

Human Exposure Assessment:

Finding Out What's Getting In



As the number of people dying worldwide from noncommunicable diseases such as cancer and heart disease continues to rise, being able to measure and qualify people's exposure to harmful environmental agents is becoming increasingly important. Exposure assessment is emerging as a scientific field thanks in large part to revolutionary advances in genetics, molecular biology, and microenvironmental and personal measurement technology. "As the methods of exposure assessment become more robust, sensitive, and inexpensive, they will dramatically change the field," says Richard Jackson, director of the National Center for Environmental Health at the Centers for Disease Control and Prevention in Atlanta, Georgia.

Jackson was one of a group of more than 400 government, academic, and industry scientists and policy makers that met in September 1999 to discuss the role of

human exposure assessment in the prevention of environmental disease. "When we're talking about creating a new science for the field of exposure assessment, what we're really talking about is new ways of understanding the dose-response relationship necessary to understand risk assessment," says Samuel Wilson, deputy director of the NIEHS.

"Exposure analysis provides the bridge . . . between traditional environmental science and toxicology and epidemiology," says Paul Lioy, deputy director of the Environmental and Occupational Health Sciences Institute in Piscataway, New Jersey. According to Lioy, researchers are developing an entirely new conceptual framework to understand how environmental exposures affect public health.

However, George Lucier, director of the NIEHS's Environmental Toxicology Program, considers it a stretch to call exposure assessment a new science and says the

field just needs some reinventing. "It is an old science that has languished, that hasn't gotten the support it deserved," he says. But he acknowledges that the discipline needs to be rethought, especially in terms of disease and determining individual sensitivity.

Whether exposure assessment is emerging as a newly defined field or merely a reinvented one, a new paradigm to link human exposure assessment to disease is crystallizing. Most experts agree that the key lies in linking the many new tools being developed for examining exposure to hypothesis-driven research.

Researchers can approach the exposure-disease relationship from two directions. From the exposure end they can learn how a person's exposure to a chemical may lead to disease. From examining a disease trend in the population or a subpopulation, they can work backward to exposure. "There's a recognition that both observational kinds of research for

providing exposure databases and hypothesis-driven research are important,” Lucier says. Programs such as the National Human Exposure Assessment Survey (which is designing a national exposure surveillance system) and the National Health and Nutrition Examination Survey (a pioneering interagency program to generate blood and urine data for estimating exposure of the U.S. population) provide an important foundation for generating reasonable hypotheses to test, he says. The National Occupational Exposure Survey, a related program, is developing an occupational exposure database.

Assessing Exposure in the Environment and the Body

Most experts agree that inadequate information currently exists regarding the type, pattern, and magnitude of human exposure to chemicals through food, the workplace, and the environment. Many believe that critical knowledge gaps will take years to fill.

“Human exposure assessment is often the weakest link in risk assessment,” says NIEHS director Kenneth Olden. This weakness restricts the public health community’s ability to evaluate low-dose effects of exposures to chemicals and identify at-risk populations. It also restricts researchers’ ability to design studies to evaluate exposure–response relationships and study gene–environment interactions, he says.

“Adverse health outcome is a function of toxicity and exposure, both duration and intensity,” Olden says. He explains that environmental monitoring, which determines what’s in the air, soil, food, and water, is not equivalent to individual exposure, which reflects concentrations of chemicals and environmental agents that actually are in people’s bodies and their resulting effects.

Traditionally, the responsibility of monitoring chemicals in the environment and in people’s bodies has been scattered across government agencies. Operating in isolation

Only a few dozen people at the EPA conduct the analyses. Of the 2,863 chemicals in production (at the rate of one million pounds per year) complete toxicity screening data exist for only 7%. And 40% of chemicals in commerce lack any screening data at all. Meanwhile, the National Toxicology Program, an interagency program established by the Department of Health and Human Services in 1978 to coordinate and strengthen toxicological testing programs and research within the Public Health Service, can provide toxicological evaluations for only 10–20 chemicals a year. And only 600 chemicals are covered in the Toxics Release Inventory, the EPA’s accounting of the chemicals that are released into the environment by industry.

The data are even sparser for exposure. “When we look at exposure information for these chemicals, I would argue that there are even fewer data sets available than exist for toxicology or hazard information [i.e., whether a substance is carcinogenic or benign],” says Lynn Goldman, the former assistant administrator for the EPA’s Office of Prevention, Pesticides, and Toxic Substances and now a visiting scholar at the Johns Hopkins University School of Public Health in Baltimore, Maryland, and a consultant to the National Toxicology Program. “Clearly the process has not done a good job of actually giving a science-based estimate of the exposure.” Moreover, understanding the potential health effects of emissions and pollution is impossible without having an understanding of exposure, Goldman says. Under current law, citizens have a right to know what the Toxics Release Inventory says has been released into the environment and whether it’s hazardous, Goldman explains, “but that information is meaningless if you

Exposure and environmental quality data are in fact often at odds, Lioy says. Data about what’s in the environment at large may reveal little about a person’s actual contact with environmental agents. Such factors as behavior and exposure mechanisms come into play, Lioy says. For example, exposure

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to lead-based paint within the same environmental background is greater for infants than for parents because most adults don’t put everything they encounter in their mouths.

Indeed, environmental levels are irrelevant unless contact occurs. “The bane has been trying to figure out the actual exposure,” Jackson says. One reason for this is that the science of exposure assessment is complex. Animal toxicity studies, for instance, which conventionally are used to extrapolate chemical exposures to humans, can be hard to interpret. Often, actual exposure levels in humans vary significantly from those in animals in the same environment. Clearly, cross-species extrapolation needs improvement, as do biologically based dose–response models, which are used to predict effects of exposure levels in humans. Moving from dose to response alone presents a whole new set of complications. “Estimation of exposure using indirect surrogates is inadequate for risk assessment,” Olden says.

“As we enter the new millennium, we still have real problems making these assessments,” says Howard Hu, a professor of medicine and public health at Harvard University in Cambridge, Massachusetts. Although physicians are the ones who often see the end points of disease, “we can’t measure exposures to the person very well,” he says. When an exposure is nonpathological, the damage often goes undetected. In the case of lead exposure, for example, a loss of IQ points can go unnoticed. “It’s still a major loss to society, but no one knows about it,” says Hu. “The impact of environmental exposure on human disease remains largely a mystery for many diseases,” he says.

Another problem is that exposures that may contribute to health effects are often cumulative or involve mixtures. Although the EPA is now required to study both aggregate and cumulative exposures under the Food Quality Protection Act of 1996, the agency’s work focuses on what’s found in the environment. Most experts agree that the goal should be to focus research on mixtures that are actually present in people’s bodies rather than in the environment.

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within various agencies, the efforts have been frustrated by a lack of coordination. As it is, the U.S. Environmental Protection Agency (EPA) faces a daunting task, given its resource level: it is charged with evaluating chemicals in the environment under the Toxic Substances Control Act of 1976 as well as the Clean Air Act and Clean Water Act. There are an estimated 85,000 chemicals in commerce today and 2,000–3,000 new ones roll onto the market each year.

don’t know if exposure occurred. Exposure monitoring is equivalent to the right to know,” she says. “The key to assessment is surveillance of disease and exposure.”

Jackson agrees that quantifying amounts of chemicals and other environmental agents in the soil, air, water, and food is only one component of assessing exposure. “The levels in the human body—not in the environment—those are the concentrations we should be paying attention to,” he says.

Yet even the reigning individual exposure assessment tools—biomarkers, physical quantifiable changes that evidence exposure—have a long way to go. Alone, biomarkers do not necessarily provide enough information for valid risk assessments to be formulated. For a long time, Lioy, like many

new world now, a world where our genetic understanding is leading to the development of an incredible panoply of early detection disease biomarkers. What's being developed now as a result of the genetic revolution, the Human Genome Project, and . . . the Environmental Genome Project is the fact

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others, believed biomarkers would be the gold standard. The precision with which researchers became capable of detecting subtle biochemical and molecular changes offered great promise. For example, after exposure to a carcinogen such as vinyl chloride, a mutant form of a protein may be found in the bloodstream of an individual even though no tumors are detected in tissues. But Lioy has since changed his stance, acknowledging that “biomarkers are one tool in a big toolbox that includes personal and microenvironmental measurement, identity patterns, and predictive models.”

In addition, says John D. Groopman, chair of the oncology department at the Johns Hopkins University School of Public Health, “No one biomarker is going to be totally complete with respect to predicting disease outcome.” There are, says Groopman, still relatively few biomarkers that have been brought through a rather complex process of validation and that scientists can use to obtain reliable information on how exposure to a suspect agent can result in a specific health end point—information that is valid for exposure assessment or for risk assessment. A tiered experimental and human investigation approach is needed to understand how biomarkers act in different populations and environments, he says. In this context, researchers argue that a greater emphasis needs to be placed on exposures to children and other potentially sensitive subpopulations.

Moreover, exposure by itself does not necessarily result in disease. “We have to recognize that things are not driven by just exposure alone in terms of some of these very long-term outcomes,” Groopman says. “There is certainly an interaction with respect to the host's genetic susceptibility that is playing an important role.”

The fact that gene–environment interactions profoundly affect whether an environmental exposure may lead to disease is a relatively new factor in the equation. Says Groopman, “We're entering a completely

that we are beginning to identify individuals at subclinical disease state [before a disease is manifested], and we need to now integrate into our paradigm what role exposure will play in either exacerbating or blunting the blossoming of that disease state when it becomes a clinically defined identity.” The Environmental Genome Project is a multi-agency effort to systematically identify the alleles of some 200 environmental susceptibility genes in the U.S. population.

Risk Assessment and Policy

“Our ability to make these measurements, do these analyses, understand the meaning of these biomarkers really only has importance if we can utilize these data in a public health setting in order to reduce morbidity and mortality of disease in individuals,” says Groopman.

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Lioy agrees: “We need to know whether body burdens of lead, polychlorinated biphenyls, dioxins, volatile organics, and other air and water pollutants are increasing, remaining at the same levels, or decreasing as regulations meant to decrease the levels of these chemicals in the environment are designed and implemented.” In general, the community needs to do a better job of determining what works in reducing human exposure. Lucier says, “If it doesn't result in a reduction in disease then it hasn't been successful.”

Policy makers are confident more answers will be coming in the next decade. “The field of exposure assessment can address many of our most visible health concerns,” Lucier says. “What's kept it from succeeding in the past has largely been people's

inability to work together effectively.”

The NIEHS hopes to change that with new interagency initiatives in exposure assessment. The idea is to coordinate traditional research fields across agencies. In cooperation with the Centers for Disease Control and Prevention and the EPA, Olden hopes to dramatically enhance both the technological sophistication of exposure assessment and the use of exposure assessment in the prevention of human disease.

“There's a recognition that a multidisciplinary approach is required,” Lucier says. “Many of the needed pieces are in place, but they need to be put together through interagency initiatives.” And an interagency funding initiative would surely help, he adds. The federal government spends a trillion dollars each year on the treatment of disease, but the importance of good public health policy based on sound environmental science can get lost in the figures. Interagency initiatives, researchers argue, will link a broader cache of hypothesis-driven research to exposure assessment and make limited dollars go farther.

To make it happen, more researchers and new methods and tools are needed to stimulate the field. Without effective use of experimental data, the decisions that can be made about chemical exposures are limited. “There is a frustration in the whole regulatory arena that many epidemiological studies for exposure assessment don't easily lend themselves to the risk assessment mantra,” says Goldman, “and the exposure assessment

information doesn't readily lend itself to outcomes research.” Advances, especially in analytical technology and molecular biology, may change that. And, says Lucier, “We need cross-training so our researchers will think like a toxicologist and an epidemiologist at the same time. We don't have those kind of people trained today.”

Experts predict that in the future improved exposure assessment will play a leading role in the prevention of environmental disease. Says Jackson, “Ten years from now in the field of environmental health, it will seem strange to talk about exposure without looking at the actual human dose.”

Julie Wakefield