New Arrival: CERHR Monograph Series on Reproductive Toxicants

The sheer number of environmental chemicals known or suspected to be reproductive toxicants—from the ingredients in paints and organic solvents to lead, pesticides, plastics, tobacco smoke, alcohol, and even hair treatments—can puzzle, frighten, and overwhelm the average parent. Their apprehensions reflect widespread concern among health professionals, scientists, and advocacy groups that exposure to some environmental agents may contribute to human reproductive and developmental disorders.

These are not idle concerns. According to the American Society for Reproductive Medicine, nearly 10% of couples desiring children have difficulty achieving pregnancy, and studies suggest that 35–50% of pregnancies do not reach successful completion. The American College of Obstetricians and Gynecologists reports that about 3% of babies are born with major birth defects.

Where can both the public and the experts go for trustworthy information on reproductive toxicants? One source is the Center for the Evaluation of Risks to Human Reproduction (CERHR). Established in 1998 by the National Toxicology Program (NTP) and the NIEHS, the center serves as a clearinghouse for reputable, up-to-date scientific information on environmental agents that could affect human reproduction and development. According to center director Michael Shelby, good, reliable information is the first line of defense against harm: "The more complete and accurate the information you have, the better decisions you can make," he says.

The center is charged with compiling and evaluating data on chemicals to assess their potential reproductive health hazards, and with making these assessments available to the public. With that driving purpose, the center recently announced the publication of new monographs on each of six phthalate esters, chemicals selected in part because of their widespread occurrence in the environment and resultant substantial potential for human exposure.

Good Information Takes Time

Anyone—from members of the scientific community, academia, government, industry, environmental, and public interest groups to individual citizens themselves—may nominate a chemical for review by the CERHR. Nomination of a chemical does not automatically lead to evaluation, however. The center may defer reviewing a nominated chemical, choosing instead to focus efforts on higher-priority chemicals or to wait until more reproductive and developmental toxicity data are available.

From the nominations tendered, selected chemicals are recommended for review by the CERHR's Core Committee, an advisory group of representatives from agencies including the NIEHS, the Centers for Disease Control and Prevention, the National Institute for Occupational Safety and Health, the Food and Drug Administration, the Environmental Protection Agency, and the Consumer Product Safety Commission. The committee bases its recommendations on several criteria, including extent of public concern, availability of research data for review, and extent of human exposure.

For each chemical or group of chemicals, the center recruits an independent panel of scientists and health experts from academia, industry, and government agencies representing wide-ranging expertise. This panel conducts a rigorous and critical review of all currently available scientific data and published literature on a particular chemical—anything that would illuminate understanding of a chemical's potential to cause developmental or reproductive toxicity in humans. The panel then meets in a public forum to draft the summary and conclusions of their deliberations. Producing an expert panel report is a laborious process that can take as long as 12 months to complete, once the initial decision to evaluate the chemical is made.

In evaluating all the evidence, the panel considers a number of potential health effects, including impaired fertility in males and/or females, adverse pregnancy outcomes, birth defects, and deficits in postnatal function. They determine patterns of chemical use and human exposure, arriving—sometimes after months of back-and-forth discussion and public comment—at a scientific consensus on the chemical's safety or potential reproductive hazards.

They don't stop there. Because their thorough review uncovers gaps in the data, the panel recommends research and testing needs, focusing on the data needed to make a true difference in the understanding of human risk. These recommendations point out the kinds of experience or data that—had they been available during the evaluation process—would have enabled the panel to achieve greater certainty about a chemical's reproductive or developmental toxicity, Shelby explains.

"Because [the expert panels] are independent bodies who also seek a lot of public input, they produce a very good output," says Robert Kavlock, director of the Reproductive Toxicology Division of the Environmental Protection Agency's National Health and Environmental Effects Research Laboratory. Kavlock chaired the CERHR expert panel on phthalates.

Maybe baby. With infertility affecting nearly 10% of couples who wish to have children, the public is demanding reliable information on reproductive hazards. Toward that end, the CERHR investigates environmental agents that may contribute to reproductive problems.

Top to bottom: CERHR; Comstock

Once the panel has completed its assessment and produced a final report, that report is submitted for public comment. The NTP then prepares a monograph on the chemical. This monograph includes any recently published data on the chemical, the expert panel report, and all public comments on the expert panel report. Supporting texts are included in the monograph, Shelby notes, so that if readers have questions, they can refer to the original documents.

Although the monographs contain technical data, they can also be used by lay readers who wish to learn more about the chemicals covered. Each monograph features an "NTP Brief" summary in a user-friendly question-and-answer format that sets forth whether and how people are exposed to the chemical, and what the possible reproductive and developmental health effects might be. This is followed by more in-depth explanations of the chemical's toxicity, toxicokinetics, and health effects, with results separated into human and animal studies.

Phthalates Lead the Way

First on the center's list of target chemicals was a group of seven phthalates, chemicals used to make polyvinyl chloride plastics more pliable. These ubiquitous plasticizers are found in countless consumer products, including shower curtains, medical devices, upholstery, raincoats, soft toys, latex adhesives, and personal care products. They pose a possible hazard because they remain chemically unbound to the plastic itself, meaning they can leach into the surrounding environment, such as a baby's mouth (from teething toys) or the bloodstream (from IV tubing). Other phthalates are present in materials used during manufacturing processes (conveyer belts, for example), exposing workers through skin contact or inhalation. Not all phthalates produce reproductive or developmental toxicity, however.

The first phthalate monograph, on di-*n*-butyl phthalate, appeared in March 2003. June saw the publication of the next five monographs, on di-isodecyl phthalate, di-*n*-octyl phthalate, di-*n*-hexyl phthalate, butyl benzyl phthalate, and di-isononyl phthalate (DINP). The seventh monograph, on di(2-ethylhexyl) phthalate (DEHP), is due in October.

Already, government and regulatory agencies have used the expert panel reports on phthalates to guide decisions regarding these chemicals. Even though the expert panel concluded that there was minimal concern for DINP's potential reproductive toxicity, its report prompted the Consumer Product Safety Commission to form its own group of experts to address concerns about the use of this chemical in teething toys. Because children ingest such low amounts of DINP from these toys, the commission did not recommend a ban on these products, although it did ask manufacturers to remove phthalates from soft rattles and teethers as a precaution until more research is done. Mouthing toys (nipples, teethers, pacifiers, and rattles) manufactured in the United States and Canada no longer contain phthalates, though plastic toys for older children may contain them, as do many foreign-made pacifiers and teething toys.

In another example, Shelby says that, following the CERHR's phthalate reviews, the Food and Drug Administration issued guidance pointing out potential harm to newborns and infants undergoing medical treatments using medical devices containing DEHP. Exposure to DEHP may harm the development of the reproductive system in male infants. Shelby adds that health

Chemicals Reviewed by CERHR Expert Panels to Date

1-Bromopropane: Used as a solvent for fats, waxes, and resins, and as an intermediate in the synthesis of pharmaceuticals, insecticides, quaternary ammonium compounds, flavors, and fragrances. Also used as a vehicle in spray adhesives and as a cold bath degreaser.

2-Bromopropane: Used as an intermediate in the synthesis of pharmaceuticals, dyes, and other compounds. Also present as a contaminant in 1-bromopropane. Bromopropanes are being considered as replacement chemicals for ozone-depleting chemicals such as hydrochlorofluorocarbons and chlorinated solvents.

Butyl benzyl phthalate: Largest use is in the production of vinyl tiles. Also used in food conveyor belts, artificial leather, automotive trim, and traffic cones.

Di-*n*-butyl phthalate: Typically used as a component of latex adhesives. Also used in cosmetics and other personal care products, as a plasticizer in cellulose plastics, and as a solvent for dyes.

Di(2-ethylhexyl) phthalate: Used in a wide variety of products, including flooring, wallpaper, vehicle upholstery, raincoats, toys, and food packaging. Currently the only phthalate plasticizer used in polyvinyl chloride medical devices such as blood bags and IV tubing.

Di-*n*-hexyl phthalate: Occurs in industrially important phthalates such as di-iso-hexyl phthalate (up to 25%) and C6–10 phthalate (up to 1%). May also occur in a variety of commercial products such as tool handles, dishwasher baskets, flooring, vinyl gloves, flea collars, and food conveyor belts.

Di-isodecyl phthalate: Used in a wide variety of products, including coverings on wires and cables, artificial leather, toys, carpet backing, and pool liners. Has only limited use in food packaging and handling.

Di-isononyl phthalate: Used in a wide variety of products, including garden hoses, pool liners, flooring tiles, tarps, and toys. Has only limited use in food packaging.

Di-*n*-octyl phthalate: No commercial uses, but makes up approximately 20% of the industrially important C6–10 phthalate mixture, which is used to manufacture a variety of commercial products, including flooring, carpet tiles, tarps, pool liners, garden hoses, seam cements, bottle cap liners, and conveyor belts. Approved by the Food and Drug Administration as an indirect food additive.

Ethylene glycol: Used as a chemical intermediate in the production of polyester compounds. Widespread public exposure due to its use in heating and cooling systems (for example, as an automotive antifreeze and a de-icer for aircraft).

Methanol: Used in chemical syntheses and as an industrial solvent. Found in a variety of consumer products such as paints, antifreeze, cleaning solutions, and adhesives. Also used in racing car fuels, with the potential for expanded use as a regular vehicle fuel or fuel additive. Created as a by-product of sewage treatment, fermentation, and paper production.

Propylene glycol: Used commercially as an intermediate in the manufacture of unsaturated polyester resins and in the production of plasticizers. Public exposure occurs through its use (approved by the Food and Drug Administration) in food, tobacco, pharmaceutical products, and cosmetics. Used in various paints and coatings, and as an antifreeze and de-icing solution.

authorities in Canada have issued similar guidance.

The reports and monographs are also stimulating further research. The Advanced Medical Technology Association, representing a coalition of medical product manufacturers, designed a study with input from the Food and Drug Administration and the CERHR to address one of the DEHP-related data gaps identified by the expert panel. "Most of the data CERHR reviewed was from oral exposure studies," explains Jon Cammack, senior research director for IV tubing manufacturer Baxter Healthcare. "These 'feeding' studies did not account for the ways people could be exposed to leaching or extraction from intravenous tubing."

The team used exposures that mirrored the type of exposures human infants would experience during a procedure called extracorporeal membrane oxygenation, which is the use of an artificial lung outside the body. They studied effects of intravenous exposure to DEHP in young male rodents, both immediately after dosage (at 21 days), as well as at maturity (approximately 90 days). Looking at both ages could help determine if immediate effects on sexual development were reversible. A second group of rodents received oral dosing, so the researchers could compare oral versus intravenous exposures.

"The most interesting and important finding from this study was that at maturity there were no residual effects on reproductive capacity as measured by sperm count, motility, and morphology," says Cammack. "Even cellular changes were completely reversed [at maturity] in all the IV groups." Shelby points out that the study also showed a significant dose-related decrease in testis weight that did not reverse, which is one effect of concern in DEHP-exposed male infants. The study was published in the May–June 2003 issue of the *International Journal of Toxicology*.

Expert panel reports—but not yet entire monographs—are available on a number of chemicals including ethylene glycol, propylene glycol, methanol, 1-bromopropane, and 2-bromopropane. Eventually, monographs will be available for all of these chemicals. As for upcoming expert panel reviews, the antidepressant fluoxetine (Prozac) and the cooking by-product acrylamide have been tapped for evaluation next.

In the past five years, the CERHR has established the reputation of an objective and scientifically sound public health resource. As the center continues to fulfill its promise of providing reliable information on reproductive and developmental toxicants, Shelby points to three important goals for the future: "to increase the rate at which we evaluate chemicals, to forge closer ties with the medical community, and to increase our visibility and service to the general public." **–Jennifer Medlin**

For More Information

CERHR homepage
http://cerhr.niehs.nih.gov/

NIEHS Fights Fat

Obesity is an enormous public health threat for Americans of all ages, but is an especially serious problem for children and minorities. The Centers for Disease Control and Prevention recently estimated that 15% of all children and 25% of black and Hispanic children are overweight. With significant increase in weight comes a host of health problems and resultant health care expenditures. Obesity, like most chronic health problems, is caused by complex interactions between genetic, environmental, and behavioral factors.

Recognizing that basic research is needed to untangle these interactions and that intervention strategies are needed to prevent the potentially catastrophic health effects of obesity, the NIEHS is launching an initiative to support studies that will elucidate the mechanisms by which the built environment influences obesity and related diseases, and to develop effective models to reverse the trend toward increased obesity.

"The NIEHS is planning a multipronged approach, involving both research and education, to enable us to understand better how the environment affects obesity and to develop appropriate interventions," says Allen Dearry, the institute's associate director for research coordination, planning, and translation. "We are planning a concerted effort in conjunction with other NIH institutes, with other federal agencies such as the Centers for Disease Control and Prevention and the Department of Housing and Urban Development, and with private foundations in order to ensure that a coordinated response is implemented to address the obesity problem."

The first step in the planned research effort will be to create and validate instruments to measure the impact that the community where one lives has on behavior and lifestyle choices affecting rates of obesity. To do this, it will be necessary to delineate the role and impact of factors such as urban/rural community design and planning, housing structure, transportation, and availability of public green spaces on issues including mental health, physical activity, nutrition, and access to healthy food for both individuals and populations. This research effort will require the input of multidisciplinary research teams from disparate fields including biomedical scientists, behavioral scientists, social scientists, clinicians, epidemiologists, planners, developers, and architects, as well as active participation of community members.

The second step in the NIEHS research approach will be to identify successful strategies for changing eating behavior, promoting a more active lifestyle, and altering the design of residential communities to make them more conducive to physical activity. Individual and communitywide interventions can be developed, implemented, and evaluated in order to assess their effectiveness in reducing obesity.

One of the more innovative educational strategies already launched by the NIEHS is the development of *Fitness Fighters*, a children's television program that would promote healthy eating behavior and an active lifestyle. The NIEHS is working with a writer and producer of the children's show *Sesame Street* to develop a pilot episode and series format. Efforts are under way to solicit cofunding for the series from industry and private foundations.

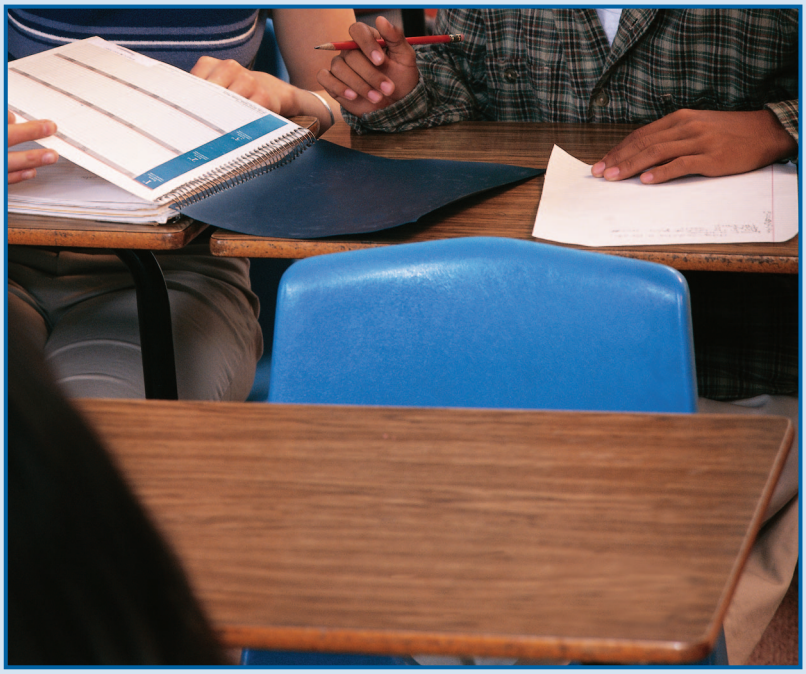
Another NIEHS effort in the initial stages of execution is a collaboration with the Robert Wood Johnson Foundation. The foundation is supporting a program titled Active Living by Design, which will provide support to 25 communities across the country to implement active living programs, policies, and communication strategies that involve local public health, planning, and transportation agencies. The NIEHS has partnered with the foundation to provide an evaluation component to this program in order to determine the efficacy of various policies and promotions in combating obesity.

To further refine a research, education, and intervention strategy to address the relationship between the environment and obesity, the NIEHS is planning a national workshop on the issue next spring. Those interested in participating may contact Dearry at dearry@niehs.nih.gov.

Ian Black

Headliners | Environmental Tobacco Smoke

NIEHS-Supported Research



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Environmental Tobacco Smoke Increases School Absenteeism

Gilliland FD, Berhane K, Islam T, Wenten M, Rappaport E, Avol E, Gauderman WJ, McConnell R, Peters JM. 2003. Environmental tobacco smoke and absenteeism related to respiratory illness in schoolchildren. Am J Epidemiol 157:861–869.

Research has shown that exposure to household environmental tobacco smoke (ETS) is responsible for respiratory illnesses among young children; however, the ETS-associated morbidity for school-age children is less well defined. Previous research by a team including NIEHS grantees Frank Gilliland, William J. Gauderman, and John Peters of the Keck School of Medicine, University of Southern California, has shown that asthma-related school absenteeism is a major problem in Southern California, accounting for a large portion of all absences. To determine the extent to which ETS exposure might be implicated in school absenteeism, these researchers and colleagues investigated the relationship between ETS exposure, asthma status, and respiratory illness–related school absences in 1,932 fourth-grade schoolchildren from 12 Southern California communities.

At study entry, more than 18% of the children were exposed to household ETS. Overall, ETS exposure was associated with a 27% increase in risk of school absences related to respiratory illness. Children living in a household with two or more smokers were at a substantially higher risk (75%) of such absences. Children with asthma were at the greatest increased risk of school absences related to respiratory illness. When exposed to one smoker, the risk for children with asthma was 2.35 times higher, and when exposed to two or more smokers, the risk increased to 4.45 times higher. Children who were exposed to ETS also had higher rates of absences related to all types of illness.

This study demonstrates that ETS exposure is associated with increased respiratory illness–related school absenteeism among school-age children, with much higher risks for children with asthma. Approximately 9 million children in the United States suffer from asthma, and related school absences cause millions of lost work hours for parents who must stay home to care for their children. This research shows that ETS plays a major part in some of these absences and points out the need for smoking cessation programs, especially for the parents of children with asthma. **–Jerry Phelps**