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Under the Microscope From an Ingredient In Cosmetics, Toys, A Safety Concern

Male Reproductive Development Is Issue With Phthalates, Used in Host of Products

Europe, Japan Restrict Them

By PETER WALDMAN

In the 12th week of a human pregnancy, the momentous event of gender formation begins, as X and Y chromosomes trigger biochemical reactions that shape male or female organs. Estrogens carry the process forward in girls, while in boys, male hormones called androgens do.

Now scientists have indications the process may be influenced from beyond the womb, raising a fresh debate over



TOXIC TRACES
New Questions
About Old
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industrial chemicals and safety. In rodent experiments, common chemicals called phthalates, used in a wide variety of products from toys to cosmetics to pills, can block the action of fetal androgens. The result is what scientists call demasculinized effects in male offspring, ranging from undescended testes at birth to low sperm counts and benign testicular tumors later in life. "Phthalate syndrome," researchers call it.

Whether phthalates—pronounced "thallets"—might affect sexual development in humans, too, is now a matter of hot dispute. Doses in the rodent experiments were hundreds of times as high as the minute levels to which people are exposed. However, last year, federal scientists found gene alterations in the fetuses of pregnant rats that had been exposed to extremely low levels of phthalates, levels no higher than the trace amounts detected in some humans.

Then this year, two direct links to humans were made. First, a small study found that baby boys whose mothers had the greatest phthalate exposures while pregnant were much more likely than other baby boys to have certain demasculinized traits. And another small study found that 3-month-old boys exposed to higher levels of phthalates through breast milk produced less testosterone than baby boys exposed to lower levels of the chemicals.

Scientists are raising questions about phthalates at a time when male reproductive disorders, including testicular cancer, appear to be on the rise in many countries. Seeking an explanation, European endocrinologists have identified what some see as a human counterpart to rodents' phthalate syndrome, one they call "testicular dysgenesis syndrome." Some think it may be due in part to exposure to phthalates and other chemicals that interfere with male sex hormones.

"We know abnormal development of the fetal testes underlies many of the reproductive disorders we're seeing in men," says Richard Sharpe of the University of Edinburgh in Scotland, a researcher on male reproduction. "We do not know what's causing this, but we do know high doses of phthalates induce parallel disorders in rats."

It isn't surprising to find traces of phthalates in human blood and urine, because they are used so widely. Nearly five million metric tons of phthalates are consumed by industry every year, 13% in the U.S. They are made from petroleum byproducts and chemically known as esters, or compounds of organic acid and alcohol. The common varieties with large molecules are used to plasticize, or make pliable, otherwise rigid plastics—such as polyvinyl chloride, known as PVC—in things like construction materials, clothing, toys and furnishings. Small-molecule phthalates are used as

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Safety Issues Arise About Phthalates, Chemicals Widely Used in Cosmetics, Toys and Even Pills

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solvents and in adhesives, waxes, inks, cosmetics, insecticides and drugs.

Users and producers of phthalates say they are perfectly safe at the very low levels to which humans are exposed. Phthalates are among the most widely studied chemicals and have proved safe for more than 50 years, says Marian Stanley of the American Chemistry Council, a trade association.

She says studies suggest primates, including humans, may be much less sensitive to phthalates than are rodents. She cites a 2003 Japanese study of marmoset monkeys exposed to phthalates as juveniles, which found no testicular effects from high doses. The study was sponsored by the Japan Plasticizer Industry Association. Scientists involved in a California regulatory review questioned the study and maintained it didn't support the conclusion that humans are less sensitive to phthalates than rodents are.

Ms. Stanley's conclusion: "There is no reliable evidence that any phthalate, used as intended, has ever caused a health problem for a human."

Societal Issue

The phthalate debate is part of the larger societal issue of what, if anything, to do about minute, once-undetectable chemical traces that some evidence now suggests might hold health hazards.

With much still unknown about phthalates, scientists and regulators at the Environmental Protection Agency are moving cautiously. "All this work on the effects of phthalates on the male reproductive system is just five years old," says the EPA's leading phthalate researcher, L. Earl Gray. "There appears to be clear disruption of the androgen pathway, but how? What are phthalates doing?"

To Rochelle Tyl, a toxicologist who works for corporations and trade groups studying chemicals' effects on animals, the broader question is: "If we know something bad is happening, or we think we do, do we wait for the data or do we act now to protect people?" Based on her own studies of rodents, Dr. Tyl says it is still unclear whether low levels of phthalates damage baby boys.

Some countries have acted. In 2003, Japan banned certain types of phthalates in food-handling equipment after traces turned up in school lunches and other foods.

The European Union has recently banned some phthalates in cosmetics and toys. In January, the European Parliament's public health committee called for banning nearly all phthalates in household goods and medical devices. In July, the full parliament asked the EU's regulatory body, European Commission, to review a full range of products "made from plasticized material which may expose people to risks, especially those used in

medical devices."

With the controversy particularly hot in Europe, the European market for the most common phthalate plasticizer, diethylhexyl phthalate, or DEHP, has fallen 50% since 2000, says BASF AG, the German chemical giant. In response, BASF says it is ceasing production of DEHP in Europe this month. A spokesman for the company says the cutback won't affect its phthalate production in the U.S.

The U.S. doesn't restrict phthalates, and has lobbied the EU hard in recent years not to burden manufacturers with new regulations on chemicals. Still, a few companies, under pressure from health groups, have agreed to abide by European standards in their products sold in the U.S. Procter & Gamble Co. said last year it would no longer use phthalates in nail polish. Last December, Unilever, Revlon Inc. and L'Oréal SA's American unit promised to eliminate all chemicals banned in European products from the same items in the U.S.

For medical bags and tubes, Baxter International Inc. pledged in 1999 to develop alternatives to phthalate-containing PVC, as did Abbott Laboratories in 2003. (Abbott has since spun off its hospital-products unit.) In a June study by Harvard researchers of 54 newborns in intensive care, infants who'd had the most invasive procedures had five times as much of the phthalate DEHP in their bodies—as measured in urine—as did babies with fewer procedures.

Researchers aren't yet sure what this means. Another study by doctors at the Children's National Medical Center in Washington, published last year, found that 19 adolescents who'd had significant exposure to phthalates from medical devices as newborns showed no signs of adverse effects through puberty.

Kaiser Permanente, the big health-maintenance organization, promised in 1999 to eliminate phthalates in hospital supplies. Demand from the HMO has helped drive development of medical gloves that don't contain phthalates, as well as non-PVC carpeting and a new line of phthalate-free plastic handrails, corner guards and wall coverings.

In the early 1990s, the EPA set exposure guidelines for several types of phthalates, based on studies that had been done decades earlier. Since then, much more has been learned about them.

Consider dibutyl phthalate, which is used to keep nail polish from chipping and to coat some pills. The EPA did a risk assessment of it 15 years ago, relying on a rodent study performed in 1953. The now half-century-old study found a "lowest adverse-effect-level"—600 milligrams a day per kilogram of body weight—that killed half of the rodents within a week.

A 2004 study of the same chemical, published in the journal *Toxicological Sciences*, found far subtler effects, at far lower exposures. It detected gene

alteration in fetuses of female rats that ingested as little as 0.1 milligram a day of the phthalate for each kilogram of body weight. That dose is one six-thousandth of the 1953 "lowest adverse-effect" level.

It's also an exposure level found in some U.S. women, says Paul Foster of the National Institute of Environmental Health Sciences, a co-author of the gene study. So "now we're talking about 'Josephina Q. Public'—real women in the general population," he says. "The comfort level is receding."

EPA Caution

Still, because researchers don't know the function of the genes that were altered in the rat study, EPA experts say it's too early to base regulatory decisions on such gene changes. "We're a long way, in my opinion, from considering changes in gene expression as 'adverse' for risk assessment," says the environmental agency's Dr. Gray.

Exxon Mobil Corp. and BASF dominate the \$7.3 billion phthalates market. An Exxon Mobil spokeswoman says risk assessments by government agencies in Europe and the U.S. confirm "the safety of phthalates in their current applications."

Phthalates are cheaper than most other chemicals that can soften plastics. But a BASF press release says European manufacturers have been replacing phthalates with plasticizers designed for "sensitive applications such as toys, medical devices and food contact."

Makers of pills sometimes coat them with phthalates to make them easier to swallow or control how they dissolve. A case study published last year in the journal *Environmental Health Perspectives* said a man who took a drug for ulcerative colitis, Asacol, for three months was exposed to several hundred times as much dibutyl phthalate as the average American. The drug's maker, Procter & Gamble, says it coats the pill with the phthalate so it will stay intact until it reaches inflamed colon areas. P&G says a daily dose of the drug has less than 1% of the 0.1 milligram of dibutyl phthalate per kilogram of body weight that the EPA regards as a safe daily dose.

Sperm Count

Attributing health effects to specific industrial chemicals is a dicey business. Scientists often look for associations: statistical correlations that suggest, but don't prove, a possible causal link.

With phthalates, they've found a few. For instance, a 2003 study divided 168 male patients at a fertility clinic into three groups based on levels of phthalate metabolites in their urine. The study found that men in the highest third for one of the phthalates were three to five times as likely as those in the lowest third to have a low sperm

count or low sperm activity. Men highest in a different phthalate also had more abnormally shaped sperm, according to the study, which was done by researchers at the Harvard School of Public Health and published in the journal *Epidemiology*.

The scientists now are extending the research to 450 men. In their next paper, they're also planning to discuss a separate Swedish study, of 245 army recruits, that found no link between phthalate exposure and sperm quality.

The latest human study, on 96 baby boys in Denmark and Finland, found that those fed breast milk containing higher levels of certain phthalates had less testosterone during their crucial hormonal surge at three months of age than baby boys exposed to lower levels.

Authors of the study, led by Katharina Main of the University of Copenhagen and published Sept. 8 in *Environmental Health Perspectives*, said their findings support the idea that the human testis is vulnerable to phthalate exposure during development—possibly even more vulnerable than rodents' genitalia. They added, however, that "before any regulatory action is considered, further studies on health effects of [phthalates] are urgently needed" aimed at "verifying or refuting our findings."

Physical Differences

A human study of 85 subjects published in June linked fetal exposure to phthalates to structural differences in the genitalia of baby boys.

Researchers measured phthalate levels in pregnant women and later examined their infant and toddler sons. For pregnant women who had the highest phthalate exposure—a level equivalent to the top 25% of such exposure in American women—baby sons had smaller genitalia, on average. And their sons were more likely to have incompletely descended testicles.

Most striking was a difference in the length of the perineum, the space between the genitalia and anus, which scientists call AGD, for anogenital distance. In rodents, a shortened perineum in males is closely correlated with phthalate exposure. A shortened AGD also is one of the most sensitive markers of demasculinization in animal studies.

Males' perineums at birth are usually about twice as long as those of females, in both humans and laboratory rodents. In this study, the baby boys of women with the highest phthalate exposures were 10 times as likely to have a shortened AGD, adjusted for baby weight, as the sons of women who had the lowest phthalate exposures.

The length difference was about one-fifth, according to the study, which was led by epidemiologist Shanna Swan of the University of Rochester (N.Y.) School of Medicine and Dentistry and

Phthalates in Beauty Products

Though seldom listed on labels, phthalates are common in personal-care products, one of many ways the chemicals enter the bloodstream.

- **Diethyl Phthalate**, solvent and fixative in fragrances. Has been linked to DNA change in human sperm.¹
- **Dibutyl Phthalate**, plasticizer and fixative. Has been linked to physical changes in male human and rodent newborns.²

	Prevalence in products tested	Concentrations (parts per million)	
		DIETHYL PHTHALATE	DIBUTYL PHTHALATE
Hairspray	63% of products tested contained...	81 to 204	16 to 54
Deodorant	67%	38 to 2,933	104
Nail polish	67% (Diethyl) 75% (Dibutyl)	1,136	742 to 59,815
Hair mousse	80%	31 to 128	31 to 43
Fragrances	100% (Diethyl) 0% (Dibutyl)	5,486 to 38,663	Not Detected

¹ Duty, SM, NP Singh et al., *Environmental Health Perspectives*, July 2003. ² Swan, SM, KM Main et al., *Environmental Health Perspectives*, June 2005.

Note: To read studies about phthalates and their effects, go to [WSJ.com](http://www.wsj.com).

Source: U.S. Food and Drug Administration

published in *Environmental Health Perspectives*. Among boys with shorter AGD, 21% also had incomplete testicular descent and small scrotums, compared with 8% of the other boys.

Does it matter? The researchers intend to track as many of the boys as possible into adulthood, to address a key question: Will they grow up with lower testosterone levels, inferior sperm quality and higher rates of testicular tumors, as do rats with phthalate syndrome?

When the boys are 3 to 5 years old, Dr. Swan plans to assess their play behavior to see if exposure to phthalates appears associated with feminized neurological development. She says such tests have shown that little girls with high levels of androgens, or male hormones, gravitate toward "masculine" play. But she says no one has studied whether boys' play is affected by fetal exposure to chemicals that block androgens.

"In rodents, the changes result in permanent effects. Future studies will be necessary to determine whether these boys are also permanently affected," Dr. Swan says.

She and others agree that a study of just 85 subjects needs to be enlarged and repeated. She notes that although boys' genitalia were affected in subtle ways, no substantial malformations or disease were detected.

Some endocrinologists call this the first study to link an industrial chemical measured in pregnant women to altered reproductive systems in offspring. "It is really noteworthy that shortened AGD was seen," says Niels Skakkebaek, a reproductive-disorder ex-

pert at the University of Copenhagen, who wasn't an author of the study. "If it is proven the environment changed the [physical characteristics] of these babies in such an anti-androgenic manner, it is very serious."

Ms. Stanley of the American Chemistry Council doubts that any study can "tease out" the cause of a human health condition, given the wide variety of chemical exposures in people's lives. She notes that some of the specific phthalates associated with reproductive changes in the two human-baby studies haven't been linked to such changes in rodents. So, she says, it's possible the changes in anogenital distance and hormone levels may merely reflect normal variability.

Dr. Tyl, the chemical-industry toxicologist, says her own rat studies confirm that AGD is very sensitive to phthalates. She says that in rats that had very high phthalate exposures, a shortened AGD at birth was closely associated with a number of serious reproductive disorders later in life. However, in rats exposed to much lower doses of phthalates, a shortened AGD at birth did not always lead to later troubles. Many of these rats grew up to breed normally, she says, despite their slightly altered anatomy.

Dr. Tyl suggests that the same may be true of humans. Dr. Swan's study is "potentially important," Dr. Tyl says, because it suggests that "at low levels of exposure, humans are responding" to phthalates. But it remains quite possible, Dr. Tyl theorizes, that the boys with shortened AGD will grow up normally. "At what point do changes like this cross the line" to become dangerous, she asks. "We don't know yet."