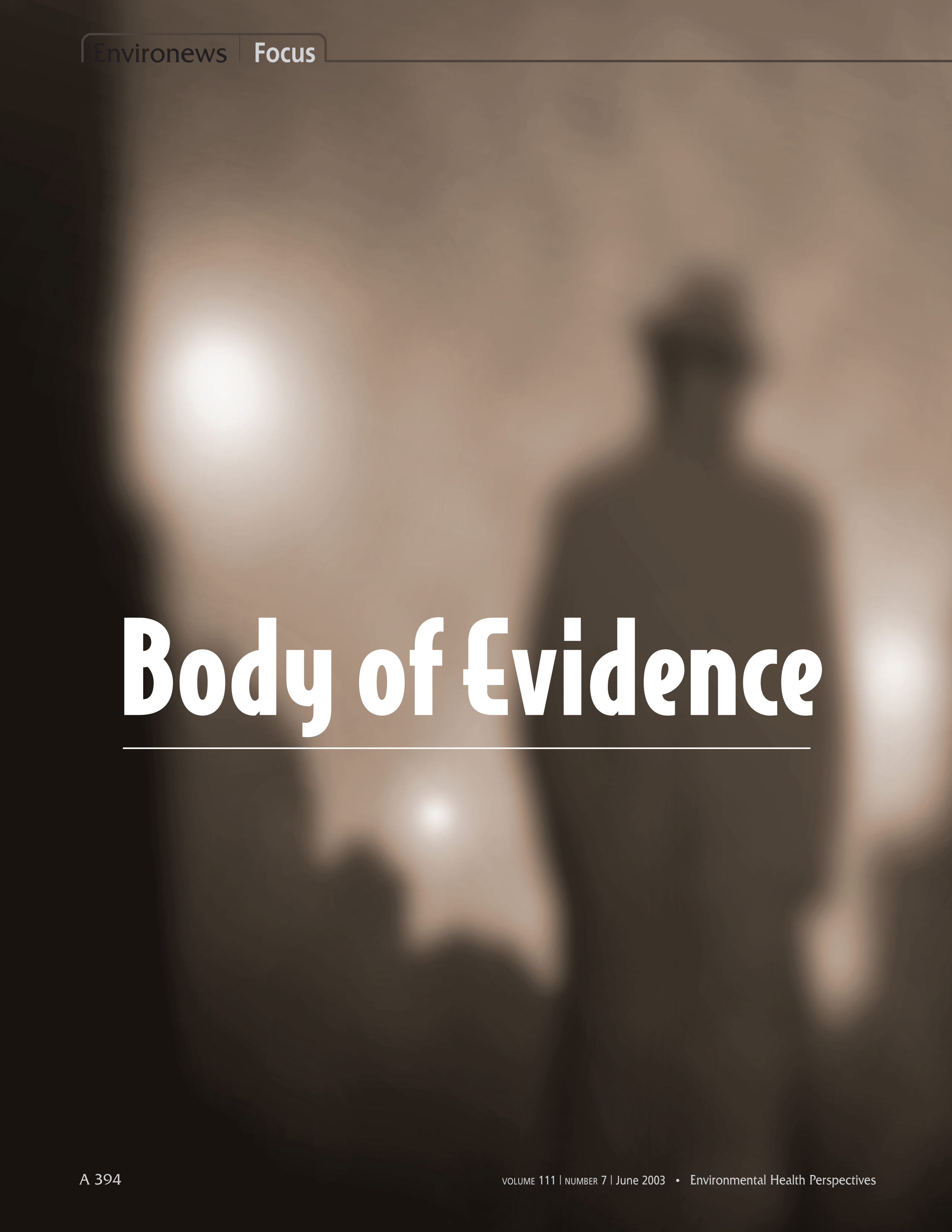

Body of Evidence

Christopher G. Reuther/EHP

More than a decade after the National Research Council pushed for broad testing of toxic substances in people and more than 40 years after the birth of the ongoing National Health and Nutrition Examination Survey (NHANES), data on human exposures to potential toxicants continue to come in. The latest contribution came with the January 2003 release of the *Second National Report on Human Exposure to Environmental Chemicals* by the Centers for Disease Control and Prevention (CDC). The report presents findings on the presence of a small selection of potentially toxic substances in a group of volunteer test subjects. It more than quadrupled the number of substances covered in the CDC's first report released two years earlier, adding in new chemicals, congeners, and naturally occurring substances. Already it is a useful tool for many organizations, physicians, and agencies.

"The ability to have a database like this as a baseline reference is very powerful," says Paul Gilman, assistant administrator for research and development in the U.S. Environmental Protection Agency (EPA) Office of Research and Development. "This work puts things in a context for us."

The CDC findings revealed some significant reductions during the past decade for some of the substances, such as lead and secondhand tobacco smoke. But the findings also unveiled many puzzles, such as large variations in some of the concentrations measured by age, sex, and race/ethnicity, and differences of 200-fold or more between concentrations found in the lowest and highest percentiles reported. These puzzles highlighted one of the main points made by the CDC with the release of the report—that much about human exposure remains a mystery, and that one of the primary uses of the data will be to help shape future research. The CDC report offered no new information on health effects from the measured exposures, another field in which the CDC acknowledged much research is needed.

The CDC's decisions on which substances to include in the *Second National Report* were influenced by six considerations: data showing exposure to U.S. residents; known or suspected serious health effects from exposures; availability of good analytical methods to evaluate a substance; testing costs; availability of adequate blood or urine samples; and a desire to track selected public health interventions over time.

The 116 substances covered in the *Second National Report* are only the tip of the iceberg as far as potential chemical exposures go. About 2,900 high production volume chemicals—regularly produced or imported in volumes of 1 million or more pounds per year—are among the chemicals under investigation by many agencies and companies. There are at least 80,000 chemicals, with largely unknown toxicity, that have ever been registered under the Toxic Substances Control Act as being in commerce in the United States (an estimated 20,000 more have ever been in commerce elsewhere in the world). There may be about 6 million chemicals that exist in the world, says John Osterloh, chief medical officer for the CDC Environmental Health Laboratory, although estimates vary and no one really knows. Many of these are not produced for commerce but rather exist as breakdown and incineration products of chemicals that are in commerce. The number of these substances that may reside for any length of time in people is a mystery. The CDC says its data can't clarify that number, but that such information is irrelevant at the moment, because scientists can't evaluate the health consequences of such complex mixtures.

But that and other missing information needs to be developed as soon as possible, says Matthew Cahillane, an environmental health specialist with the New Hampshire Department of Health and Human Services. At the moment, "we're basically firefighters," he says. "We're playing catch-up all the time."

What's in There?

With the advent of U.S. environmental programs in the 1970s, the first efforts to gauge the impacts of toxic substances on people focused on measuring them indirectly—in the environment—in part because that was more technically feasible. But those methods, while a key element in understanding the overall exposure picture, provide only rough parameters. They can't track what actually gets into people through all the potential pathways—such as inhalation, ingestion, or dermal absorption—and can't evaluate what stays in. Plus, the amount of any one chemical detected in a biomonitoring sample presents only a snapshot taken at one point in time. The exposure reflected may be recent or old, chronic or isolated. A single biomonitoring event is insufficient for understanding the magnitude, frequency, or duration of exposure, or the absorption, distribution, metabolism, or excretion of a substance.

With those limitations in mind, some researchers began to probe what was actually in people. One of the earliest efforts began in 1976 with studies of lead. The findings of worrisome concentrations in many people eventually led to campaigns to remove lead from gasoline and paint. In response to public concerns about pollution that built in the 1980s and 1990s, the National Academies' National Research Council recommended in 1991 that the country should create a national program to track chemicals in human tissues. That helped lead to the adoption and expansion of several efforts. In 1993, the EPA began its National Human Exposure Assessment Survey, which assessed 46 chemicals in 460 participants in 3 U.S. regions. The results have yet to be fully analyzed, but have been evaluated for some associations between levels of environmental exposure and biomarkers.

Many other independent studies, including those performed by companies investigating their own chemicals, have provided clues about various substances. But these studies often focus on occupational exposures to specific chemicals under specific conditions, and thus do not apply when estimating background exposures for the general U.S. population. Furthermore, numerous barriers, such as funding limitations, variations in study methodologies

PhotoDisc

and data systems, and lack of coordination between government agencies, have stymied the development of any extensive information, the U.S. General Accounting Office concluded in its May 2000 report *Toxic Chemicals: Long-Term Coordinated Strategy Needed to Measure Exposures in Humans*.

The first substantial breach in that gridlock came 21 March 2001, when the CDC released its first *National Report on Human Exposure to Environmental Chemicals*. That report covered 27 substances, including lead and 12 other metals, 6 pesticide metabolites, the nicotine metabolite cotinine, and 7 metabolites of phthalates, a class of chemicals used in products such as fragrances, industrial solvents, and flexible plastic products. For that study, researchers evaluated blood and urine samples from about 3,800 representative volunteers who participated in the 1999 NHANES.

On 31 January 2003, the CDC unveiled its *Second National Report*. The CDC expects the report to be used in a number of ways. One of the primary uses will be to determine what substances people are exposed to, at what concentrations, and whether those concentrations are toxic. For the few substances that do have established toxicity thresholds, such as lead, it will also help determine how many people may have unsafe levels.

As the database grows, it will provide increasingly reliable information on what the typical concentration ranges are for various population groups, providing physicians and public health officials with valuable perspective on what is "normal" in the United States. It can also provide key information on the success or failure of intervention programs, such as antismoking initiatives, lead control programs, and bans and other efforts aimed at reducing pesticide body burden.

Most Extensive Assessment So Far

The new report offers a greatly expanded body of information, including both old and new data on the initial 27 substances and new data on 89 other substances or their metabolites, including dioxins, furans, polychlorinated biphenyls (PCBs), polycyclic aromatic hydrocarbons, plant estrogens, and an expanded list of pesticides. With the additional data available, based on blood and urine samples drawn in 1999 and 2000 from about 1,700–8,000 people per substance, the CDC has been able to provide the first breakdowns by age, sex, and race/ethnicity. "It's a giant step forward," says Jim Pirkle, deputy director for science at the Environmental Health Laboratory.

To find out more about the potential adverse health impacts of the substances found in the CDC study, researchers will be scrutinizing the findings for years to come. Some of their focus will be on the variations in exposure by demographic strata that popped up in the CDC study.

For instance, urine concentration of barium, which occurs naturally and is used in products such as paint, rubber, and ceramics, was about 65% higher in children aged 6–11 than in people 20 and older, and was nearly twice as high in non-Hispanic whites as in Mexican Americans. For the naturally occurring plant estrogen genistein, found primarily in foods such as soybeans, Mexican Americans have a mean urine concentration about 65% higher than non-Hispanic blacks. Although associated with health benefits including lowering the risk of osteoporosis and some cancers, phytoestrogens such as genistein also are suspected of reducing reproductive capacity and promoting other cancers.

Mercury concentrations in blood were about three times higher in females aged 16–49 than in children aged 1–5, and were more than 40% higher in non-Hispanic blacks than in non-Hispanic whites or Mexican Americans. About 8% of women of reproductive age had mercury levels over the EPA's reference dose for organic mercury. The health effects of mercury depend on whether it is a metallic, organic, or inorganic form, and on the timing, route, amount, and length of exposure. Fetuses exposed to organic mercury may experience damage to neurological systems, and adults exposed long-term can suffer neurological, pulmonary, and gastrointestinal damage. Kristina Thayer, a senior scientist with the Environmental Working Group, an environmental organization, suspects that something as simple as higher consumption of canned tuna—a known source of mercury—may play a part. Mercury also comes from sources such as coal-fired power plants (whose emissions can travel many miles), medical devices, dental amalgams, and cosmetics.

Lead concentrations were still high in some people, but the mean concentration in blood samples of children aged 1–5 was about 17% lower than the mean concentration detected in NHANES III in the early 1990s. Males in the latest study had 47% higher concentrations than females.

Chemicals in the same class can be absorbed, metabolized, and excreted by

Is It Enough to Avoid Exposures?

A pilot study by the Mount Sinai School of Medicine, in collaboration with two environmental organizations, the Environmental Working Group and Commonweal, revealed that nine volunteers had an average of 91 toxic substances in their bodies. Out of 210 substances tested—which included polychlorinated biphenyls, metals, phthalates, pesticides, and volatile substances—167 showed up in at least one person, the groups said with the release of their report on 30 January 2003. Each test subject had a total of anywhere from 77 to 106 substances in his or her blood or urine. On average, participants had 53 carcinogens, 58 known endocrine disruptors, 53 chemicals that are toxic to the immune system, and 55 that are linked to birth defects or abnormal development. The health effects of chemical combinations, or even single substances, remain poorly understood, however.

The study is not peer-reviewed, and, due to the small sample size, the results don't reflect what might be found in the U.S. population. But Kristina Thayer, a senior scientist with the Environmental Working Group, is concerned by the results, in part because the nine volunteers—who included environmental health activists, health care professionals, and a journalist familiar with environmental health issues—likely lead "less toxic" lives than many people. "Our folks are pretty savvy and know what to avoid, but it wasn't good enough," she says. "Even when you try to avoid exposure, you can't."

U.S. residents shouldn't have to be so savvy, says one critic of U.S. toxic substance policies. "This study merely confirms what we've known for a long time," says Samuel Epstein, a professor emeritus of environmental and occupational medicine at the University of Illinois School of Public Health in Chicago and chairman of the Cancer Prevention Coalition—that a wide range of toxic substances are getting into people. He has followed similar studies for decades, and says that government agencies should have taken more aggressive action years ago to slash exposures to toxic substances. **–Bob Weinhold** people in very different ways. Mono-ethyl phthalate, created in the body from diethyl phthalate, was present in the urine of adults aged 20 and older at nearly twice the concentration found in children aged 6–11. Diethyl phthalate is used in products such as fragrances, soaps, and hand lotions. In contrast, mono-benzyl phthalate, created in the body from benzylbutyl phthalate, was present in the urine of children aged 6–11 at a concentration more than three times higher than that found in people aged 20 and older. Benzylbutyl phthalate is used in products such as adhesives, sealants, and car care products.

Along with the differences in age, sex, and race/ethnicity, there were some large differences in concentrations between the upper and lower percentiles. In the case of 2,5-dichlorophenol, a urine metabolite of *p*-dichlorobenzene, which is used in products such as insect repellents and deodorizers, concentrations in the 95th percentile were about 230 times higher than those found in the 25th percentile. And with several of the plant estrogens, the differences between the 95th and 10th percentiles ranged from 100-fold to nearly 200-fold.

Does Exposure Cause Health Problems?

Large variations between percentiles can be caused for three reasons, says George Lucier, an advisor to the National Toxicology Program. First, people are exposed to varying amounts of different chemicals. Second, some chemicals are rapidly degraded by the body, and the time between exposure and sampling is critical to attaining comparable measures. Third, different people degrade chemicals at different rates for reasons related to age, sex, genetics, and diet.

The large differences in the CDC report raised a red flag for Thayer, who noted that the few toxic substances that do have health standards typically have only a 10-fold safety margin built into them as a hedge against variations in human vulnerability and uncertainties in regulatory assumptions. Current hedge factors may not address the ranges of exposure found in the CDC report, she observes, and should be addressed in future investigations and regulations.

Very little is known about the health effects that might be caused by the concentrations found in the test subjects in the CDC study, or from the combined effects of these substances. Some industry representatives suggest there may not be much to worry about. "It hasn't been determined that reducing exposure would result in improved health," says Jennifer Biancaniello, a spokeswoman for the American Chemistry Council.

Among the studies of potentially toxic substances that have been conducted, some are showing adverse health effects at what are considered low doses. For instance, monoethyl phthalate, at concentrations present in our environment, causes DNA damage in sperm, reported Susan Duty of the Harvard School of Public Health and colleagues in December 2002 in *EHP* online. The EPA has established a peer-review panel to assess the so-called low-dose hypothesis, which holds that endocrine-disrupting chemicals cause adverse health effects at extremely low doses. In a 26 March 2002 statement on the findings of the panel, the agency said the panel found that "there were credible studies supporting a low-dose effect, but that the effects were '. . . dependent on the compounds studied and the endpoint measured.'" The panel also identified credible studies that did not support a low-dose effect.

Given all the complex interactions that studies suggest can occur with exposure to toxic substances and other stressors, and given the role of other poorly understood factors such as the avenues and timing of human exposure, information on substances in people alone isn't a magic bullet. "[The *Second National Report*] is just a snapshot in the middle of the biological story," Gilman cautions.

Using the Results

Nonetheless, human exposure data are an important part of the bigger picture. For instance, they likely will help shape the work of one of the developing research tools—the Environmental Genome Project—when actual testing of yet-undetermined substances is ready to begin in the next five years or so, says Raymond Tennant, director of the National Center for Toxicogenomics. Any methods adopted may be useful for examining human body burdens in relation to people who are at increased risk due to genetic predisposition.

Agencies and organizations tracking chronic diseases also are following the release of human exposure data with great interest, and the CDC report will improve scientists' ability to design more sensitive epidemiologic studies, Lucier says. One likely topic will be chronic diseases such as cancer, asthma, and diabetes. Such diseases play a part in 7 of every 10 U.S. deaths each year, cause major limitations in activity for 25 million Americans, and affect a total of about 90 million Americans to some degree, according to the CDC National Center for Chronic Disease and Health Promotion. Many chronic diseases have suspected environmental links. Laura Segal, director of communications for the Trust for America's Health, a Washington, D.C.–based advocacy organization, says the report will "give us a fighting chance against chronic diseases" by providing some of the first data regarding potential linkages with toxic substances.

The data are already shaping some research efforts. Cahillane says that New Hampshire was going to investigate radon as part of its work with the CDC's chronic disease studies, but has decided after reviewing the *Second National Report* that mercury is a better research topic.

To help expand the limited national data on chronic diseases, the CDC received its first funding in 2002 for a national environmental public health tracking network. But it will be many years before the accumulating data on diseases and toxic substances in people and the environment will be meshed. "Each of these huge mountains of data have to be made much more orderly and understandable," says Richard J. Jackson, director of the CDC National Center for Environmental Health.

Despite much missing information, public health officials have already begun to use the CDC data to assess environmental health issues. In their study of the unusually high number of acute lymphocytic leukemia cases in Fallon, Nevada (where suspected exposures include agricultural, military, mining, and naturally occurring pollutants), the CDC and the Agency for Toxic Substances and Disease Registry (ATSDR) used the *Second National Report* to put their local data in context. They found that tungsten concentrations in Fallon residents were far higher than the national mean cited in the report, and also found slight elevatations in concentrations of antimony, barium, cesium, cobalt, molybdenum, uranium, and 7 pesticides, as well as detectable concentrations of 18 PCBs. However, the agencies are saying so far that there is no proof that such exposures led to the leukemia increase, although some research continues.

Community activists in Anniston, Alabama, home to extensive PCB pollution, are comparing the CDC's data on substances such as PCBs to their own data, and say they are confirming their suspicions that their residents are being exposed to high levels of pollutants. "We have residents with godawful numbers that are a lot higher than what [the CDC] found," says Shirley Baker, a health consultant to Anniston's Community Against Pollution organization. She adds that the community group likely will use the CDC data in its requests for grants and other funding, and in litigation. The ATSDR is developing a proposal for a multiyear, multimillion-dollar study of Anniston, and will use the *Second National Report* to help put its findings in context, says John Abraham, chief of the ATSDR's Exposure Investigations and Consultations Branch in the Health Assessment and Consultation Division.

Industry groups, too, are already using the CDC studies. "They do inform our industry on better ways to do things," says Angelina Duggan, director of science policy for CropLife America, a pesticide industry organization.

Now What?

The CDC plans to keep building its database and report the results every two years. The *Second National Report* cost $6.5 million in direct laboratory expenses, with other expenses included in the $25 million that NHANES spends each year for its overall study. The next exposure study should also cost about $6.5 million, which already has been committed, Osterloh says.

Blood and urine samples for the next report, covering 2001 and 2002, have already been drawn from volunteers, following protocols similar to the two earlier studies. Samples from sources in the body other than blood and urine—such as fat or bone—likely would reveal additional body burden information, but have not been taken because they require more invasive techniques.

The number of substances that will be analyzed will expand, and may include about 30 volatile organic compounds (including some chlorination by-products), arsenic, bisphenol A, polybrominated diphenyl ethers, perchloroethylene, and a number of other substances.

Lynn Goldman, a professor of occupational and environmental health in the Johns Hopkins Bloomberg School of Public Health, appreciates the data that are available, but is looking forward to even better information. "Some of the things I'm most interested in are yet to come," she says. For instance, body burden data for children aged 5 and under would be very helpful in her work as a pediatrician. However, that information will be difficult to obtain with the present testing methods, she and the CDC acknowledge, because blood and urine samples from small children often aren't large enough to do extensive testing.

Researchers at the CDC are tweaking the analytical techniques within the three general methods they already use: isotope dilution mass spectrometry, inductively coupled plasma mass spectrometry, and graphite furnace atomic absorption spectrometry. One benefit to this tweaking will be lower limits of detection for many substances. For the next report, "some of the detection limits would improve dramatically," says Osterloh.

Jackson hopes to be able to transfer these continually refined methods to other laboratories around the country, because such capabilities are rare right now. He would also like to see the data broken out geographically in the future. "At some point, we hope to provide state-by-state data," he says. He cautions that in order to acquire enough data, such an effort would take a substantial investment by individual states. Some states, however, have already expressed interest in the idea.

Bob Weinhold

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