced by reacting 2-ethylhexanol with phthalic anhydride. In 2002 the Agency for Toxic Substances and Disease Registry (ATSDR) estimated that 241 million pounds of dioctyl phthalates (including DEHP) were produced in the United States in 1999.

Are People Exposed to DEHP?*

Yes. There are several ways that people may be exposed to DEHP at home, at work, or through medical procedures. Human exposure to DEHP can occur during the manufacture of DEHP, the manufacture of DEHP-containing products, the use of such products, and through the presence of DEHP in the environment.

Environmental exposures can occur through air, water, or food. The primary source of DEHP exposure for most people is through food. DEHP migrates into foods, particularly fatty foods, from DEHP-containing materials that are used to process and package food. Indoor air is another common source of exposure. In the National Health and Nutrition Examination Survey (NHANES) 1999–2000 conducted by the Centers for Disease Control and Prevention, a DEHP urinary metabolite, mono (2-ethylhexyl) phthalate (MEHP), was detected in 78% of the 2541 samples tested. This may be an underestimate of the portion of people exposed to DEHP because two other urinary metabolites of DEHP not screened for in the 1999–2000 study were subsequently reported to occur in higher concentrations in human urine (Silva et al., 2004).

Can DEHP Affect Human Development or Reproduction?

Probably. Although there is no direct evidence that exposure of people to DEHP adversely affects reproduction or development, studies with laboratory rodents clearly show that exposure to DEHP can cause adverse effects on development and reproduction (See Figures 2a & 2b). Based on recent data on the extent to which humans absorb, metabolize and excrete DEHP, the NTP believes it is reasonable and prudent to conclude that the results reported in laboratory animals indicate a potential for similar or other adverse effects in human populations.

Scientific decisions concerning health risks are generally based on what is known as the “weight-of-evidence.” In this case, recognizing the lack of sufficient data on the effects of

* Answers to this and subsequent questions may be: *Yes, Probably, Possibly, Probably Not, No or Unknown*

DEHP in humans and the clear evidence of effects in laboratory animals, the NTP judges the scientific evidence sufficient to conclude that DEHP may adversely affect human reproduction or development if exposures are sufficiently high (See Figure 3).

Supporting Evidence

The CERHR Expert Panel Update Report on DEHP (Appendix II) provides details and citations regarding studies on the possible reproductive and developmental toxicity of DEHP.

Several human studies were evaluated by the panel but none provided sufficient evidence

that DEHP causes developmental toxicity when exposure occurs prenatally or during childhood. There was also insufficient evidence that DEHP causes reproductive toxicity in studies of DEHP-exposed adults. Some of the experimental factors limiting the usefulness of these studies were small sample size, lack of exposure measurements, and uncertainty in the interpretation of the study endpoints.

As presented in both the earlier and present DEHP expert panel reports, a large body of data addresses the adverse developmental and reproductive effects of DEHP in laboratory animals. Results from developmental toxicity

Figure 2a. The weight of evidence that DEHP causes adverse developmental or reproductive effects in humans

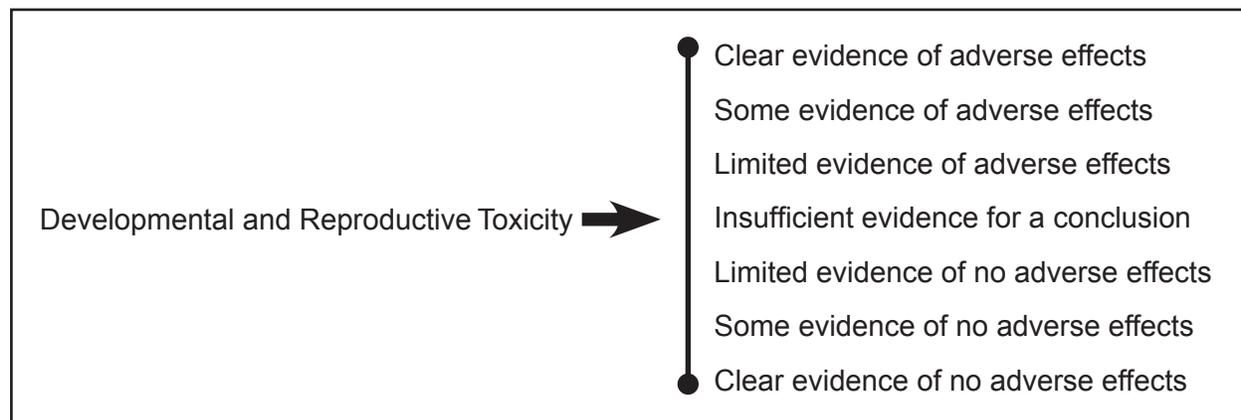


Figure 2b. The weight of evidence that DEHP causes adverse developmental or reproductive effects in laboratory animals

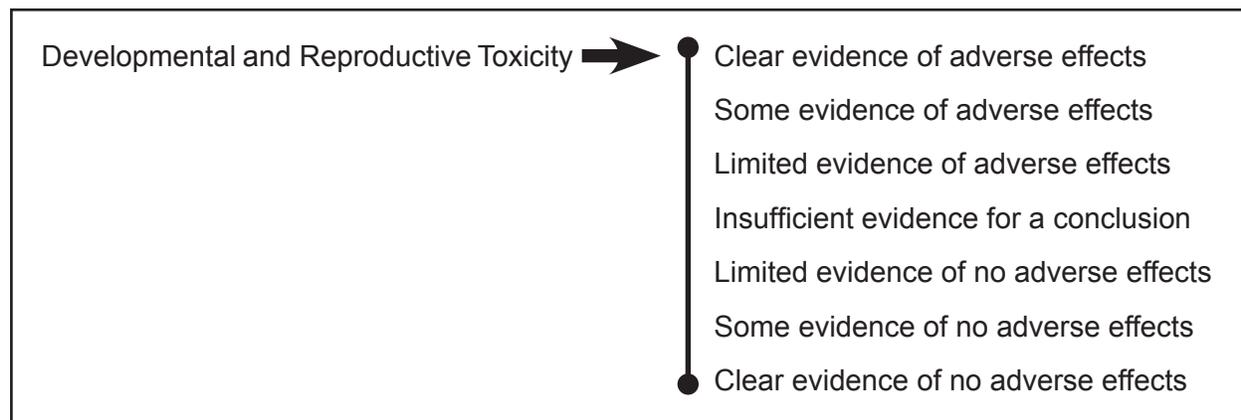
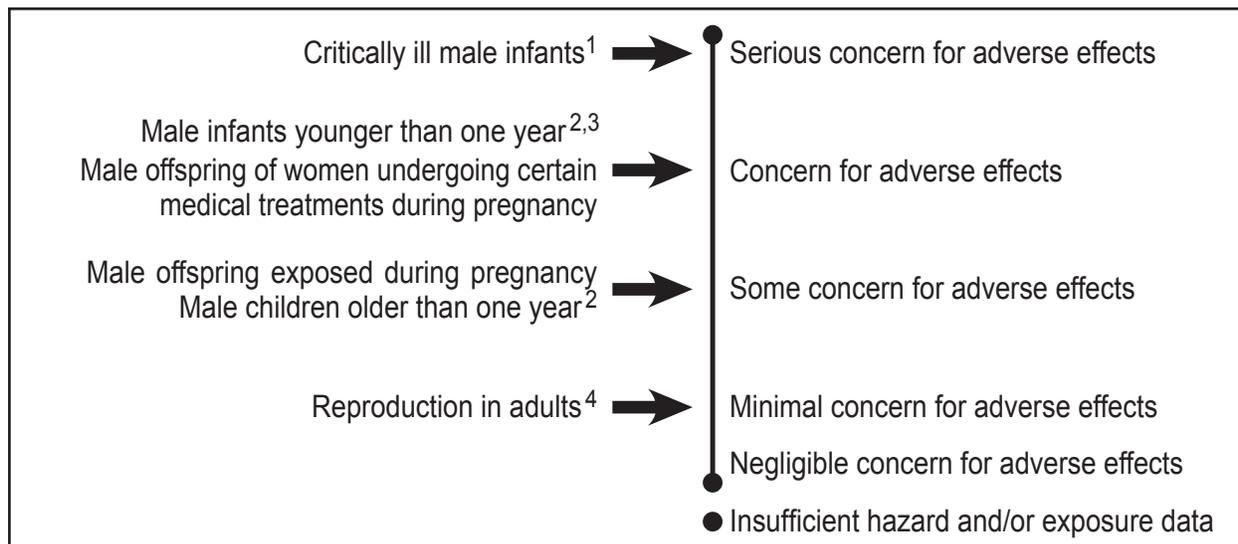


Figure 3. NTP conclusions regarding the possibilities that human development or reproduction might be adversely affected by exposure to DEHP



¹ Based on estimated DEHP exposures as high as 6000 µg /kg bw/day

² Based on exposures at the high end of an estimated exposure range of 1–30 µg/kg bw/day

³ Includes exposure through breast-feeding in infants younger than 1 year

⁴ Based on estimated exposures of 1–30 µg/kg bw/day

studies in mice and rats provide a consistent pattern of adverse effects following DEHP exposure. Oral exposure to approximately 100–200 mg/kg bw/day of DEHP during gestation typically results in skeletal and cardiovascular malformations, neural tube defects, developmental delays, and intrauterine death of the offspring. Studies such as these, in which examination of pups occurs in the prenatal or immediate postnatal period, provide only limited information on the effects of DEHP. This is because adverse effects on the reproductive tract may become apparent only at later stages of development. DEHP exposure has been shown to adversely affect reproduction in several species including mice, rats, guinea pigs, and ferrets. While effects have been reported in both males and females, the early development of the reproductive system of males appears to be more sensitive to the adverse effects of DEHP.

Exposure of rats to DEHP-containing feed

during gestation and/or early postnatal life at 14–23 mg/kg bw/day or greater results in adverse effects on the developing male reproductive tract, effects such as abnormally small or absent male reproductive organs. Other studies at higher doses result in similar adverse effects on the developing male reproductive tract. Adverse effects on the developing female reproductive tract occur in rats exposed to 1088 mg/kg bw/day DEHP in the feed.

One new reproductive toxicity study in non-human primates was available to the DEHP Update Panel. Following 65 weeks oral exposure of marmosets from the juvenile stage through young adulthood to 100, 500, or 2,500 mg/kg bw/day DEHP no adverse changes in the male reproductive tract were observed. Because of differences between marmosets and humans in intestinal lipase activity, absorption and excretion of DEHP, and testosterone levels during development of the male reproductive tract, there is uncertainty as to the utility of the

marmoset as a model for studying the possible effects of DEHP on development of the human male reproductive tract. In addition, this marmoset study encountered problems with the health and growth of the study animals and did not investigate the most sensitive stage in the development of the male reproductive tract, i.e., the perinatal period.

Are Current Exposures to DEHP High Enough to Cause Concern?

Yes. Potentially high exposures of fetuses and infants to DEHP may lead to adverse effects on the developing male reproductive tract. High DEHP exposures of fetuses and infants can occur when pregnant and breast-feeding women undergo certain medical procedures involving DEHP-containing polyvinyl chloride medical devices. Infants may also be exposed to high levels of DEHP through medical procedures, diet, and/or mouthing of DEHP-containing objects. Based on the estimated high levels of exposure that can occur during intensive medical treatments of ill infants and on the apparent sensitivity of the developing male reproductive tract to DEHP, there is particular concern for this subpopulation. The general adult population presently appears to be exposed to DEHP at levels that are not expected to cause adverse effects to the reproductive system. However, more data are needed to better understand human DEHP exposure levels and how these exposures vary across the population. The NTP offers the following conclusions regarding the potential for DEHP to adversely affect human reproduction and development of children.

The NTP concurs with the CERHR DEHP Update Expert Panel that there is serious concern that certain medical treatments of male infants may adversely affect development of the male reproductive tract.

This conclusion is based on the apparent sensitivity of the developing male reproductive

tract and the estimated high levels of DEHP exposure that can occur during intensive medical treatments of ill infants. Such exposures were estimated to be as much as 100 to 1000 times higher than exposures in the general population. The NTP also acknowledges, as did the expert panel, that the health benefits of these medical procedures may outweigh any risks. It is noteworthy that both the U.S. Food and Drug Administration (FDA, 2001) and Health Canada (Health Canada, 2002) used the CERHR Phthalates Expert Panel Report on DEHP in conducting their own assessments of the safety of DEHP-containing medical devices. Both agencies point out that infants and children undergoing certain medical procedures may be at increased risk for adverse effects of exposure to DEHP.

The NTP concurs with the CERHR DEHP Update Expert Panel that there is concern for adverse effects on male offspring of pregnant and breast-feeding women undergoing certain medical procedures that may result in high levels of exposure to DEHP.

DEHP exposure levels in adults undergoing certain medical procedures can be as much as 1000-fold greater than exposure of the general population. Because DEHP metabolites can cross the placenta and enter breast milk, fetuses and nursing infants may experience elevated DEHP exposures if their mothers undergo such medical procedures.

The NTP concurs with the CERHR DEHP Update Expert Panel that there is concern for effects on development of the male reproductive tract for infants less than one year old.

This level of concern is based on the uncertainty regarding DEHP exposure levels in this population, the greater activity of enzymes (lipases) that convert DEHP to its toxic form, and the possibility that the developing male reproduc-

tive tract will be more sensitive to the adverse effects of DEHP than in children older than one year. Although there is uncertainty regarding levels of DEHP exposure in this age group, there is the potential for DEHP exposures to exceed those of the general population. Such elevated exposures may occur through medical procedures, diet (to include breast-feeding), and/or mouthing of DEHP-containing objects.

The NTP concurs with the CERHR DEHP Update Expert Panel that there is some concern for exposure of male children older than one year.

This level of concern is based on the apparent sensitivity of the developing male reproductive tract to the adverse effects of DEHP and the potential for DEHP exposures in children to exceed those of the general population. Recent studies provide greater confidence in DEHP exposure levels in children, exposures that may occur through medical procedures, diet, and/or mouthing of DEHP-containing objects.

The NTP concurs with the CERHR DEHP Update Expert Panel that for pregnant women not medically exposed to DEHP, available toxicity data and estimates of human exposure to DEHP lead to a conclusion of some concern for adverse effects on male offspring.

“Some concern” is a lower level of concern than that expressed for pregnant and breast-feeding women by the previous CERHR Phthalates Expert Panel. This lower level of concern is based on a greater confidence in the estimated DEHP exposure levels in women of childbearing age, a greater confidence in the DEHP exposure levels at which adverse effects are observed in laboratory rodents, and evidence that humans have lower levels of enzymes (lipases) that activate DEHP than rodents. Further, exposure estimates for women of childbearing age, i.e., the age group that would be pregnant or breast-

feeding, not medically exposed to DEHP are the same as for the general population (1–30 $\mu\text{g}/\text{kg}$ bw/day). While studies of DEHP effects in humans and non-human primates are not sufficient to draw conclusions, data from recent studies in rodents provide evidence that no adverse effects are observed in development of the male reproductive tract following DEHP exposure of the pregnant dams to less than 10 mg/kg bw/day.

The NTP concurs with the CERHR DEHP Update Expert Panel that there is minimal concern for reproductive toxicity in exposed adults. This level of concern is not altered for adults medically exposed to DEHP or MEHP.

This conclusion for the general population is based on an estimated range of DEHP exposures of 1–30 $\mu\text{g}/\text{kg}$ bw/day. Based on data from rodent studies the adult reproductive tract is expected to be much less sensitive than the developing reproductive tract to the adverse effects of DEHP exposure. Finally, adult rodents have higher intestinal lipase activity than adult humans and are expected to produce higher levels of MEHP, a biologically active metabolite. Thus, adult humans are expected to be less sensitive than adult rodents to the reproductive toxicity effects of a given dose of DEHP.

These conclusions are based on the information available at the time this brief was prepared. As new information on toxicity and exposure accumulates, it may form the basis for either lowering or raising the levels of concern expressed in the conclusions.

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