



Cover Story

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Panel Ranks Risks of Common Phthalate

Additional research underscores concerns about DEHP that were first expressed in 2000 report

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Di(2-ethylhexyl) phthalate (DEHP) is the most widely used plasticizer for polyvinyl chloride products in the world. It is also used in lubricants, perfumes, hairsprays, cosmetics, construction materials, floorings, paints, toys, and medical devices. But the safety of DEHP has been under a cloud for a decade, and the latest analysis of health effects studies expresses some serious concerns about how the compound is used.

The concern is the possible effect of DEHP on the reproductive systems of human infants, especially males. It is widely recognized that when male rodents are exposed in the womb or shortly after birth, DEHP causes a variety of developmental and reproductive effects. Studies completed over the past two years have strengthened the case that this phthalate may create similar problems in humans.

Because of these serious concerns, the European Union has banned DEHP and a number of other phthalates in children's toys. In 1998, the Toy Manufacturers of America—now the [Toy Industry Association](#)—entered into a voluntary agreement with the [U.S. Consumer Product Safety Commission](#) not to use DEHP in pacifiers, rattles, and teething rings. The U.S. government, however, has placed no mandatory restrictions on the chemical, and low levels are still showing up in toys for very young children.

The National Toxicology Program's [Center for the Evaluation of Risks to Human Reproduction \(CERHR\)](#) produced a report in 2000 on the health risks of DEHP, expressing various degrees of concern about different types of exposures. And in mid-October 2005, a new panel organized by CERHR came to conclusions similar to those reached in 2000.

For example, the panel determined that critically ill male infants undergoing medical treatment with vinyl medical equipment can receive doses of DEHP that may adversely affect reproductive development.

The reevaluation was prompted by a large volume of research—about 150 studies—published since the 2000 evaluation. The CERHR panel assessed the available scientific evidence in three primary areas: human exposure, reproductive toxicity, and developmental toxicity. It also identified data gaps and research needs.

Even though the conclusions do not differ greatly from those reached earlier, they are backed by much more data. “The certainty of the conclusions is much higher” than it was in 2000, but the conclusions aren’t changed much, said panel member Kim Boekelheide, a toxicologist at Brown University.



Photos by Bette Hileman

Shelby Schettler Chapin

The panel is not a regulatory body. It can only express concern or a lack of it about various exposures. Nevertheless, its reports are “fairly important for policy decisions,” said Michael D. Shelby, director of CERHR. The monographs, which are essentially the final versions of the reports, are influential in California’s decisions under Proposition 65, he said. Proposition 65 mandates that a list of chemicals known to cause cancer or reproductive toxicity must be published annually.

The panel established five levels of concern: negligible concern, minimal concern, some concern, concern, and serious concern. It expressed concern that DEHP exposure can adversely affect the reproductive development in infants less than one year old and some concern that exposure to the chemical can adversely affect reproductive development in male children older than one year.

The panel decided that male infants undergoing medical procedures with vinyl equipment can be at considerable risk from DEHP. These infants receive doses as high as 6,000 µg/kg of body weight per day. The panel made particular note of a study that is the first to quantify real-world exposures resulting from the use of multiple DEHP-containing medical

devices in a contemporary, neonatal intensive care unit. DEHP doses received by infants in intensive care are close to toxic doses in rodents, the panel said.

Furthermore, panel members noted that compared with older children, premature infants may be especially susceptible to DEHP. Their metabolic systems may be immature, their gastrointestinal tracts may absorb more DEHP, and the blood-testes barrier may be more permeable to the chemical, the members said.

Tested

DEHP Found In Baby Products

In 1998, the Toy Manufacturers of America entered into a voluntary agreement with the U.S. Consumer Product Safety Commission not to use di(2-ethylhexyl) phthalate (DEHP) in toys intended for children younger than three years old. At that time, the commission also asked the industry to find a substitute for phthalates in other products for children under three.

However, [according to a report](#) prepared by the Environment California Research & Policy Center and U.S. Public Interest Research Group, two activist organizations, DEHP can still be found in common toys for children under three and other phthalates can be detected in popular toys made for very young children. The report describes test results documenting DEHP in teething rings and bath books.

The groups contracted with Environmental Protection Agency-accredited labs for phthalate analyses on 18 children's products from major manufacturers. Of the 18 products tested, 15 contained one or more phthalates. Twelve of them had detectable DEHP ranging from 20 to 840 ppm. These items included bath books, bath toys, infant toys, and one teething ring. The detection limits ranged from 6.8 to 9.4 ppm.

Furthermore, some of the teething rings and toys contained other phthalates, such as DBP (di-*n*-butyl phthalate) and DNOP (di-*n*-octyl phthalate). For example, an infant toy called Gloworm was found to contain three phthalates: DEHP (82 ppm), DBP (9.5 ppm), and DNOP (17,000 ppm). A Baby Gund Jungle Collection teething ring had 760 ppm of DBP, and a Little Teethers teething ring contained 410 ppm of DEHP.

The European Union has banned DEHP and DBP in all toys and child care articles, and DNOP in all toys for children underthree.

Environment California says: "Parents have a right to know about chemicals in the products they purchase for their children." Manufacturers of chemicals, it says, "should be required to conduct an alternatives analysis in order to determine if they really are

selling the least hazardous chemical for each application” and should be required to provide all hazard and health-impact information about their products to state and local governments. Also, Environment California says, toy makers should be required to label their products with the names of the chemicals contained.

“Parents do not have the information they need to adequately protect their children from toxic chemicals,” says Rachel Gibson, a report coauthor who is staff attorney for Environment California.

The levels of phthalates found in the baby products are actually very low, says Marian K. Stanley, manager of the Phthalate Esters Panel at the American Chemistry Council. For example, a DEHP level of 840 ppm found in a baby book is just 0.084%, she says, which is not enough to add flexibility to any vinyl product and could result inadvertently from lab contamination. Products with a phthalate level less than 1% are considered to be phthalate-free, she says. Such levels are far below those that cause problems in rodents and are harmless for children, she claims. The Environment California report is “needlessly alarming parents,” she says.

Gibson, however, says the important issue is not the exposure received from any single toy, but the aggregate exposures from all the toys and other phthalate-containing items, such as shower curtains and vinyl flooring, that children are exposed to. “Kids are exposed to these chemicals through a variety of pathways,” she says.

The panel expressed “serious concern” that “such exposures may adversely affect male reproductive tract development and function.” The medical procedures can save lives, but hospitals should strive to purchase DEHP-free medical equipment for infants, the panel said.

The panel also suggested that when pregnant women undergo repeated medical treatments with DEHP-plasticized devices, they could receive exposures large enough to have adverse effects on male fetuses.

It is easy to avoid the dangers posed by DEHP-plasticized medical devices, said Ted Schettler, science director of the Science & Environmental Health Network, a public interest group. “Cost-competitive medical products that do not contain DEHP and that perform equally well are readily available for nearly all uses.”

In the new CERHR report, DEHP exposure levels (primarily from food and ingestion of dust) of various population groups were updated. The median exposure level for toddlers of 25.8 $\mu\text{g/kg}$ body weight per day is below the tolerable daily intake of 37 $\mu\text{g/kg}$ body weight per day set by the European Commission. Toddlers at the high end of the exposure curve, however, experience doses higher than the EC limit.

In remarks to the panel, Ralph Parod of BASF described a study reporting that DEHP does not harm the male reproductive system in marmosets. Parod argued that the marmoset, a primate, is a better animal model for predicting toxic effects on humans than rodents are. In the study, marmosets were given DEHP doses as large as 2,500 mg/kg body weight from the age of three months until maturity at 18 months. The study reported no differences in testicular or prostate weight or any other aspect of the reproductive system between the dosed animals and the controls, he said.

The CERHR panel decided, however, that the marmoset is not a good animal model for humans for two reasons: The rate of absorption of MEHP (a metabolite of DEHP) from the marmoset's gut is low compared with that of rats and humans. Also, new information suggests that marmosets may be less susceptible to hormonal disruption, believed to be a key feature of DEHP toxicity, than most other species, said panel member Robert E. Chapin, a toxicologist with Pfizer Global Research & Development. "The marmoset data were discarded because marmosets have fundamental biological differences from humans," he said. Studies of the effects of DEHP in rhesus or macaque monkeys would be more relevant to humans, he explained.

In rodent fetuses, high doses of DEHP act as antiandrogens and block the synthesis of testosterone. The high doses result in undescended testicles, abnormalities in the penis, and a reduced anogenital distance—the distance between the anus and base of the penis. Anogenital distance is considered the most sensitive indicator of demasculinization of the male genitalia. It is important to consider this constellation of effects when evaluating the impact of DEHP on rodents, Chapin said.

In May, Shanna H. Swan, an epidemiologist at the University of Rochester School of Medicine & Dentistry, and colleagues reported in *Environmental Health Perspectives* on a study of phthalate exposure in 85 male babies. Phthalate exposure was assessed by measuring metabolites in the mothers' urine during pregnancy. Swan reported that those babies whose mothers were exposed to higher levels of four phthalates—diethyl phthalate, dibutyl phthalate, benzyl phthalate, and isobutyl phthalate—had shorter anogenital indexes (the anogenital distance adjusted for weight) and were more likely to have small genitalia and partially undescended testicles. The associations between the three metabolites of DEHP measured in this study and the anogenital index were not statistically significant. However, the regression coefficients—which reflect change in the anogenital index with increasing metabolite level—were large for two of three metabolites.

Swan also looked at total phthalate-exposure for each of the 85 boys. "Of the 10 boys whose phthalate scores were high, all but one had a short anogenital index," she tells C&EN. Conversely, among the 11 boys with the lowest total phthalate exposure, only one had a short anogenital index, she explains.

EXPOSED**Toddlers receive the greatest exposure to DEHP**

AGE GROUP	MEDIAN INTAKE ^a
Adult	8.2
Teen	10.0
Child, 5–11 years	18.9
Toddler, 7 months–4 years	25.8
Infant, 0–6 months	
Formula fed	5.0
Breast fed	7.3

^a Micrograms per kilogram of body weight per day.**SOURCE:** Center for the Evaluation of Risks to Human Reproduction panel draft report

The panel concluded that the Swan study is useful for the evaluation process, but the data are insufficient to show that prenatal exposure to DEHP is harming male infants. Swan is now conducting more research with a larger sample of boys. This new study may come to more definitive conclusions about DEHP, she says.

Panel member Boekelheide said it was not unreasonable for Swan to consider the effect of a mixture of phthalates because some of them share the same mode of action. Overall, “we should be trying to reduce exposure to certain phthalates, particularly in developing male fetuses and infants,” he said.

“CERHR's assessment of DEHP was generally fair, although very conservative,” says Marian K. Stanley, manager of the Phthalate Esters Panel at the American Chemistry Council. Based on the panel's conclusions about the level at which no effects are observed in animals, the safety margin for the general human population is roughly 100 to 1,000, she says. In other words, the general population is exposed to DEHP in the range of micrograms per kilogram of body weight per day, although effects begin to appear in rodents at milligrams per day.

The final expert panel report from the reevaluation of DEHP will be posted on the CERHR website sometime this month. After a public comment period, which will be announced in the *Federal Register*, CERHR will prepare a monograph on DEHP consisting of the final expert panel report and all public comments. The monograph will go to various federal health and regulatory agencies.

Even though CERHR has no authority to regulate DEHP, the monograph could affect the market for the large, high-production-volume chemical. According to the European Council for Plasticizers & Intermediates, 300,000 tons of DEHP are annually consumed in Europe, and DEHP accounts for half of the world market for plasticizers. U.S. production is a trade secret. The European Chemicals Bureau has classified DEHP as a Category 2 reproductive toxicant, and the new report is not likely to convince it to downgrade that classification. In addition, the CERHR monograph could lead the Food & Drug Administration to place mandatory restrictions on the use of DEHP in medical devices. An

evaluation by FDA in 2002 concluded that DEHP-plasticized vinyl can be used safely in some applications but may pose a problem for newborns.

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