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A COLLECTION OF ARTICLES CONCERNING THE CHEMICALS LEFT BEHIND IN PARTIALLY TREATED SEWAGE (also known as “tertiary-treated” wastewater) AND THEIR HEALTH IMPLICATIONS

Article published - Sep 6, 2006

More 'Intersex Fish' Found in Potomac

By MATTHEW BARAKAT
Associated Press Writer

Some species of male fish in the Potomac River and its tributaries are developing female sexual traits at a frequency higher than scientists have seen before, raising concerns about pollutants in a waterway that provides drinking water for millions of people.

The so-called "intersex fish," which produce immature eggs in their testes, were discovered in the Potomac rivershed in 2003 and have also been found in other parts of the country.

But the frequency that the U.S. Geological Surveys found last year is much higher than what has been found elsewhere, said fish pathologist Vicki Blazer.

In some Potomac tributaries, nearly all of the male smallmouth bass caught in last year's survey were the abnormal fish. In the Potomac itself, seven of 13 largemouth bass exhibited female characteristics, including three that were producing eggs.

Although the frequency discovered was surprisingly high, Blazer cautioned that the sample size was relatively small, with about 10 male and 10 female fish taken from each of eight locations in Maryland, Virginia and the District of Columbia.

Researchers were reluctant to remove large numbers of bass from the rivers because of conservation concerns, she said.

Female fish caught in the survey did not develop any unusual sex traits, though fish of both sexes exhibited lesions and other pollution-related problems, said Blazer, who coordinated the survey.

Smallmouth bass appear to be more susceptible to intersex development than largemouth bass, Blazer said.

Blazer said researchers are still waiting on data that would help them determine the water quality at the time the fish were caught, but preliminary data taken from the Potomac found a variety of chemical pollutants.

It is not exactly clear what is causing the changes, though it is likely a combination of pollutants, scientists say.

Certain chemicals and pesticides are believed to stimulate estrogen production. Also, estrogen

from birth control pills and human waste can make its way from sewage treatment plants to the waterways.

The Environmental Protection Agency has been studying the issue of so-called "endocrine disruptors" since 1996, but currently does not issue guidelines to water treatment plants for allowable levels of estrogenic compounds.

Jeanne Bailey, a spokeswoman for Fairfax Water, said the findings are a concern.

The water authority, which draws from the Potomac and Occoquan rivers to provide service to roughly 1.5 million people, is working with USGS and other agencies to research and develop ways to improve water treatment to eliminate potentially harmful compounds.

The water treatments used by Fairfax Water, including ozone and activated charcoal, have been shown to reduce levels of estrogenic compounds, she said.

Bailey cautioned against drawing dire conclusions about the impact on human health. She said, "Fish are a great indicator of the health of our waters, but they are not a great indicator of what may translate to humans."

April 17, 2007

Bringing Cancer to the Dinner Table: Breast Cancer Cells Grow Under Influence of Fish Flesh

Tests of river fish indicate their flesh carries enough estrogen-mimicking chemicals to cause breast cancer cells to grow

Many streams, rivers and lakes already bear warning signs that the fish caught within them may contain dangerously high levels of mercury, which can cause brain damage. But, according to a new study, these fish may also be carrying enough chemicals that mimic the female hormone estrogen to cause breast cancer cells to grow. "Fish are really a sentinel, just like canaries in the coal mine 100 years ago," says Conrad Volz, co-director of exposure assessment at the University of Pittsburgh Cancer Institute. "We need to pay attention to chemicals that are estrogenic in nature, because they find their way back into the water we all use."

Volz and colleagues, including biochemist Patricia Eagon, took samples from 21 catfish and six white bass donated by local anglers as part of a study presented at the American Association for Cancer Research meeting in Los Angeles this week. The fish were caught in five places: a relatively unpolluted site 36 miles upstream from Pittsburgh on the Allegheny River; an industrial site on the Monongahela River; an Allegheny site downstream from several industries that release toxic chemicals; and the confluence of the Allegheny and Monongahela rivers, where Pittsburgh dumps much of its treated sewage and sewer outflows. "This is the largest concentration of

combined sewer outflows in the U.S.," Volz notes, about the confluence, known as the Point. The researchers also bought several fish at the store as controls.

Using an organic solvent, the researchers created an extract from the skin, flesh and fat of the various fish. They then bathed a breast cancer cell line—known as MCF-7—in the extract. "We used this cell line because it has estrogen receptors in it, meaning that if estrogens are present it causes this cell line to proliferate," Volz explains. "If you put something on it and it grows, then it must be stimulating the estrogen receptor." In addition to responding to pure estrogen applied as a positive control, the extract from two of the white bass and five of the catfish caused the breast cancer cells to thrive.

The highest response came from fish caught in the industrial section of the Monongahela River. "The Monongahela River area is the area in Pittsburgh that was the site of most of the steel production over the last 100 years," Volz says. "That area is still an industrial beehive." But the broadest response came from where the sewer outflows and sewage treatment plants flow into the rivers from Pittsburgh; three of the four catfish caught here caused the breast cancer cells to proliferate. "Sewage might be more responsible for putting estrogenic chemicals in the water than the industries alone," Volz adds. "All of the hormone replacement products that women use go down the drain, along with birth control pills, antibacterial soaps, and many of the plastics we use, like Bisphenol A, have such effects."

It remains unclear exactly what estrogen-mimicking chemicals were actually present in the fish and what kind

of cancer-causing role they might have. But their effects on the fish themselves were clear: the gender of nine of the fish could not be determined. "Increased estrogenic active substances in the water are changing males so that they are indistinguishable from females," Volz says. "There are eggs in male gonads as well as males are secreting a yolk sac protein. Males aren't supposed to be making egg stuff."

And this estrogen burden is widespread. The store-bought white bass caused breast cancer cells to grow like its river-caught counterparts (as well as containing higher levels of mercury, arsenic and other contaminants) after being trucked to Pittsburgh from Lake Erie. "These fish, again, were in waters that were seeing industrial waste as well as possible combined sewer outflows," Volz notes. "This isn't just happening in Pittsburgh, this is happening everywhere in the industrialized world."

Volz says he and his fellow researchers are launching a broader survey this summer that will entail sampling fish all along the Allegheny River. Efforts will be made to determine if it is industrial waste, sewage or agricultural runoff—or all three—that is responsible for the problem. In the meantime, cooking the fat out of fish may be the best defense. "If you broil fish and let the fats drip out that will take most of the contaminants out," Volz says, though that may not be enough given other exposures to potentially tainted water. "What our study does show us is that there is exposure potential to vast populations that use water from our rivers as their drinking water supply."

from birth control pills and human waste can make its way from sewage treatment plants to the waterways.

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The New York Times
nytimes.com

September 18, 2006

Study: Drugs, Chemicals in Sewage Sludge

By THE ASSOCIATED PRESS
http://www.nytimes.com/aponline/us/AP-Waste-Contamination.html
TACOMA, Wash. (AP) -- Promoted as a great way to dispose of treated waste, the sewage sludge sold to homeowners to spray on their lawns and gardens may also be adding drugs, flame retardants and other chemicals to the landscape, according to a study.

Chad Kinney, an assistant professor of chemistry and biochemistry at Eastern Washington University, found dozens of medicinal, industrial and household compounds in treated sewage sludge, also known as biosolids, that government agencies sell as lawn-and-garden enhancements.

"No matter what biosolid we looked at, there were some of these compounds in it," said Kinney, whose research on the subject was published in online editions of the journal Environmental Science & Technology. The U.S. Geological Survey's Toxic Substance Hydrology Program supported his work, which began while he was a postdoctoral fellow at the U.S. Geological Survey.

Kinney and his team studied nine biosolid products from seven states: Washington, Arizona, Wisconsin, Kansas, Colorado, Texas and Iowa.

The scientists found that it didn't matter what wastewater treatment method was used, 25 compounds were found in each of the samples. They were looking for 87 different compounds and found 55 in one or more of the biosolids and at least 30 in each of the samples. The product with the most compounds had 45.

Although government regulators and health officials said there is no immediate risk to public health, the study's authors called for more research on the long-term impact on the environment.

"We've been using biosolids for over 30 years safety," said Peggy Leonard, biosolids program manager for King County's waste treatment division, which produces GroCo. "As far as I know, there is no risk."

Thomas Burke, a professor of public health policy at Johns Hopkins University in Baltimore, said Kinney's research and other studies should be a wake up call for the U.S. Environmental Protection Agency.

"I don't think people understood before this that they might be applying pharmaceuticals and disinfectants to their front lawns," Burke said.

The EPA has promoted the benefits of biosolids for decades because they contain the same nutrients -- nitrogen and phosphorus -- found in fertilizers.

Rick Stevens, national biosolids coordinator for the EPA, said in an e-mail to The News Tribune

of Tacoma that the agency stands by its existing biosolids regulations. State officials also said they do not think people should worry about exposure to chemicals in biosolids.

In King County, Leonard called Kinney's research a "good start," but said it fails to answer whether the chemicals break down in soils and whether they pose danger.

Dan Thomas, Tacoma's wastewater operations manager, said the issues raised by Kinney's report are not new.

"It's something we need to keep our eye on but we're not super-concerned at this time. We know these constituents are here. There's no reason to believe there's a health threat," Thomas said.

Soil scientists at Cornell University's Waste Management Institute have been asking for more regulatory scrutiny of biosolids.

"I certainly would not use this material on my garden" said Ellen Harrison, director of the Waste Management Institute.

Burke of Johns Hopkins called the EPA regulations out of date, adding that some of the chemicals identified in the study have been shown to disrupt fish reproduction.

"These are things that have biological implications and we have to understand them better," Burke said.

Information from: The News Tribune, http://www.thenewstribune.com

Environ. Sci. Technol., **ASAP Article** 10.1021/es0509073 S0013-936X(05)00907-7
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Transformation of Acetaminophen by Chlorination Produces the Toxicants 1,4-Benzoquinone and *N*-Acetyl-*p*-benzoquinone Imine

Mary Bedner* and William A. MacCrehan

Analytical Chemistry Division, National Institute of Standards and Technology, Mailstop 8392, Gaithersburg, Maryland 20899-8392

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Abstract:

The reaction of the common pain reliever acetaminophen (paracetamol, 4-acetamidophenol) with hypochlorite was investigated over time under conditions that simulate wastewater disinfection. Initially, the reaction was studied in pure water at neutral pH (7.0), a range of reaction times (2-90 min), and a molar excess of hypochlorite (2-57 times) relative to the acetaminophen concentration. The reaction was monitored using reversed-phase liquid chromatography (LC) with ultraviolet absorbance, electrochemical, and mass spectrometric detection. At 1 μmol/L (150 ppb) and 10 μmol/L (1.5 ppm) levels, acetaminophen readily reacted to form at least 11 discernible products, all of which exhibited greater LC retention than the parent. Two of the products were unequivocally identified as the toxic compounds 1,4-benzoquinone and *N*-acetyl-*p*-benzoquinone imine (NAPQI), which is the toxicant associated with lethality in acetaminophen overdoses. With a hypochlorite dose of 57 μmol/L (4 ppm as Cl_2), 88% of the acetaminophen (10 μmol/L initial) was transformed in 1 h. The two quinoidal

oxidation products 1,4-benzoquinone and NAPQI accounted for 25% and 1.5% of the initial acetaminophen concentration, respectively, at a 1 h reaction time. Other products that were identified included two ring chlorination products, chloro-4-acetamidophenol and dichloro-4-acetamidophenol, which combined were approximately 7% of the initial acetaminophen concentration at 1 h. The reaction was also studied in wastewater, where similar reactivity was noted. These results demonstrate that acetaminophen is likely to be transformed significantly during wastewater chlorination. The reactivity of the chlorine-transformation products was also studied with sulfite to simulate dechlorination, and 1,4-benzoquinone and NAPQI were completely reduced.

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Stay calm everyone, there's Prozac in the drinking water

Mark Townsend
Sunday August 8, 2004
The Observer

It should make us happy, but environmentalists are deeply alarmed: Prozac, the anti-depression drug, is being taken in such large quantities that it can now be found in Britain's drinking water.

Environmentalists are calling for an urgent investigation into the revelations, describing the build-up of the antidepressant as 'hidden mass medication'. The Environment Agency has revealed that Prozac is building up both in river systems and groundwater used for drinking supplies.

The government's chief environment watchdog recently held a series of meetings with the pharmaceutical industry to discuss any repercussions for human health or the ecosystem.

The discovery raises fresh fears that GPs are overprescribing Prozac, Britain's antidepressant of choice. In the decade up to 2001, overall prescriptions of antidepressants rose from nine million to 24 million a year.

A recent report by the Environment Agency concluded Prozac could be potentially toxic in the water table and said the drug was a 'potential concern'.

However, the precise quantity of Prozac in the nation's water supplies remains unknown. The government's Drinking Water Inspectorate (DWI) said Prozac was likely to be found in a considerably 'watered down' form that was unlikely to pose a health risk.

Dr Andy Croxford, the Environment's Agency's policy manager for pesticides, told The Observer: 'We need to determine the effects of this low-level, almost continuous discharge.'

Norman Baker, the Liberal Democrat's environment spokesman, said the revelations exposed a failing by the government on an important public health issue. He added that the public should be told if they were inadvertently taking drugs like Prozac.

'This looks like a case of hidden mass medication upon the unsuspecting public,' Baker said. 'It is alarming that there is no monitoring of levels of Prozac and other pharmacy residues in our drinking water.'

Experts say that Prozac finds its way into rivers and water systems from treated sewage water. Some believe the drugs could affect their

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reproductive ability.

European studies have also expressed disquiet over the impact of pharmaceuticals building up in the environment, warning that an effect on wildlife and human health 'cannot be excluded'.

'It is extremely unlikely that there is a risk, as such drugs are excreted in very low concentrations,' a DWI spokesman said. 'Advanced treatment processes installed for pesticide removal are effective in removing drug residues,' he added.

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May 30 2006

Health news

The Times August 05, 2005

Where rivers run high on cocaine

By Nigel Hawkes

Analysis of waste water in Italy shows a startlingly high level of drug abuse

THE rivers of Italy are flowing with cocaine, say scientists who have adopted a new approach to measuring the extent of drug misuse. The biggest river, the Po, carries the equivalent of about 4kg (8lb 13oz) of the drug a day, with a street value of about £20,000.

Cocaine users among the five million people who live in the Po River basin in northern Italy consume the drug and excrete its metabolic by-product, benzoylecgonine (BE). This goes from sewers into the river. So a team led by Dr Ettore Zuccato, of the Mario Negri Institute for Pharmacological Research in Milan, estimated the use of cocaine by testing the waters of the Po for BE, and for any cocaine that had passed through the body unaltered or reached the sewers in other ways.

What they found surprised them. They calculated that for every 1,000 young adults in the catchment area, about 30 must be taking a daily dose of 100 milligrams of cocaine, which greatly exceeds official national figures for cocaine use.

According to official Italian statistics, 1.1 per cent of people between the ages of 15 and 34 admit to having used cocaine “at least once in the preceding month”. Almost all cocaine use occurs in this age group.

Assuming that there are 1.4 million young adults in the Po River basin, the official statistics suggest that there would be 15,000 cocaine-use events per month. But the evidence from the water suggests that the real usage is about 40,000 doses a day, a vastly greater figure.

“The economic impact of trafficking such a large amount of cocaine would be staggering,” Dr Zuccato said. “The large amount of cocaine — at least 1,500kg — that our findings suggest is consumed per year in the River Po basin would amount, in fact, to about $150 million in street value, based on an average US street value of $100 per gram.”

To confirm their findings, the team also sampled urban waste water from Cagliari in Sardinia, Latina

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in central Italy, and from Cuneo and Varese in the north — all medium-sized cities. The values they obtained from the undiluted waste water were far higher than those in the Po, as would be expected. But when translated into likely local use of the drug, they produced very similar figures — which suggests that the Po region is not exceptional in its cocaine consumption. The results cannot be explained by assuming that some drug trafficker was panicked into dumping his stash down the lavatory. If so, much more pure cocaine would have been found, and much less of its human metabolite, BE. In fact, the ratio of cocaine to BE was consistent throughout all the samples.

If anything, Dr Zuccato said, the method would be expected to underestimate rather than to overestimate cocaine use, because some would be lost or absorbed in sediments. So the real consumption may be even higher.

This method has previously been used by the same team to measure the by-products of widely-used prescription drugs, and has produced results consistent with known prescribing patterns. So it seems to work.

The technique has been developed by the Italian team and is complex, as it needs to be to detect such tiny residues — of the order of billionths of a gram per litre of water.

The scientists say that the method needs to be tested further before being brought into general use, but suggest that it would be a more reliable and much cheaper way of tracking trends in drug use than by using population surveys.

“The approach tested here, which is in principle adaptable to other illicit drugs, could be refined and validated to become a general, rapid method to help estimate drug abuse at the local level,” they report in the journal *Environmental Health.*

“With its unique ability to monitor changing habits in real time, it could be helpful to social scientists and authorities for continuously updating the appraisal of drug abuse.”

The levels of the drug and the metabolite found in river water are so low that any effect on natural life is very unlikely. But this is not true of all chemicals. Research indicates that chemicals that mimic natural hormones are having an effect on fish in many rivers, including “feminising” many male fish. The sources of these chemicals include hormones excreted by the human body and industrial chemicals that reach the waterways.

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Article published - Mar 5, 2007

Panel looks at safety of chemical in popular plastic

Bisphenol A could cause complications with pregnancy

By TINA HESMAN
ST. LOUIS POST-DISPATCH

The safety of a chemical that's probably in your cell phone, eyeglass lenses, car, computer, baby bottles, microwaveable dishes - and hundreds of other popular products - will face public scrutiny today.

The chemical bisphenol A is used to make lightweight clear plastics and resins used as adhesives and coatings in everyday products.

Critics are concerned that the chemical could harm human health, particularly the development of fetuses and children, because it works like the female sex hormone estrogen. Other chemicals that mimic estrogen, notably the banned pesticide DDT, have been shown to interfere with hormone function and cause abnormalities in wildlife and laboratory animals.

The chemical industry contends that the weight of scientific evidence on bisphenol A doesn't support the claims of harm. But the chemical has been the subject of much controversy recently.

The San Francisco City Council passed a measure to bar bisphenol A and some other components of plastics, from products for children. But the European Union recently increased the level of exposure it considers safe for human health.

Starting toay, a panel of 15 scientists convened by the National Institutes of Health's Center for the Evaluation of Risks to Human Reproduction will hold three days of meetings in Alexandria, Va., to examine the safety of bisphenol A. The panel issued a draft report in December but will finalize the report and release its conclusions and recommendations this week. The

panel has no regulatory authority, and the findings are not binding.
Frederick vom Saal of the University of Missouri-Columbia, one of the leading experts on low-level exposure to bisphenol A, intends to address the scientific panel during a public comment period today.
Like everyone else wishing to comment on the draft report, he will get seven minutes to make his remarks. Scientists who study bisphenol A, such as vom Saal, were not invited to participate on the panel.
Bisphenol A was originally developed in the 1930s as an estrogen for birth control, said vom Saal. It was never used for that purpose because scientists quickly discovered that multiple molecules of bisphenol A could link together to form clear, hard plastics, vom Saal said. More than 6 billion pounds of bisphenol A plastics are made globally each year, vom Saal said.
The chemical is ubiquitous and almost unavoidable, vom Saal said.
Most people carry the chemical around in their bodies at low levels - about 1 part per billion in blood, urine and tissues.
"That seems like a staggeringly small number until you realize that the natural hormone it's acting like works at levels 10,000 times lower than that," vom Saal said.
The increase in bisphenol A production parallels the rise in obesity, vom Saal said. That's no coincidence, he says. His work with mice suggests that exposure to the chemical during pregnancy can lead to obesity in adulthood.
He points to more than 140 government-sponsored studies that have linked exposure to the chemical to breast cancer, prostate cancer, changes in reproductive organs, brain changes, obesity and other indications of harm. No industry-sponsored studies have uncovered evidence of harm from bisphenol A, vom Saal said.
Industry representatives say looking at individual studies is the wrong approach.
"This isn't a basketball game. You don't just count up studies and see what the score is," said Steven Hentges, executive director of the Polycarbonate Bisphenol A Global Group of the American Chemistry Council.
The studies must be considered in aggregate and evaluated for reproducibility, consistency and relevance to human health, Hentges said.
"In every case in which the evidence is evaluated together, the conclusion is bisphenol A is not a risk to human health, particularly at the low levels to which we are exposed," he said.

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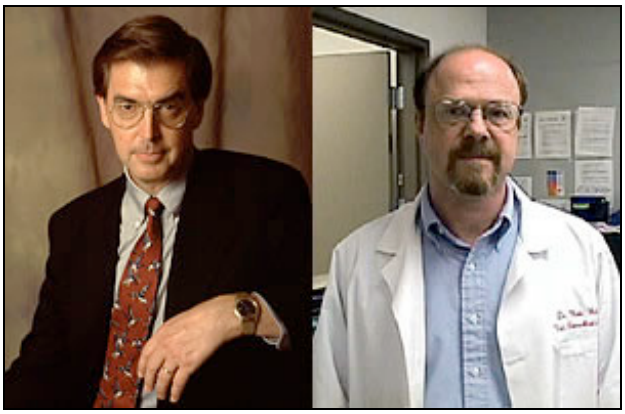
MIZZOU NEWS

Uncovering a Hidden Danger

By Matt McGowan

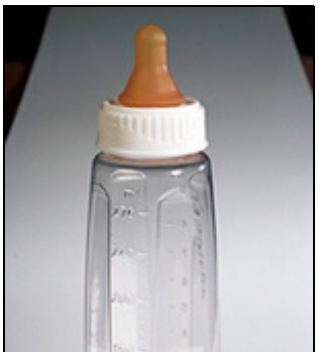


MU researchers Fred vom Saal, left, and Wade Welshons have conducted landmark studies on the potential health effects of chemicals in the home and environment. For more information about their work, go to the Endocrine Disruptors Group web site. Photos courtesy of MU Publications and Alumni Communication and the College of Veterinary Medicine

By nature, Fred vom Saal is not a crusader, but he doesn't want to wait 10 years for a governmental agency to ban a chemical that his research shows harms animals. He doesn't want to wait for thousands of people to show severe abnormalities from years of eating foods packaged in plastic.

Since their landmark findings in 1997 on low-dosage effects of Bisphenol A (BPA) on mice, vom Saal and Wade Welshons, researchers at the University of Missouri-Columbia, have labored to warn the public and government agencies of the dangers associated with the prevalent chemical that is used in many plastic products, including baby bottles, food-storage containers and toys.

In May vom Saal presented new scientific evidence about this chemical at the Toxicology and Risk Assessment Conference, an annual conference sponsored by several governmental agencies, including the U.S. Environmental Protection Agency, to examine the possible dangers of toxic chemicals.



During the conference near Dayton, Ohio, vom Saal argued that scientific findings in more than 35 publications in peer-reviewed scientific journals provide credible evidence that the chemical is harmful to every type of animal that has been studied, and this chemical is thus very likely to produce the same types of abnormalities in humans. These findings are based on independent academic research that has studied the effects of BPA.

"This evidence will ultimately convince federal regulatory

agencies that BPA should be illegal for use in food and beverage containers," vom Saal said. "It's only a matter of time."

Bisphenol A is an artificial estrogen, but it is bonded together in a chain of bisphenol A molecules to create the plastic called polycarbonate as well as resins that are used to line cans and as dental sealants. Each day, consumers use several plastic products that contain BPA, a chemical found in the 1930s by a Nobel-prize winning scientist to act like estrogen. In the 1950s, chemists linked BPA together to create polycarbonate material, and companies began using the chemical in plastics production. Today, BPA, one of the top 50 chemicals in production in the United States, generates billions of dollars for the plastics industry, which produces about 2.5 billion pounds of the chemical per year.

Vom Saal said scientists have known for many years that the polycarbonate bond created by BPA was unstable and that the chemical would eventually leach into food or beverages in contact with the plastic. The obvious concern today is that it may leach into food products, ranging from microwavable dinners to baby formula, that are packaged in polycarbonate plastic.

"The idea that this is a strong, durable product is an illusion," vom Saal said. "The chemists have known that the Bisphenol A chemical is constantly leaching and coming into contact with food or water. It's going to damage your body."

Researchers also have known that supplemental estrogens are harmful to animals and people, especially during fetal development. Vom Saal, Welshons and other scientists were particularly interested in BPA because they knew blood proteins involved in protecting against effects of natural estrogens would not protect against the chemical. Thus, this artificial hormone could travel directly through the blood into cells and damage them.

In 1997, the MU researchers published the first scientific article detailing the effects in animals of very low environmental exposure to BPA. Vom Saal and Welshons performed a prostate and sperm count study on male mice and demonstrated that BPA caused prostate hyperplasia — excessive growth of prostate tissue, a pre-condition of cancer. Since then, other studies, both theirs and those from other academic laboratories have shown that low-level exposure to BPA caused decreased sperm production in males, accelerated rate of growth, sex reversal in frogs, early onset of puberty, chromosome damage in female ovaries and a variety of behavioral changes.

With funding from the National Institutes of Health, Vom Saal and Welshons have shifted their research efforts toward an explanation of how and why BPA has such a powerful effect on an animal's endocrine system and reproductive organs. They have begun the process of identifying the molecular mechanisms at work when the hormone enters an animal's cells.

"There are safe alternatives," vom Saal said of products made with BPA. "There are plastic products that do not have Bisphenol A or other toxic chemicals. They can be made safely and used safely. There is no reason to keep using a chemical that has such a high potential to cause harm."

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"Gender benders" cause sperm burn out

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NewScientist.com news service
Claire Ainsworth, Vienna

The first direct evidence that "gender bender" chemicals affect the fertilising ability of sperm has been revealed - but it is unclear whether this would boost or harm fertility.

Researchers told the European Society for Human Reproduction and Embryology conference in Vienna that chemicals that mimic the effects of the female sex hormone oestrogen can prime sperm into becoming prematurely active, burning out before they have a chance to meet an egg.

"It's certainly very exciting work," says Chris Barratt at the University of Birmingham. "Sperm and the fertilisation process may be much more sensitive to artificial oestrogens than we thought."

Chemicals that mimic action of oestrogen abound in food and the environment. Many occur naturally in plants such as soy and hops, and are eliminated from the body within a few hours. Others take the form of synthetic chemicals such as pesticides and plasticisers, and build up in body tissues.

Research had already suggested a link between environmental oestrogens, testicular problems and low sperm counts, but this is the first time anyone has looked at their effect on sperm function, according to Lynn Fraser at King's College London, who led the new study.

Turn on

Oestrogen in semen and in the vagina is vital for fertilisation because it literally turns sperm on. The hormone stimulates a sperm to swim, and triggers physical changes that prime it for meeting with an egg - a process called capacitation.

Once a primed sperm docks with the egg, the cap on its head ruptures and releases a cocktail of enzymes that help it burrow inside and fertilise the egg. Normally, proteins in semen restrain this process, making sure it does not occur too soon.

If it does, the sperm will be unable to enter the egg. "Once they have undergone this reaction, they cannot fertilise, no matter how much they wiggle," explains Fraser.

Fraser and her team tested the effect of oestrogen and three oestrogen mimics - genistein, found in soya, 8-prenylnaringen, found in hops, and nonylphenol, found in paints, herbicides and pesticides.

They mixed the chemicals with mouse sperm and found all the compounds triggered capacitation and enzyme release. But the oestrogen mimics were far more powerful, triggering capacitation at concentrations a thousand times lower than oestrogen itself.

What's more, when the team tested the compounds on sperm that had already capacitated, they found that the oestrogen mimics triggered the premature release of the enzymes, whereas oestrogen did not.

Doubled fertilisation

However, when researchers mixed sperm with eggs and then treated them with the compounds, the number of eggs fertilised was doubled. This could be a benefit for IVF techniques, said Fraser.

"At first sight, these results might suggest that oestrogens, particularly those found in the environment, could help fertility. However, the responses we have seen could have negative effects over time," said Fraser.

Asked if oestrogen mimics could harm fertility in real life, Fraser said: "The potential answer to that question would be yes." Premature capacitation and enzyme release of sperm might not be a serious problem for normal fertile men, but it could be for men with lower sperm counts.

On the other hand, if the proteins that normally keep sperm under control still do their job, then the extra oestrogen-like activity could actually make sperm more fertile by increasing the numbers primed for fertilisation.

Barratt agrees that the jury is out until more research is done. But he adds that human sperm is known to be more sensitive than mouse sperm to progesterone, a hormone in the same class as oestrogen, meaning that oestrogen mimics could in theory have an even greater effect on humans.

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Chemicals in plastics harming unborn boys

Scientists say chemicals have gender bending effect

Ian Sample, science correspondent
Friday May 27, 2005

Guardian

Scientists in America have found the first evidence that common chemicals used in products as diverse as cosmetics, toys, clingfilm and plastic bags may harm the development of unborn baby boys.

Researchers have long known that high levels of substances called phthalates have gender-bending effects on male animals, making them more feminine and leading to poor sperm quality and infertility. The new study suggests that even normal levels of phthalates, which are ubiquitous, can disrupt the development of male babies' reproductive organs.

The discovery poses a huge problem for the chemical industry, which is already embroiled in a battle with the government over EU proposals on chemical safety.

Several types of phthalates, which are used to make plastics more pliable, and have been around for more than 50 years, have been banned, but many are still produced in vast quantities.

The study was carried out by scientists from centres across the US, including the University of Rochester and the National Centre for Environmental Health.

The researchers measured the levels of nine widely used phthalates in the urine of pregnant women and compared them with standard physiological measurements of their babies.

Tests showed that women with higher levels of four different phthalates were more likely to have baby boys with a range of conditions, from smaller penises and undescended testicles to a shorter perineum, the distance between the genitals and the anus. The differences, say the authors, indicate a feminisation of the boys similar to that seen in animals exposed to the chemicals.

Shanna Swan, an obstetrician at the University of Rochester, and lead scientist on the study, said researchers must now unravel what kinds of products are most to blame. One way that phthalates get into the bloodstream is when they seep into food from plastic packaging.

"It's going to take a while to work out which of these sources is most relevant to human exposure," she said.

Although the observed differences in body measurements were subtle, they indicate that what is generally regarded as the most ubiquitous class of chemicals is having a significant effect on newborns.

"Every aspect of male identity is altered when you see this in male animals," said Fred vom Saal, professor of reproductive biology at the University of Missouri-Columbia. Levels of aggression, parenting behaviour and even learning speeds were affected, he said.

Andreas Kortenkamp, an expert in environmental pollutants at the School of Pharmacy in London, said: "If it's true, it's sensational. This is the first time anyone's shown this effect in humans. It's an indicator that something's gone seriously wrong with development in the womb and that's why it's so serious."

He added: "These are mass chemicals. They are used in any plastic that is pliable, whether it's clingfilm, kidney dialysis tubes, blood bags or toys. Sorting this out is going to be an interesting challenge for industry as well as society."

The work, which is to appear in the journal Environmental Health Perspectives, is due to be presented at the Endocrine Disrupting Chemicals Forum in San Diego on June 3.

Gwynne Lyons, toxics adviser to the WWF, said: "At the moment regulation of the chemicals industry is woefully inadequate."

She added: "Right now the government is looking at how the regulation of hormone disrupting chemicals could be made more effective under new EU chemicals law, but the chemicals industry is lobbying very hard to water down this legislation.

"Political agreement on this legislation is not expected until later this year so it remains to be seen whether the UK government has the guts to stand up to industry lobbying. If they don't, wildlife and baby boys will be the losers."

Breast Cancer and the Environment: Science News from Silent Spring Institute
May 2005

Pollution Hits Home

In 1987, Dr. Ana Soto at Tufts University faced a perplexing problem. She was studying how exposure to estradiol – a natural estrogen – makes estrogen-sensitive human breast cancer cells grow. But, unexpectedly, the unexposed control cells in her lab began to proliferate! It took years to figure out that new plastic test tubes in her laboratory were to blame. The tubes were leaching nonylphenol, a synthetic chemical found in many common products, such as detergents, plastics and pesticides.

With this discovery, Dr. Soto began a new area of research that has led her laboratory and others to identify more than 150 chemicals that mimic estrogen, block androgen, or otherwise affect hormones. These chemicals are known as endocrine disrupting compounds (EDCs). They are found in building materials, furniture, and everyday products – detergents, pesticides, plastics, cosmetics – and in air and water pollution.

Given that natural estrogen and pharmaceutical estrogens, such as HRT, increase breast cancer risk, it makes sense to target estrogen mimics and other EDCs in breast cancer research. If we find links between these chemicals and breast cancer, we will be a big step closer to breast cancer prevention.

In order to study the links between chemicals and breast cancer, we need to first measure and understand how women are exposed. Because many of the EDCs are in consumer products and because all of us, and especially women, spend a lot of time at home, Silent Spring Institute decided to tackle EDCs in a study of exposures in homes.

We tested for 89 EDCs in air and dust in 120 homes on Cape Cod, where we have been studying possible environmental links to breast cancer for the last ten years. Results were published in the scientific journal *Environmental Science and Technology*, which called the study "the most comprehensive assessment to date" of pollutants in homes. For 30 of the chemicals we tested, ours are the first measurements ever reported from indoor environments.

- We found 67 target compounds in all, with an average of about 20 per home. That's a reminder that when we think about effects of chemicals on health, we have to take into account multiple exposures rather than the one-at-a-time approach that is currently used for chemicals regulation.
- The study showed that chemicals break down very slowly indoors. We found DDT, which was banned more than 30 years ago, in about two thirds of the homes. As toxicologist Ruthann Rudel says, "Think about what your furniture would look like if you left it out on the street for thirty years. Now think about it in your living room. Protected from sun, rain, and wind, materials stay pretty much in tact." The lesson here is that we need to be more careful about testing chemicals before we put them into use, because banning them later won't get them out of our homes.
- The most abundant pollutants were phthalates (from plastics and personal care products, such as nail polish and hair spray) and certain phenols from disinfectants, detergents, and adhesives, for example in furnishings.
- We found phthalates in every home. Researchers have found phthalates are associated with androgen-blocking effects in males, including lowered sperm count and certain hormonal birth defects. Their effects on girls and women have not been investigated much yet. Many breast cancer activists have joined the recent effort to remove phthalates from

cosmetics, as the Europeans are doing; and 116 cosmetics manufacturers have agreed. (Go to www.safecosmetics.org to learn more.)

- We found 27 different pesticides in all.
- We found the flame retardant PBDE's at ten times the levels reported in Europe, where these chemicals are not used as much.

_____Julia G. Brody, Ph.D., Silent Spring Institute

For more scientific detail, please visit the Silent Spring Institute web site resources on household exposure: http://library.silentspring.org/news/hesresults.asp.

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National Drinking Water Advisory Council
Water Infrastructure Security

Consumer Factsheet on: DI (2-ETHYLHEXYL) PHTHALATE

List of Contaminants

As part of the Drinking Water and Health pages, this fact sheet is part of a larger publication:
National Primary Drinking Water Regulations

This is a factsheet about a chemical that may be found in some public or private drinking water supplies. It may cause health problems if found in amounts greater than the health standard set by the United States Environmental Protection Agency (EPA).

What is DEHP and how is it used?

Di (2-ethylhexyl) Phthalate, or DEHP, is the most commonly used of a group of related chemicals called phthalates or phthalic acid esters. The greatest use of DEHP is as a plasticizer for polyvinylchloride (PVC) and other polymers including rubber, cellulose and styrene. A number of packaging materials and tubings used in the production of foods and beverages are polyvinyl chloride contaminated with phthalic acid esters, primarily DEHP.

The list of trade names given below may help you find out whether you are using this chemical at home or work.

Trade Names and Synonyms:

DEHP
BEHP
Dioctyl phthalate
Pittsburgh PX-138
Platinol AH
RC Plasticizer DOP
Reomol D79P
Sicol 150
Staflex DOP
Truflex DOP
Vestinol AH
Vinicizer 80
Palatinol AH
Hercoflex 260
Kodaflex DOP
Mollan O
Nuoplaz DOP
Octoil
Eviplast 80

Fleximel
Flexol DOP
Good-rite GP264
Hatcol DOP
Ergoplast FDO
DAF 68
Bisoflex 81

Why is DEHP being Regulated?

In 1974, Congress passed the Safe Drinking Water Act. This law requires EPA to determine safe levels of chemicals in drinking water which do or may cause health problems. These non-enforceable levels, based solely on possible health risks and exposure, are called Maximum Contaminant Level Goals.

The MCLG for phthalate has been set at zero because EPA believes this level of protection would not cause any of the potential health problems described below.

Based on this MCLG, EPA has set an enforceable standard called a Maximum Contaminant Level (MCL). MCLs are set as close to the MCLGs as possible, considering the ability of public water systems to detect and remove contaminants using suitable treatment technologies.

The MCL has been set at 6 parts per billion (ppb) because EPA believes, given present technology and resources, this is the lowest level to which water systems can reasonably be required to remove this contaminant should it occur in drinking water.

These drinking water standards and the regulations for ensuring these standards are met, are called National Primary Drinking Water Regulations. All public water supplies must abide by these regulations.

What are the Health Effects?

Short-term: EPA has found phthalate to potentially cause the following health effects when people are exposed to it at levels above the MCL for relatively short periods of time: mild gastrointestinal disturbances, nausea, vertigo.

Long-term: Phthalate has the potential to cause the following effects from a lifetime exposure at levels above the MCL: damage to liver and testes; reproductive effects; cancer.

How much DEHP is produced and released to the environment?

Disposal of polyvinyl chloride and other DEHP-containing materials by incineration, landfill, etc., will result in the release of DEHP into the environment. DEHP has been detected in the effluent of numerous industrial plants.

From 1987 to 1993, according to EPA's Toxic Chemical Release Inventory, DEHP releases to land and water totalled over 500,000 lbs., of which about 95 percent was to land. These releases were primarily from rubber and plastic hose industries. The largest releases occurred in Wisconsin and Tennessee.

What happens to DEHP when it is released to the

environment?

DEHP will adhere to soil, and so will neither evaporate nor leach into groundwater. DEHP has a strong tendency to adsorb to soil and sediments. In water, it will be degraded by microbes in a matter of weeks. DEHP does have a tendency to accumulate in aquatic organisms.

How will DEHP be Detected in and Removed from My Drinking Water?

The regulation for phthalate became effective in 1994. Between 1993 and 1995, EPA required your water supplier to collect water samples every 3 months for one year and analyze them to find out if phthalate is present above 0.6 ppb. If it is present above this level, the system must continue to monitor this contaminant.

If contaminant levels are found to be consistently above the MCL, your water supplier must take steps to reduce the amount of phthalate so that it is consistently below that level. The following treatment methods have been approved by EPA for removing phthalate: Granular activated charcoal.

How will I know if DEHP is in my drinking water?

If the levels of phthalate exceed the MCL, 6 ppb, the system must notify the public via newspapers, radio, TV and other means. Additional actions, such as providing alternative drinking water supplies, may be required to prevent serious risks to public health.

Drinking Water Standards:

Mclg: zero

Mcl: 6 ppb

DEHP Releases to Water and Land, 1987 to 1993 (in pounds):

	Water	Land
TOTALS* (in pounds)	**16,910**	**471,191**

Top Five States*		
WI	500	255,000
TN	3,491	80,419
OH	268	62,982
NJ	3,956	23,139
NY	500	13,284

Major Industries		
Misc rubber products	274	311,900
		80,019

Rubber, plastic hose	10	80,019
Cyclic crudes, intermed.	3,099	12,200

* Water/Land totals only include facilities with releases greater than 100 lbs.

Learn more about your drinking water!

EPA strongly encourages people to learn more about their drinking water, and to support local efforts to protect and upgrade the supply of safe drinking water. Your water bill or telephone book's government listings are a good starting point.

Your local water supplier can give you a list of the chemicals they test for in your water, as well as how your water is treated.

Your state Department of Health/Environment is also a valuable source of information.

For help in locating these agencies or for information on drinking water in general, call: EPA's Safe Drinking Water Hotline: (800) 426-4791.

For additional information on the uses and releases of chemicals in your state, contact the: Community Right-to-Know Hotline: (800) 424-9346

List of Contaminants

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Last updated on Tuesday, February 28th, 2006
URL: http://www.epa.gov/safewater/dwh/c-soc/phthalat.html

'Gender-bending' chemicals found to 'feminise' boys

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17:17 27 May 2005
NewScientist.com news service
Andy Coghlan

"Gender-bending" chemicals mimicking the female hormone oestrogen can disrupt the development of baby boys, suggests the first evidence linking certain chemicals in everyday plastics to effects in humans.

The chemicals implicated are phthalates, which make plastics more pliable in many cosmetics, toys, baby-feeding bottles and paints and can leak into water and food.

All previous studies suggesting these chemicals blunt the influence of the male hormone testosterone on healthy development of males have been in animals. "This research highlights the need for tougher controls of gender-bending chemicals," says Gwynne Lyons, toxics adviser to the WWF, UK. Otherwise, "wildlife and baby boys will be the losers".

The incriminating findings came from a study of 85 baby boys born to women exposed to everyday levels of phthalates during pregnancy. It was carried out by Shanna Swan at the University of Rochester School of Medicine and Dentistry, New York, US, and colleagues.

As an index of feminisation, she measured the "anogenital distance" (AGD) between the anus and to the base of the penis. She also measured the volume of each boy's penis. Earlier studies have shown that the AGD is twice in boys what it is in girls, mainly because in boys the hormone testosterone extends the length of the perineum separating the anus from the testicles.

Undescended testicles

In animals, AGD is reduced by phthalates - which mimic oestrogen - which keep testosterone from doing its normal job. At higher doses, animals develop more serious abnormalities such as undescended testicles and misplaced openings to the urethra on the penis - a group of symptoms called "phthalate syndrome" in animals.

When Swan's team measured concentrations of nine phthalate metabolites in the urine of pregnant women, they found that four were linked with shorter AGD in sons born to women showing high exposure levels.

Although none of the boys developed abnormal genitals, the quarter of mothers who were exposed to the highest concentrations of phthalates were much more likely to have had boys with short AGDs compared with the quarter of mothers who had the lowest exposures to the chemicals.

And although all the boys had genitals classified as “normal”, 21% of the boys with short AGDs had incomplete testicular descent, compared with 8% of other boys. And on average, the smaller the AGD, the smaller the penis.

Changing masculinisation

Swan believes that at higher exposures, boys may suffer from testicular dysgenesis syndrome - the human collection of more serious abnormalities which corresponds to “phthalate syndrome”.

“We’re not exactly seeing testicular dysgenesis syndrome, but a cluster of endpoints consistent with it,” said Swan on at an international conference on Endocrine Disrupting Chemicals in San Diego, US.

“If you see this, you’re very likely to see every other aspect of masculinisation changed too,” says Fred vom Saal, professor of reproductive biology at the University of Missouri-Columbia, US.

Vom Saal says this could include behavioural changes like those seen in animals, including an aversion to “rough-and-tumble” play and a reduction in aggressiveness.

Criticising methods

Environmentalists say the results strengthen the case for a ban or restriction on some phthalates in baby toys, as has been proposed in Europe and California.

But phthalate manufacturers maintain that the chemicals have been thoroughly tested and are safe. They are also critical of aspects of the study. David Cadogan, director of the European Council for Plasticisers and Intermediates, points out that just one urine sample was taken from each pregnant woman, which cannot rule out drastic variations in exposure over time.

Also, he says that all AGD measurements should have been taken in babies exactly the same age, not in babies ranging from three to 24 months in age as in the study. The disparity in ages meant that complicated mathematical analyses had to be applied which may have made it more difficult to distinguish genuine differences in AGD from differences accounted for by age or weight.

Swan’s results will appear in the journal *Environmental Health Perspectives*.

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http://www.fcm.missouri.edu/faculty/swan.html

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European Council for Plasticisers and Intermediates
http://www.ecpi.org/

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http://www.panda.org/about_wwf/what_we_do/toxics/problems/edcs.cfm

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Nurses: Taking Precautionary Action on a Pediatric Environmental Exposure: DEHP

Anna Gilmore Hall

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Posted 04/11/2006

Abstract and Introduction

Abstract

Di(2-ethylhexyl) phthalate, or DEHP, is a chemical used to soften rigid polyvinyl chloride (PVC) plastic. Medical devices made of flexible PVC, such as intravenous (IV) bags and tubing, contain DEHP to make them pliable and soft. Animal studies show that exposure to DEHP can damage the liver, kidneys, lungs, and reproductive system, particularly the developing testes of prenatal and neonatal males. Because of this, the U.S. Food and Drug Administration (FDA) has issued a Public Health Notification on PVC devices containing DEHP, urging health care providers to use DEHP-free devices for certain vulnerable patients. Many hospitals and health systems have successfully transitioned away from use of DEHP, particularly in neonatal intensive care units (NICUs).

Introduction

June 9, 2005, The Los Angeles Times - "A new Harvard study of infants treated in neonatal intensive care units finds that a substance used in medical supplies shows up in babies' bodies. What's more, the substance shows up in those babies in roughly direct proportion to the amount to which the babies are exposed. The substance, dubbed "DEHP," is a chemical used in PVC plastic products that has been shown to cause testicular damage in animal studies."

As a pediatric nurse, are you aware of the health risks associated with DEHP-containing medical devices, and do you know what the alternatives are?

Prenatal and neonatal children are two of the most vulnerable populations to receive health care. Every day, nurses do everything in our power to ensure that our most vulnerable patients are protected from harm. When chemicals and materials used in the delivery of health care are linked to adverse health effects, protecting these ultra-vulnerable populations is of particular concern. Learn about just such an instance, and the safer alternatives that are available, below.

What It Is

Polyvinyl chloride (PVC) is one of the most widely used plastics in medical care, used in everything from blood bags to exam gloves. Because this type of plastic is naturally hard and brittle, chemicals are added to make it soft and flexible. Medical products made of PVC are usually softened with a plasticizer from the family of chemicals known as phthalates (pronounced THAH-lates).

Di(2-ethylhexyl) phthalate, or DEHP, is the specific phthalate commonly used in PVC to provide flexibility and

resistance to temperature fluctuations. DEHP can be found in a wide variety of medical products, such as bags containing blood, plasma, intravenous fluids, and total parenteral nutrition, tubing associated with their administration, nasogastric tubes, enteral feeding tubes, umbilical catheters, extracorporeal membrane oxygenation (ECMO) circuit tubing, hemodialysis tubing, respiratory masks, endotracheal tubes, and examination gloves (Green et al., 2005).

Outside the health care setting, people are exposed to DEHP and other phthalates from a variety of sources, including PVC toys, vinyl shower curtains, car seats, wallpaper, floor coverings, and many other consumer products.

The Problem With DEHP

In addition to the characteristics that make it useful for medical devices, DEHP is also highly lipophilic (fat soluble). When used in PVC plastic, DEHP is loosely chemically bonded to the plastic and readily leaches into blood or other lipid-containing solutions in contact with the plastic. The rate of DEHP leaching depends on many factors. The type of solution in contact with the plastic, temperatures during storage and at the time of use, storage time, and percent DEHP in the plastic product all play a part (Marcel, 1973).

This leaching of DEHP into humans via the solution with which it is in contact increases the risk of certain adverse health outcomes. Animal studies show that exposure to DEHP can damage the liver, kidneys, lungs, and reproductive system, particularly the developing testes of prenatal and neonatal males. The FDA and National Toxicology Program's Center for Evaluation of Risks to Human Reproduction conclude that these animal studies are relevant to people.

As stated in the 2002 *Aggregate Exposures to Phthalates in Humans* report, "[d]eveloping organisms are uniquely vulnerable to phthalate exposures, and in particular, the developing male reproductive tract appears to be the most sensitive organ system. Abnormal development of the testes, penis, and other components of the male reproductive tract occurs at levels of exposure that are hundreds or thousands of times lower than those necessary to cause damage in adults (DiGangi, Schettler, Cobbing, & Rossi, 2002).

More recently, researchers at Harvard School of Public Health have found that babies in neonatal intensive care units have high exposure levels to this reproductive toxicant. For the peer-reviewed study, researchers measured the level of a DEHP metabolite in the urine of neonates treated in the NICUs, and were able to correlate the level of exposure to DEHP-containing products to the level of DEHP metabolite found in the babies' urine. Infants who received intensive treatments with PVC medical devices were exposed, on average, to levels of DEHP that were 25 times higher than levels measured in the general population by the U.S. Centers for Disease Control. As their medical treatments intensified, the sick infants were exposed to progressively higher exposures of DEHP (Green et al., 2005).

Government Actions

Several government agencies have concluded that some patients are likely to be exposed to potentially unsafe amounts of DEHP while receiving medical care. The U.S. Food and Drug Administration (FDA) has issued an FDA Safety Assessment and a Public Health Notification on DEHP-containing PVC devices, urging health care providers to use alternatives for certain vulnerable patients (U.S. Food and Drug Administration, 2001).

According to the FDA Public Health Notification: "Two factors determine the degree of risk posed by exposure to DEHP in a medical setting. The first is the patient's sensitivity to DEHP. Based on the evidence cited above, the male fetus, male neonate, and peripubertal male would appear to be high-risk groups. The second factor is the dose of DEHP received by the patient. This is determined largely by the type of procedure performed, as well as the frequency and duration of these procedures."

FDA identified the following procedures as posing the highest risk of exposure to DEHP:

- Exchange transfusion in neonates
- ECMO in neonates
- Total Parenteral Nutrition (TPN) in neonates (with lipids in PVC bag)
- Multiple procedures in sick neonates (high cumulative exposure)
- Hemodialysis in peripubertal males
- Hemodialysis in pregnant or lactating women

- Enteral nutrition in neonates and adults
- Heart transplantation or coronary artery bypass graft surgery (aggregate dose)
- Massive infusion of blood into trauma patient
- Transfusion in adults undergoing ECMO

The initial FDA safety assessment followed closely on the heels of an October 2000 report by the National Toxicology Program's Center for the Evaluation of Risks to Human Reproduction. The expert panel report expressed "serious concern" that exposure to DEHP may adversely affect male reproductive tract development in critically ill infants and "concern" over the levels of DEHP exposure to pregnant women, breast-feeding mothers and healthy infants and toddlers (U.S. Department of Health and Human Services, 2000). In Canada, an expert advisory panel to Health Canada, the Canadian equivalent to the U.S. FDA, has recommended that health care providers not use DEHP-containing devices in the treatment of pregnant women, breastfeeding mothers, infants, males before puberty, and patients undergoing cardiac bypass hemodialysis or heart transplant surgery (Health Canada, 2003).

Alternatives: What's Already Been Done

Cost effective alternatives to DEHP-containing medical devices are available for most uses in health care. With the weight of the evidence suggesting that exposure to this reproductive toxicant should be eliminated where possible, many hospitals and health systems have successfully transitioned away from use of DEHP, particularly in neonatal intensive care units (NICUs).

June 9, 2005, San Francisco Chronicle, Toxic agent found in treated newborns is linked to plastic: "Kaiser Permanente, Alta Bates Summit Medical Center, Catholic Healthcare West and the John Muir Medical Center in Walnut Creek, among others, already are buying mostly DEHP-free plastic devices, and pressuring manufacturers and suppliers to produce safe alternatives, according to representatives."

John Muir Medical Center in Walnut Creek, CA, first considered eliminating DEHP from its NICU when a resident pediatrician brought the issue to the attention of the intensive care nursery (ICN) staff. The information he provided, as well as the 2002 FDA public health notification, prompted the ICN staff to look closely at ways to reduce the potential risks of DEHP. They evaluated the NICU's product list and identified which products contained DEHP and which were DEHP-free. Once this step was accomplished, the hospital's clinical nurse specialist led the DEHP reduction effort, working together with the medical and nursing staff to develop a short- and long-term DEHP reduction plan. John Muir was able to announce a virtually DEHP-free NICU within 6 months of beginning this effort (Health Care Without Harm [HCWH], 2003a).

A similar DEHP elimination story on a much larger scale comes from Kaiser Permanente, the nation's largest nonprofit health plan that operates 29 medical centers in 9 states and the District of Columbia. Beginning in July 2001, after learning of the potential hazards to neonatal patients from DEHP exposure, Kaiser Permanente staff underwent a process to identify DEHP-containing medical devices used in NICUs and to evaluate alternatives. Staff used a risk-management process to target products and began a series of clinical trials to test alternatives. Based on their results, the health system chose to switch to non-DEHP products for three commonly used NICU devices: umbilical vessel catheters, PICC lines, and enteral feeding products (HCWH, 2003b).

At Miller Children's Hospital in Long Beach, CA, a patient safety approach framed their DEHP elimination efforts. Because numerous scientific studies show that TPN bags and tubing pose the highest risk of DEHP exposure to neonates, this was their first priority product to eliminate, followed by IV sets. With help from the pediatric department's medical staff, clinical products committee, central supply products manager, and the hospital's risk management attorney, Miller Children's Hospital attained its target of 100% DEHP elimination in IV and TPN products in December 2002 (HCWH, 2003c).

What You Can Do

One of the first steps to eliminating PVC from health care facilities is to identify which products contain it. Health Care Without Harm has developed a PVC/DEHP Audit Tool for help with this; see www.noharm.org/pvcDehp/reducingPVC.

Once DEHP-containing products have been identified, an evaluation of safer alternatives must be performed. Often it

is beneficial to organize a committee of stakeholders to perform this evaluation and determine a plan for replacing DEHP-containing products with their safer DEHP-free counterparts.

The Environmental Health Hot Topics column focuses on issues, information, and practical guidelines related to environmental health problems, including sources of toxicants and resources for nurses to prevent, minimize, or treat adverse environmental exposures particularly as they relate to children. To suggest topics, obtain author guidelines, or to submit queries or manuscripts, contact Ann Pike-Paris, MS, RN, Section Editor; Pediatric Nursing, East Holly Avenue Box 56; Pitman, NJ 08071-0056; (856) 256-2300 or FAX (856) 256-2345.

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- U.S. Food and Drug Administration. (2002). Public health notification: PVC devices containing the plasticizer DEHP. Retrieved September 6, 2005, from http://www.fda.gov/cdrh/safety/dehp.html

Sidebar: Resources

For More Information

Health Care Without Harm
PVC & DEHP: The Issue
www.noharm.org/PVCdehp/issue
Aggregate Exposures to Phthalates in Humans Report
www.noharm.org/library/docs/Phthalate_Report.pdf

Government Reports and Advisories

U.S. Food and Drug Administration
FDA Public Health Notification: PVC Devices Containing the Plasticizer DEHP
www.fda.gov/cdrh/safety/dehp.html

U.S. Food and Drug Administration
Safety Assessment of DEHP Released from PVC Medical Devices
www.noharm.org/details.cfm?ID=740&type=document

Center for the Evaluation of Risks to Human Reproduction, National Toxicology Program, U.S. Department of Health and Human Services
NTP-CERHR Expert Panel Report on Di(2-ethylhexyl) Phthalate
www.noharm.org/details.cfm?type=document&id=744

Health Canada
Draft Position Statement on DEHP in Medical Devices
www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/md-im/dehp_position_draft_ebauche_e.pdf

Tools, Alternatives, and Case Studies

Alternatives to PVC and DEHP Medical Devices
www.noharm.org/pvcDehp/pvcFree

PVC/DEHP Audit Tool
www.noharm.org/details.cfm?type=document&id=741

Replacing DEHP: Hospital Case Studies
www.noharm.org/pvcDehp/reducingPVC#case

A series of fact sheets on reducing exposure to DEHP
www.noharm.org/pvcDehp/reducingPVC#tools

Sidebar: Latest Science Indicates

- Intensive use of DEHP-containing medical devices in NICU infants results in higher exposure to DEHP as reflected by elevated urinary levels of MEHP, the chemical's metabolite. (Harvard study)
- Patients receiving certain intensive medical treatments may receive unsafe amounts of DEHP. (FDA Safety Assessment)

Sources: Green et al. (2005); U.S. Food and Drug Administration (2001).

Sidebar: Hot Box - DEHP

Chemical name: di(2-ethylhexyl) phthalate

Chemical family: phthalates

Use in health care: as a plasticizer in flexible PVC plastics

Exposure risks: damage to liver, kidneys, lungs, and reproductive system

Most vulnerable populations: pregnant women and children, particularly prenatal and neonatal males

Anna Gilmore Hall, **RN**, is Executive Director, Health Care Without Harm, Arlington, VA. HCWH is an international coalition of 443 organizations in 52 countries working together to transform the health care industry so it is ecologically sustainable. Ms. Hall received her CAE certification in association management from the American Society of Association Executives in 2003.

Groundwater Replenishment System

Studies Conclude Water Produced by Groundwater Replenishment System Will Be Safe, Improve Basin's Quality

Water quality has always been a top priority of the Orange County Water District (OCWD). This commitment – along with the need to ensure enough safe, high-quality water for the future – came to the forefront nearly a decade ago when the sponsoring agencies proposed the Groundwater Replenishment (GWR) System.

The GWR System will provide a new supply of reliable, high-quality water for north and central Orange County by purifying highly treated sewer water through state-of-the-art microfiltration, reverse osmosis and ultraviolet light and hydrogen peroxide treatment. The result will be water of near-distilled quality from the GWR System in 2007.

To underscore its commitment to safety and quality, OCWD commissioned water quality studies on the project in 2000. The studies were intended to provide additional information on the proposed treatment processes along with information on how the GWR System water will be used to replenish the groundwater basin underlying north and central Orange County.

The water quality study tested the proposed treatment processes on the same source water as that for the full-scale GWR System. Real operating data (not a textbook study) was used as the basis for the water quality evaluation.

Published Findings Confirm Safety

In findings released in 2001, the studies concluded that the water produced by this system would be safe for consumers and actually improve the groundwater basin's overall quality. The findings were published in a report called the "Groundwater Replenishment System Water Quality Evaluation – Risk Assessment" (EOA, Inc., November 2000).

The Groundwater Replenishment System "will produce very safe, high-quality water through a process similar to that used by bottled water companies."

Sandra Smoley, R.N.
Former Agency Secretary, California Health and Welfare Agency

OCWD and Orange County Sanitation District (OCSD) also appointed an independent advisory committee to provide an additional level of expertise and review of the studies. The advisory committee concurred with the report's findings. The advisory committee was composed of recognized experts in the fields of public health, microbiology, environmental engineering, toxicology and risk assessment, including professors from University of California, Davis; University of California, Berkeley; and the University of North Carolina.

Even before the water quality studies were completed, the GWR System underwent rigorous scrutiny by interested citizens, water experts and local, state and federal officials. The first extensive study, an environmental impact report/statement prepared in 1998-99, found the project will have no significant adverse environmental impacts and noted that "…the quality of the recycled water is expected to be better than that of alternative water supplies" available to Orange County.

Following the environmental review, OCWD decided to further confirm these findings and took the additional step of conducting the water quality studies.

Conducting the Studies

The purpose of the studies was to compare different water sources representing two alternatives. Under one option ("No Action"), the groundwater basin would continue to receive water from the Santa Ana River and the county's two imported supplies, the Colorado River and Northern California, just as it does today. Under the other alternative ("Proposed Action"), water produced by the GWR System would be added to the existing blend of Santa Ana River and imported water from the two imported supplies.

The experts who conducted the studies employed methods consistent with the U.S. Environmental Protection Agency's guidance for risk assessment. They used estimates of the relative risks to human health associated with each alternate water source. They analyzed samples from the three sources (Santa Ana River, imported water from Northern California and Colorado River) and identified constituents of potential concern in each.

"The Groundwater Replenishment System will greatly reduce Orange County's reliance on imported water by rejuvenating valuable water lost to the ocean as well as provide a creative, new, safe and reliable water supply to meet our growing demand for high-quality water."

Hoag Memorial Hospital Presbyterian

Conclusions Concerning Public Health

In keeping with standard practices in such analyses, the studies divided the possible health risks associated with the three water supplies into three categories: non-carcinogenic, carcinogenic and microbiological contaminants. In brief, the conclusions drawn about the three categories follow:

Risks associated with non-carcinogenic health effects

Water from any of the three sources should not cause significant non-carcinogenic risk to public health. Indeed, the potential risk posed by GWR System water is lower than the other two sources.

Risks associated with carcinogenic health effects

The carcinogenic risks associated with direct consumption of water from the GWR System should be lower than that associated with either Santa Ana River or imported (purchased) supplies from the Colorado River and Northern California.

Arsenic is the constituent that accounts for the majority of the risk in both alternatives ("No Action" and "Proposed Action.") The levels of arsenic in all three water sources, however, are below the existing regulatory minimum levels for public safety.

N-nitrosodimethylamine (NDMA) and 1,4 dioxane – which are used primarily as commercial chemicals – present more carcinogenic risk than any other constituent identified in GWR System water. At the time this study was performed, the California Department of Health Services had not established regulations regarding maximum levels of NDMA or 1,4 dioxane in drinking water. It should be noted, however, that the membrane technologies – microfiltration and thin-film composite reverse osmosis and ultraviolet light and hydrogen peroxide – will remove emerging compounds such as NDMA and 1,4 dioxane. All of these technologies will be used on 100 percent of the water purified by the GWR System.

Risks associated with microbiological contaminant health effects

GWR System water is "…projected to pose much less risk than Santa Ana River or imported water supplies from bacteria, parasites and viruses, provided that all processes in the system treatment facility are operating fully and properly," the report said. It is important to note that for purposes of the studies, the experts assumed that each supply was consumed directly, before being used to recharge the groundwater basin. In fact, GWR System product water will be percolated into the groundwater basin where it will remain for at least one year. This will allow the GWR System water to undergo a natural filtering process while blending with water from the Santa Ana River, Northern California and the Colorado River.

Recommendations Concerning Operations

The conclusions about public health risks assume that the full-scale GWR System produces water of a quality similar to that evaluated in the studies. To ensure such production, the study concludes that the system should incorporate a detailed monitoring program to ensure ongoing, reliable operations in both treatment and pipeline conveyance. The program should include a plan to dispose of water that does not meet standards, the study said (the GWR System will include constant monitoring programs).

"The project will produce the safest and highest quality water available from any source – imported or local."

Taiwanese Medical and Dental Association of Orange County

Conclusion of Independent Advisory Committee

The independent advisory committee reviewed the report and summarized its findings. The committee agreed with the report's findings and concluded that "…the health risk associated with the quality of recharge water expected under the 'Proposed Action' (GWR System) will be less than or equal to that associated…" with the existing water supplies.

Preparation of Risk Assessment

EOA Inc., an environmental and public health engineering firm based in Oakland, Calif., conducted the risk assessment studies. In addition, OCWD organized the independent advisory committee. The committee members were:

- Robert C. Cooper, Ph.D., professor at University of California, Berkeley (microbiology, virology, public health)
- George Tchobanoglous, Ph.D., P.E., professor at University of California, Davis (environmental engineering)
- Eddie Wei, Ph.D., professor at University of California, Berkeley (toxicology)
- Douglas Crawford-Brown, Ph.D., professor at University of North Carolina (environmental science)
- Margie Nellor, M.S., Los Angeles County Sanitation District (health effects)

OCWD also assembled a group of six ex-officio advisors to ensure that local stakeholders and staff from the appropriate health and regulatory agencies understood and accepted the assessment. The advisors represented the California Department of Health Services, the Santa Ana Regional Water Quality Control Board, the City of Anaheim and also included a congressional fellow.

To see a copy of the Executive Summary of the report, please contact the Orange County Water District public affairs department at 714-378-3206. Copies of the full report are in the OCWD Technical Library.

The Groundwater Replenishment System "…will provide a long-term public health benefit to Orange County residents."

John Balbus, M.D., M.P.H.
Director, Environmental Health Program
Environmental Defense

How the System Works

The Groundwater Replenishment System, a joint project of the Orange County Water District and the Orange County Sanitation District, will use state-of-the-art membrane technology and ultraviolet light to produce water of near-distilled quality that exceeds state and federal drinking water standards. The water will then be used as another source to replenish Orange County's groundwater basin, along with water from the Colorado River, Northern California and the Santa Ana River.

The process will begin with highly treated sewer water from OCSD's Fountain Valley facility. This water will undergo several additional treatment steps, also referred to as an "integrated treatment process," that includes microfiltration, thin-film composite reverse osmosis and ultraviolet light and hydrogen peroxide treatment.

After undergoing this additional treatment, the water will be used to replenish the groundwater basin underlying north and central Orange County. The purified water will be pumped to spreading basins and travel the same natural filtering path that rainwater takes as it moves underground. It also will be used to expand the Seawater Intrusion Barrier that keeps the Pacific Ocean out of the groundwater basin.

Once in the basin, the purified water will blend with other groundwater from the Santa Ana River and imported sources.

What Other Public Health, Medical Professionals and Scientists Have Said About the Groundwater Replenishment System

"I am confident that on balance, the System will make a substantial contribution to the prevention of disease transmission and maintenance of overall public health within the county."

Sanford Brown, M.P.H., Ph.D.
Professor Emeritus of Health Science, California State University, Fresno

The Groundwater Replenishment System "will be approved and monitored by the California Department of Health Services, the Regional Water Quality Control Board and Orange County Health Agency…this should provide adequate oversight and public health protection."

Christine L. Moe, Ph.D.
Associate Professor, Rollins School of Public Health, Emory University

"I am confident that the advanced treating technologies that will be applied to previously treated wastewater – microfiltration, reverse osmosis and ultraviolet light and hydrogen peroxide – will produce output flows of clean, high-purity water."

H. John Blossom, M.D.
Director, California Area Health Education Center, University of California, San Francisco-Fresno

"The Groundwater Replenishment System will provide ample protection from waterborne disease for Orange County residents."

Ralph Morris, M.D., M.P.H.
Public Health Physician

"Hospitals in Orange County are significant users of water..." The Groundwater Replenishment System "will help assure the availability of this valuable resource in the future."

Hospital Association of Southern California

"Having completed my assessment, I wish to commend the Orange County Water District and Orange County Sanitation District for moving forward with this project."

Kellogg J. Schwab, Ph.D.
The Center for Water and Health, Johns Hopkins Bloomberg School of Public Health

http://www.sciencedaily.com/releases/2007/05/070507071807.htm

Premature Births Peak Seasonally When Pesticides And Nitrates In Surface Water Are Highest

Science Daily — The growing premature birth rate in the United States appears to be strongly associated with increased use of pesticides and nitrates, according to work conducted by Paul Winchester, M.D., professor of clinical pediatrics at the Indiana University School of Medicine. He reports his findings May 7 at the Pediatric Academic Societies' annual meeting, a combined gathering of the American Pediatric Society, the Society for Pediatric Research, the Ambulatory Pediatric Association and the American Academy of Pediatrics.

Dr. Winchester and colleagues found that preterm birth rates peaked when pesticides and nitrates measurements in surface water were highest (April-July) and were lowest when nitrates and pesticides were lowest (Aug.-Sept.).

More than 27 million U.S. live births were studied from 1996-2002. Preterm birth varied from a high of 12.03% in June to a low of 10.44% in September. The highest rate of prematurity occurred in May-June (11.91%) and the lowest for Aug-Sept (10.79%) regardless of maternal age, race, education, marital status, alcohol or cigarette use, or whether the mother was an urban, suburban or rural resident. Pesticide and nitrate levels in surface water were also highest in May-June and lowest in August -- September, according to the U.S. Geological Survey.

For the past four years, Dr. Winchester and colleagues have focused attention on the outcomes of pregnancy in Indiana and the United States in relation to environmental pesticides and nitrates in surface and drinking water. Last year at the Pediatric Academic Societies' annual meeting, Dr Winchester reported that birth defects peak in Indiana and in the United States as a whole during April through July, the same months as pesticides and nitrates reach their maximum concentrations in surface water. This year's presentation expands upon that work.

"A growing body of evidence suggests that the consequence of prenatal exposure to pesticides and nitrates as well as to other environmental contaminants is detrimental to many outcomes of pregnancy. As a neonatologist, I am seeing a growing number of birth defects, and preterm births, and I think we need to face up to environmental causes," said Dr Winchester, who is also director of Newborn Intensive Care Services at St. Francis Hospital in Indianapolis.

"Preterm births in the United States vary month to month in a recurrent and seasonal manner. Pesticides and nitrates similarly vary seasonally in surface water throughout the U.S. Nitrates and pesticides can disrupt endocrine hormones and nitric oxide pathways in the developing fetus," he said.

"I believe this work may lay the foundation for some of the most important basic and clinical research, and public health initiatives of our time. To recognize that what we put into our environment has potential pandemic effects on pregnancy outcome and possibly on child development is a momentous observation, which hopefully will help transform the way humanity cares for its world," said James Lemons, M.D., Hugh McK. Landon Professor of Pediatrics at the IU School of Medicine. Dr. Lemons is director of the section of neonatal-perinatal medicine at the IU School of Medicine and heads the Riley Hospital for Children of Clarian Health's section of neonatal-perinatal medicine.

Collaborating with Dr. Winchester on this study were Akosua Boadiwaa Adu-Boahene and Sarah L. Kosten of the IU School of Medicine, Alex K Williamson of the U.S. Geological Survey, and Ying Jun,

Ph.D. of the University of Cincinnati. The work was funded by the Division of Neonatology, Department of Pediatrics of the IU School of Medicine.

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AMERICAN ACADEMY OF PEDIATRICS

TECHNICAL REPORT

Katherine M. Shea, MD, MPH, and the Committee on Environmental Health

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.[1] They are also used in solvents, lubricating oils, fixatives, and detergents and in products such as cosmetics and wood finishes.[2] Phthalates are not covalently 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.[3]

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.[2] 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.[2,4,5] 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.[1,6,7] 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,[8–10] so

The guidance in this report does not indicate an exclusive course of treatment or serve as a standard of medical care. Variations, taking into account individual circumstances, may be appropriate.

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.[11] It is estimated that the total intake of DEHP, excluding nondietary ingestion, is higher in all children younger than 19 years than in adults.[7] Highest estimated intakes are in children 0.5 to 4 years old (Table 1).

Nondietary ingestion of phthalates can occur when children mouth, suck, or chew on phthalate-containing toys or other objects.[12–14] This source of exposure is difficult to quantify directly. Estimates are made by combining data on the amount of time children mouth nonfood items[15,16] and leaching rates of DEHP and DINP from 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.[17] Nondietary ingestion can be expected to increase total exposure by an order of magnitude or more.[15,17–19] 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.[2] DINP has been substituted for the more toxic DEHP in many other toys intended for older children.[17]

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.[2]

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[20–23] and during hemodialysis.[24–26] Beginning in the 1980s, investigators measured DEHP and MEHP delivered during neonatal exchange transfusions.[27–29] More recently, large exposures have been documented during ECMO[30,31] and cardiac surgery.[32] Preliminary data also show possible exposure during mechanical ventilation if PVC circuitry is used.[33,34] PVC infusion lines for lipid-containing parenteral nutrition may also deliver large amounts of DEHP to neonates.[35,36] 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[27] 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.[27,28] Because very ill neonates receive multiple medical interventions, it is likely that total exposures to DEHP and MEHP could be even higher.[2,37]

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.[38–40] A single case-control study found higher serum levels of several phthalates in girls with premature thelarche compared with girls in a control group.[41] 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.[2] 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)[7]

Substrate/Medium	Age (Years)				
	0.0–0.5	0.5–4	5–11	12–19	20–70
Ambient air: Great Lakes region	0.00003–0.0003	0.00003–0.0003	0.00004–0.0004	0.00003–0.0003	0.00003–0.0003
Indoor air	0.86	0.99	1.2	0.95	0.85
Drinking water	0.13–0.38	0.06–0.18	0.03–0.10	0.02–0.07	0.02–0.06
Food	7.9	18	13	7.2	4.9
Soil	0.000064	0.000042	0.000014	0.000004	0.000003
Total estimated intake	8.9–9.1	19	14	8.2	5.8

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.[2]

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.[2] In infants, pancreatic lipase systems are not fully mature until 6 to 12 months of age,[42–44] 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.[45,46] Neither premature nor full-term infants have mature glucuronidation until about 3 months of age.[47] 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.[31] 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.[48] 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.[49]

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[50] and DINP causes kidney and liver cancers in rodents.[49] 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,[51] but this theory remains to be confirmed.[52] 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.[53] 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 know 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.[54]

Phthalates can produce fetal death, malformations, and reproductive toxicity with different profiles for each chemical.[55] 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.[2,56–58]

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-

uolization 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).[59,60] 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.[60] 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).[61] In vitro studies demonstrated that the Sertoli cell is the primary cellular target and that MEHP is the toxic metabolite.[62] Evidence suggests that the mechanism of reproductive toxicity in rodents is different from the mechanism of carcinogenesis.[63]

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.[49] 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.[49]

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,[64] and in the United States, manufacturers have voluntarily changed patterns of use.[2] 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[a] (the "Koop report") concluded "that DEHP, as used in medical devices, is unlikely to pose a health risk to even highly exposed humans."[65(p25)] 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[b] released a report based on a different interpretation of the same literature.[66] This report concluded "the weight of the evidence indicates a significant potential for serious adverse effects on human health from DEHP-containing medical devices."[66(p53)] 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.[67]

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[c] reaches a similar conclusion, but Fiala[d] recommends removal of DINP (and DEHP) from children's toys because exposure may be high enough to cause concern.[18,68] The European Union has banned certain uses of phthalates in response to ongoing assessment of their expert committee and public concern.[64] For DINP, which is acknowledged to be less toxic to laboratory animals than is DEHP, the controversy centers around uncertainties about the magnitude of human exposures, particularly from nondietary ingestion by infants and toddlers.[15,17,19,69]

Recent Reports

In July 2000, the first expert panel convened by the Center for the Evaluation of Reproductive Risks to Humans[2] (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-

[a]"The American Council on Science and Health, Inc, is a consumer education consortium concerned with issues related to food, nutrition, chemicals, pharmaceuticals, lifestyle, the environment, and health." It is a nongovernmental, nonprofit organization partially supported by industry. Information is available online at: http://www.acsh.org/about/index.htm.

[b]"The Lowell Center of Sustainable Production develops, studies and promotes environmentally sound systems of production, health work environments, and economically viable work organizations." It is composed of faculty and staff at the University of Massachusetts Lowell and can be accessed online at: http://www.uml.edu/centers/lcsp.

[c]Authors of this evaluation cite funding by Jellinek, Schwartz & Connolly Inc, of Arlington, Virginia.

[d]Authors of this evaluation work for the Consumer Council, Austrian Standards Institute and the Institute of Food and Chemistry and Food Technology at Vienna University of Technology.

ductive risks to humans of 7 phthalate esters, including DINP and DEHP.[55]

For DEHP, the CERHR expert panel[e] 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.[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"[2(p101)] 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.[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.[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.[74] Dibutyl phthalate (DBP) is also teratogenic and toxic to the testes in laboratory animals, though less potent than DEHP.[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*,[76] which includes analysis of urinary metabolites for the same 7 phthalates as in the Blount study.[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 aide 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

[e]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.[2] 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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