Pediatric Exposure and Potential Toxicity of Phthalate Plasticizers

ABSTRACT. Phthalates are plasticizers that are added to polyvinyl chloride (PVC) products to impart flexibility and durability. They are produced in high volume and generate extensive though poorly defined human exposures and unique childhood exposures. Phthalates are animal carcinogens and can cause fetal death, malformations, and reproductive toxicity in laboratory animals. Toxicity profiles and potency vary by specific phthalate. The extent of these toxicities and their applicability to humans remains incompletely characterized and controversial. Two phthalates, diethylhexyl phthalate (DEHP) and diisononyl phthalate (DINP), have received considerable attention recently because of specific concerns about pediatric exposures. Like all phthalates, DEHP and DINP are ubiquitous contaminants in food, indoor air, soils, and sediments. DEHP is used in toys and medical devices. DINP is a major plasticizer used in children's toys.

Scientific panels, advocacy groups, and industry groups have analyzed the literature on DEHP and DINP and have come to different conclusions about their safety. The controversy exists because risk to humans must be extrapolated from animal data that demonstrate differences in toxicity by species, route of exposure, and age at exposure and because of persistent uncertainties in human exposure data. This report addresses sensitive endpoints of reproductive and developmental toxicity and the unique aspects of pediatric exposures to phthalates that generate concern. DEHP and DINP are used as specific examples to illustrate the controversy.

ABBREVIATIONS. PVC, polyvinyl chloride; DEHP, diethylhexyl phthalate; DINP, diisononyl phthalate; MEHP, monoethylhexyl phthalate; ECMO, extracorporeal membrane oxygenation; NOAEL, no observable adverse effect level; LOAEL, lowest observable adverse effect level; CERHR, Center for the Evaluation of Reproductive Risks to Humans; DBP, dibutyl phthalate.

BACKGROUND INFORMATION

Sources, Uses

Phthalates are plasticizers that impart flexibility and durability to polyvinyl chloride (PVC) products, including building materials, food packaging, clothing, toys, children's products, blood bags, intravenous fluid bags and infusion sets, and other medical devices. They are also used in solvents, lubricating oils, fixatives, and detergents and in products such as cosmetics and wood finishes. Phthalates are not co-valently bound to the plastic matrix and leach out of PVC when they come in contact with lipophilic substances. In addition, they are released directly into the environment during production and use and after disposal of PVC and other phthalate-containing products. Phthalates bioaccumulate in invertebrates, fish, and plants but do not biomagnify, because higher animals efficiently metabolize and excrete phthalates. They are ubiquitous contaminants in food, indoor air, soils, and sediments.

Human Exposure

Levels of human exposure are estimated on the basis of annual production volumes and usage patterns of phthalate-containing products as well as environmental monitoring data, dietary surveys, and mathematical modeling of human activity patterns. These exposure estimates are imprecise and subject to error. Environmental monitoring data are best for diethylhexyl phthalate (DEHP), which is produced in volumes approaching 2 million tons per year. In the general population, the major source of human exposure is food contaminated during growth, production, processing, or packaging. Food surveys have documented the highest levels in fatty foods, such as dairy (including infant formulas), fish, meat, and oils. These surveys vary significantly among nations and over time because of differences in food production and consumption patterns, but the most recent analyses of infant formulas show significant decreases in contamination with DEHP and all other phthalates tested. The second highest source of exposure is indoor air, where DEHP adheres strongly to aerosol particles. Because of its low water solubility and low vapor pressure, little DEHP is found in outdoor air or water. It is estimated that exposure to DEHP in the general population (excluding occupational exposure, medical exposures, and nondietary ingestions in children) is in the range of 3 to 30 µg/kg of body weight per day. Exposures to other phthalates, including diisononyl phthalate (DINP), are usually assumed to be lower primarily because production volumes are lower.

Pediatric Exposure

Phthalates have been shown in animal studies to cross the placenta and pass into breast milk, so
prenatal exposure and exposure from breastfeeding may occur in humans. Infants and young children consume more calories per kilogram of body weight, consume relatively more dairy and other fatty foods, and have higher minute ventilation than do adults, so dietary exposures and exposure from indoor air would be expected to be higher in infants and young children. It is estimated that the total intake of DEHP, excluding nondietary ingestion, is higher in all children younger than 19 years than in adults. Nondietary ingestion can be expected with leaching rates in mouthing studies, so simple phthalate content of a product does not correlate with the amount of exposure or with phthalate-containing objects in mouthing studies performed in adults. The phthalate content of a product does not correlate with leaching rates in mouthing studies, so simple extrapolation of exposure from phthalate content is not possible. Nondietary ingestion can be expected to increase total exposure by an order of magnitude or more. In the United States and Canada, this uncertainty in predicting exposure levels, especially in very young children and infants, has led to the removal of all phthalates from infant bottle nipples, pacifiers, teethers, and infant toys intended for mouthing. DINP has been substituted for the more toxic DEHP in many other toys intended for older children.

### Pediatric Medical Exposures

Neonates can have high exposures to DEHP and its toxic monoester metabolite, monoethylhexyl phthalate (MEHP), when undergoing replacement of blood products, exchange transfusion, extracorporeal membrane oxygenation (ECMO), and other life-saving procedures. DEHP is the only phthalate currently used in medical devices.

PVC medical devices contain, on average, 20% to 40% DEHP by weight. DEHP imparts important qualities to PVC products, such as flexibility, strength, broad-range temperature tolerance, stability during sterilization, resistance to kinking, and optical clarity. It has been known since the early 1970s that DEHP and MEHP are infused with blood products and during hemodialysis. Beginning in the 1980s, investigators measured DEHP and MEHP delivered during neonatal exchange transfusions. More recently, large exposures have been documented during ECMO and cardiac surgery. Preliminary data also show possible exposure during mechanical ventilation if PVC circuitry is used. PVC infusion lines for lipid-containing parenteral nutrition may also deliver large amounts of DEHP to neonates. Empirical data have shown that neonatal medical exposure can be 3 orders of magnitude or more above exposures in the general population. For example, Sjoberg has documented neonatal exposure to DEHP of up to 3300 μg/kg (3.3 mg/kg) per exchange transfusion. The same investigator measured MEHP exposures and found that MEHP could be infused at 100 and 360 μg/kg (0.1 and 0.36 mg/kg) per exchange transfusion. Because very ill neonates receive multiple medical interventions, it is likely that total exposures to DEHP and MEHP could be even higher.

### Toxicology of Phthalates

Phthalates have not been shown to be acutely toxic. Chronic toxicity has been studied only in laboratory animals. A few occupational studies in humans have suggested some excess risk of adverse health effects with chronic exposure. A single case-control study found higher serum levels of several phthalates in girls with premature thelarche compared with girls in a control group. No short- or long-term follow-up studies have evaluated possible phthalate toxicity in medically exposed infants. Because human toxicity has not been well studied, animal toxicology data must be examined for relevance to human exposures. The toxicity of each phthalate ester depends on conversion of the parent compound to a toxic metabolite. The amount of conversion varies with route of exposure (ingestion, dermal absorption, inhalation, or intravenous exposure), the animal species studied, and age at which animals are exposed. These differences in toxicokinetics are well demonstrated by the data available on DEHP.

### Route of Exposure

The toxicokinetics of DEHP via all exposure routes have been studied in rodents. When DEHP is administered orally, it is rapidly metabolized by pancreatic lipases in the lumen of the gut to the toxic metabolite MEHP. MEHP, not DEHP, is readily absorbed across the intestine. Dermal absorption of DEHP is poor. Inhaled DEHP is absorbed as the parent compound and metabolized to MEHP, and both are broadly distributed throughout tissues in experimental animals. In rats, DEHP administered parenterally is converted to MEHP much less efficiently than is DEHP administered orally, and higher

### TABLE 1. Estimated Daily Intake of DEHP (μg/kg of Body Weight per Day)

<table>
<thead>
<tr>
<th>Substrate/Medium</th>
<th>0.0–0.5</th>
<th>0.5–4</th>
<th>5–11</th>
<th>12–19</th>
<th>20–70</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ambient air: Great Lakes region</td>
<td>0.00003–0.0003</td>
<td>0.00003–0.0003</td>
<td>0.00004–0.0004</td>
<td>0.00003–0.0003</td>
<td>0.00003–0.0003</td>
</tr>
<tr>
<td>Indoor air</td>
<td>0.86</td>
<td>0.99</td>
<td>1.2</td>
<td>0.95</td>
<td>0.85</td>
</tr>
<tr>
<td>Drinking water</td>
<td>0.13–0.38</td>
<td>0.06–0.18</td>
<td>0.03–0.10</td>
<td>0.02–0.07</td>
<td>0.02–0.06</td>
</tr>
<tr>
<td>Food</td>
<td>7.9</td>
<td>18</td>
<td>13</td>
<td>7.2</td>
<td>4.9</td>
</tr>
<tr>
<td>Soil</td>
<td>0.000064</td>
<td>0.000042</td>
<td>0.000014</td>
<td>0.000004</td>
<td>0.000003</td>
</tr>
<tr>
<td>Total estimated intake</td>
<td>8.9–9.1</td>
<td>19</td>
<td>14</td>
<td>8.2</td>
<td>5.8</td>
</tr>
</tbody>
</table>
doses are required to produce toxicity by the parenteral route.

Species Differences
The differences of most interest among species are those between rodents (for which the most toxicity data exist) and primates. Data on primates are limited but do illustrate important differences. Rodents have more intestinal lipase than primates do, so for any given oral dose, more toxic metabolite is likely to be absorbed in rodents than in primates. Metabolism and excretion pathways for MEHP are different in rodents than in primates, so the half-life of the toxic metabolite may differ. Absorption through rat skin, although poor, is better than through human cadaver skin; absorption of phthalates through the skin of premature infants has not been studied.

Age at Exposure
The toxicokinetics of DEHP are potentially quite different in very young and premature infants. In mature humans, like in rodents, DEHP is metabolized to MEHP by pancreatic lipase and absorbed through the gut. It is then glucuronidated and excreted, resulting in little or no tissue accumulation. In infants, pancreatic lipase systems are not fully mature until 6 to 12 months of age, suggesting a possible protective effect of immaturity by decreasing the creation and absorption of MEHP from oral DEHP exposures. Breast milk, salivary, and gastric lipases may, however, compensate and allow conversion of orally acquired DEHP to MEHP. Neither premature nor full-term infants have mature glucuronidation until about 3 months of age. Thus, this important clearance mechanism for MEHP is not fully available to neonates and young infants, and MEHP may have a longer half-life in the body. Levels of DEHP in plasma of children undergoing ECMO (parenteral exposure) are higher early in the course of treatment than they are toward the end, but it is not known whether this represents increased metabolism, improved elimination, or redistribution into the tissues. DEHP levels are higher at necropsy in premature neonates who have received varying levels of blood products compared with infants who have not received blood products. The toxicokinetics of MEHP have not been well studied in humans. Although less well studied, DINP and the other phthalates are likely to demonstrate similar toxicokinetic differences by route, species, and age at exposure.

General Toxicity (Toxicity in Mature Animals)
In mature animals, each phthalate has a different toxicity profile. The liver, kidneys, thyroid, and testes are common targets for general toxicity from oral exposures. Much of the concern about phthalates arises from reports beginning in the 1980s showing several to be carcinogens in rodents. DEHP causes liver cancers and DINP causes kidney and liver cancers in rodents. The mechanism of liver neoplasia caused by DEHP is believed to be attributable to peroxisome proliferation and a cascade of cellular events that do not occur in the human liver, but this theory remains to be confirmed. The mechanism of carcinogenesis of DINP in rodent liver is not fully understood but may also involve peroxisome proliferation. The development of kidney neoplasms in rodents caused by DINP may also be mediated through a mechanism that is not relevant in humans. No studies exist that evaluate perinatal phthalate exposure as a risk factor for adult cancers in humans. Nonetheless, research indicates that carcinogenic risk to humans from at least some of the phthalates may be lower than that to laboratory animals, and focus has shifted to other toxic endpoints.

Developmental and Reproductive Toxicity
Developmental (teratogenic) and reproductive toxicity are studied in laboratory animal systems by exposing adult males and females to chemicals before mating, during some or all of gestation and lactation, or continuously for multiple generations. Different conclusions can be drawn about developmental and reproductive toxicities depending on doses tested, route of administration, timing of exposure, and endpoints studied. Some studies use only high doses of a chemical to determine if any hazard exists. Other study designs use finer dose increments to establish the dose-response relationship to determine if there is a dose that is not associated with any adverse effect, also known as “no observable adverse effect level” (NOAEL). Some studies look at endpoints, such as gross malformations and fetal demise, and others examine tissues for histologic or biochemical abnormalities. Conclusions about human toxicity must be extrapolated from animal studies after considering the extent and strength of existing data sets, assessing the uncertainties remaining, and making judgments about the similarity of animal systems to human systems. As new studies accumulate, these conclusions are continuously revised.

Phthalates can produce fetal death, malformations, and reproductive toxicity with different profiles for each chemical. The different phthalates can also have quite different potencies. The extent of these toxicities and their applicability to humans remain incompletely characterized and controversial. Brief summaries of these animal data on DEHP and DINP follow.

Animal Data on DEHP
DEHP causes skeletal, cardiovascular, and eye abnormalities; neural tube defects; intrauterine death; increased postnatal death; and decreased intrauterine and postnatal growth in rodent pups whose dams received DEHP in feed or by gavage during pregnancy. A “lowest observable adverse effect level” (LOAEL) is observed with fetal toxicity occurring at the same dose or a lower dose than that causing mild maternal toxicity. Thus, fetal toxicity could occur without evidence of maternal toxicity after oral exposure.

The most sensitive system is the reproductive tract of immature males. Pathologic changes in the testes and decreased sperm numbers are consistent effects across studies. Changes in weight of the testes, vac-
onalization of Sertoli cells, and atrophy of the seminiferous tubules have been observed in rodent pups exposed to DEHP in utero via dietary exposure of dams (LOAEL, 38–141 mg/kg per day; NOAEL, 3.7–14 mg/kg per day). In a multigenerational study in which rodent pups of both sexes were exposed throughout prenatal and postnatal life and then mated, complete infertility was observed in females, and decreased fertility was observed in males. A rodent study of intravenous exposure found histologic abnormalities in Sertoli cell endoplasmic reticulum and changes in spermatocyte structure (LOAEL, 250 mg/kg per day; NOAEL, 25 mg/kg per day). In vitro studies demonstrated that the Sertoli cell is the primary cellular target and that MEHP is the toxic metabolite. Evidence suggests that the mechanism of reproductive toxicity in rodents is different from the mechanism of carcinogenesis.

Animal Data on DINP

The evidence on the toxicity of DINP is not as complete as that on the toxicity of DEHP. In general, DINP shows similar patterns of developmental toxicity, but at higher exposure levels. DINP has not been shown to cause reproductive toxicity. DINP causes skeletal and genitourinary abnormalities when rodent pups are exposed in utero at maternal oral doses of 500 to 1000 mg/kg per day (LOAEL), and as with DEHP, fetal toxicity can be seen at lower doses than can maternal toxicity. The single reported reproductive toxicity study in rodents found normal reproductive system structure and function at very high exposure levels but did not evaluate the full range of endpoints tested for DEHP.

Statement of Problem—Extrapolation to Risks to Humans

Expert panels, advocacy groups, and industry groups have analyzed the literature on DEHP and DINP and have come to different conclusions. The European Parliament has recommended bans on certain uses of phthalates and in the United States, manufacturers have voluntarily changed patterns of use. The controversy exists because risk to humans must be extrapolated from data on laboratory animals for chemicals that demonstrate differences in toxicity by species and route of exposure. Also, experimental exposures often differ from human exposure patterns in terms of dose (high versus low) and timing (acute versus chronic). It is not surprising that consensus has not been achieved.

The most intense disagreement surrounds DEHP and exposures from medical uses. The American Council on Science and Health (the “Koop report”) concluded “that DEHP, as used in medical devices, is unlikely to pose a health risk to even highly exposed humans.” The report stressed the benefits of DEHP in successful medical interventions, many of which are life saving. Citing decreased conversion of DEHP to its toxic metabolite, MEHP, in primates versus rodents, lack of evidence in humans of DEHP toxicity, and the fact that medical exposures are intravenous in contrast to the oral exposures in most animal studies, the Koop report concluded that carcinogenesis and developmental and reproductive toxicity from DEHP are not likely at anticipated exposure levels. In contrast, the Lowell Center for Sustainable Production released a report based on a different interpretation of the same literature. This report concluded “the weight of the evidence indicates a significant potential for serious adverse effects on human health from DEHP-containing medical devices.” Stressing the data showing that liver cancer is caused by a different mechanism than are other toxicities and that intravenous exposures to DEHP often involve concomitant exposure to the toxic metabolite MEHP, uncertainties in exposure estimates, and unknowns about metabolism of DEHP in infants, the Lowell report assumed a precautionary stance and called for minimizing human exposure to DEHP from medical devices, including using available alternative medical devices that do not contain DEHP.

Controversy also surrounds childhood exposures to DINP. The Koop report concludes that DINP is unlikely to pose a health risk for children on the basis of wide differences between estimated exposure doses in children and the much higher doses required to cause adverse effects in laboratory animals. A risk assessment by Wilkinson reaches a similar conclusion, but Fiala recommends removal of DINP (and DEHP) from children’s toys because exposure may be high enough to cause concern.

Recent Reports

In July 2000, the first expert panel convened by the Center for the Evaluation of Reproductive Risks to Humans (CERHR) under the direction of the National Toxicology Program, funded by the National Institutes of Health, and housed at the National Institute of Environmental Health Sciences completed a 15-month analysis of the developmental and repro-
ductible risks to humans of 7 phthalate esters, including DINP and DEHP.\textsuperscript{55}

For DEHP, the CERHR expert panel\textsuperscript{1} expressed minimal concern over the exposure to the general adult population. The panel expressed concern that infants and young toddlers, because of their dietary preferences and mouthing behaviors, might have higher exposures to DEHP at a time when the male reproductive tract is still developing and potentially vulnerable.\textsuperscript{70} Of similar concern was the possibility that pregnant and lactating women might deliver higher levels of DEHP and MEHP to their infants via placental transfer and breast milk than is estimated for the general population, which is potentially more dangerous to males with developing reproductive tracts. Pointing out that levels of documented single-source intravenous exposures in newborn humans can exceed NOAELs in rodents and approach toxic intravenous doses in rodents, the CERHR expert panel expressed “serious concern”\textsuperscript{29,101} that critically ill boys undergoing intense medical or surgical treatment might receive doses of DEHP and MEHP that could damage the reproductive tract. The panel acknowledged that the benefits of such intense therapies outweigh the risks of these exposures. It stressed the need for more precise human exposure data, particularly for multiple simultaneous medical exposures, and for better data on primate toxicity and toxicokinetics to evaluate more precisely the risks and benefits of medical exposures. The US Food and Drug Administration and Health Canada recently issued reports that reiterate the concern that some subpopulations of medically exposed individuals, including highly exposed male infants, could be at risk of testicular toxicity from exposure to DEHP.\textsuperscript{71,72}

For DINP, the CERHR panel expressed minimal concern for exposures via food consumed by pregnant women. Models of mouthing behavior suggest that young children may experience higher exposures than the general population if they chew or suck on toys or products containing DINP. This uncertainty was enough to raise the concern from minimal to low with respect to DINP toxicity in young children. Some manufacturers are voluntarily decreasing DINP content in toys in response to consumer concerns.\textsuperscript{73}

The National Toxicology Program also sponsored a study assessing biomarkers of several phthalates, which indicates that exposures to some other phthalates may be higher than previously assumed relative to both DEHP and DINP.\textsuperscript{74} Dibutyl phthalate (DBP) is also teratogenic and toxic to the testes in laboratory animals, though less potent than DEHP.\textsuperscript{75} Using 289 nonrandom urine samples collected for the Third National Health and Nutritional Examination Survey, the authors found that the monoester metabolite of DBP (one of the phthalates used in cosmetics), was higher than anticipated. The levels of MEHP and the toxic metabolite of DINP were lower than expected compared with the monoester metabolite of DBP, raising questions about the accuracy of previous exposure estimates and assumptions about human metabolism, excretion, and tissue sequestration for these phthalates. As with DEHP and DINP, the toxicity of DBP to humans depends on level of exposure and efficiency of conversion to the toxic metabolite, coupled with the potency and toxicity of the toxic metabolite. The discrepancy between exposures estimated from secondary data and presumed use patterns and those inferred from this small, initial study of specific biomarkers of exposure in a human population highlights the need for better exposure data for all phthalates.

This work has been extended by the Centers for Disease Control and Prevention, the National Toxicology Program, and the National Institute of Environmental Health Sciences in the Second National Report of Human Exposure to Environmental Chemicals,\textsuperscript{76} which includes analysis of urinary metabolites for the same 7 phthalates as in the Blount study.\textsuperscript{74} This larger study used a representative random sample of 2541 US residents and included urinary samples from 328 children from 6 to 11 years of age and 752 children from 12 to 19 years of age. Urinary concentrations of the monoester metabolites were similar to or slightly lower than those found in the smaller previous study, but significant differences were found in concentrations depending on age and sex. For 3 of the phthalate esters, DEHP, DBP, and monobenzyl phthalate, monoester metabolite concentrations were highest in the youngest age category and decreased significantly with increasing age. Females tended to have higher concentrations than did males. This is strong evidence of the importance of performing thorough investigation of exposures through the entire pediatric age spectrum.

CONCLUSIONS

The 1990s began a period of increased attention to the special vulnerabilities of children to environmental hazards. The conflicting conclusions on the safety of phthalates under current exposure conditions provide important illustrations of the subtlety and complexity of the science and policy components required to protect children from environmental hazards. Pediatricians are well positioned to provide leadership in advocating for child-protective standards and policy on phthalates and all areas of children’s environmental health. Conclusions about health risks specific to DEHP and DINP can be generalized to many environmental toxicants and aid the development of research priorities and policy decisions that will promote and protect children’s environmental health.

1. Phthalates are important components of PVC and other consumer products and are widely distributed environmental contaminants. DEHP and DINP are phthalates of particular concern because of their known toxicities and the potential for significant exposure in sensitive populations.

2. Human exposure to phthalates is universal. Levels of exposure in the general population are estimated to be on the order of tens of μg per kg

\textsuperscript{*}Katherine Shea, MD, MPH, lead author of this technical report, was a member of the CERHR Expert Panel on Phthalates.
per day. Food is considered to be the major source of exposure to DEHP and DINP, excluding occupational exposure, nondietary ingestions, and for DEHP only, medical exposures.

3. Human data on exposure to phthalates are very limited. In particular, data on the magnitude and distribution of exposures in sensitive subpopulations, such as women of childbearing age, neonates, infants, and toddlers in the general population and medically exposed fetuses, premature infants, neonates, young children, and adolescents, are lacking. New biomarker data from the Centers for Disease Control and Prevention cast doubt on the accuracy of previous estimates of human exposure, which have been used for risk assessment to date.

4. DEHP and DINP are animal carcinogens, but most recent information suggests that the mechanisms of carcinogenesis may not be relevant to human systems. DEHP is a reproductive toxicant, and DEHP and DINP are developmental toxicants in animals. The most sensitive system is the immature male reproductive tract. The mechanisms of reproductive toxicity are distinct from the mechanism of carcinogenesis.

5. No studies have been performed to evaluate human toxicity from exposure to these compounds.

6. As with many environmental toxicants, children may be at higher risk of adverse effects of phthalates because of anticipated higher exposures during a time of developmental and physiologic immaturity. In response to this theoretical concern, measures to decrease possible exposure through nondietary ingestion are underway. In the United States and Canada, all phthalates have been removed from infant bottle nipples, teethers, and toys intended for mouthing. Manufacturers have voluntarily begun to substitute the less toxic DINP for DEHP in other toys.

7. Pediatric medical exposures to DEHP are of concern. DEHP has been documented to be toxic to the male reproductive tract in laboratory animals at doses near those resulting from intensive medical procedures in humans.5 Although some of the species and route differences suggest a lower risk to human infants of testicular damage from DEHP exposure, some medical exposures involve concomitant exposure to MEHP, the toxic metabolite. Sertoli cells continue to increase in number through puberty; therefore, medical exposures beyond the newborn period may also be of concern.71 There are no studies that have evaluated the effect of medical exposures to DEHP and MEHP on testicular function in humans.67

8. In light of recent toxicology and exposure evidence and the concern of the CERHR expert panel for the medically exposed infant, medical institutions, including neonatal and pediatric intensive care units and dialysis units, may find it necessary to look at the risk-benefit relationship between DEHP-containing medical devices and their alternatives. Interventions designed to minimize DEHP exposure in the medical setting could be designed. DEHP has important characteristics that improve the function of medical devices. Any substitutes must be shown to be toxicologically safer and functionally equivalent. Publication of a comprehensive comparison of developmental and reproductive toxicities between DEHP and proposed alternatives would be useful. In addition, studies designed to evaluate total DEHP and MEHP exposure from multiple concurrent medical procedures could be very valuable in resolving this controversy.

9. Improved data on pediatric exposures to phthalate esters, including transplacental, breast milk, medical, and nondietary ingestion, would significantly facilitate accurate risk assessments.

10. Improved understanding of the toxicokinetics of phthalates, including creation, distribution, and excretion of the toxic metabolites in subhuman primates or exposed humans, would enable more accurate evaluation of acceptable exposure levels. Determination of the toxicokinetics of phthalates in sensitive subpopulations, including pregnant and lactating women, premature infants, full-term infants, and small children, is also needed.

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