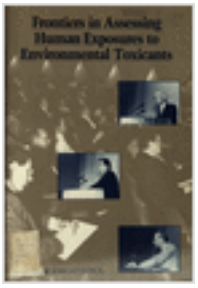

Frontiers in Assessing Human Exposures to Environmental Toxicants: Report of a Symposium (1991)

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Frontiers in Assessing Human Exposures to Environmental Toxicants

Report of a Symposium

Committee on Frontiers in Toxic Exposure Detection and Assessment

Board on Environmental Studies and Toxicology

Commission on Life Sciences

National Research Council

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Preface

The concept of disease as a manifestation of an imbalance between the environment and the individual is now, once again, receiving serious scientific attention. If we are to prevent diseases which are caused by exposure to toxic chemicals, we must learn how to measure the many aspects of exposure. The United States Public Health Services' Agency for Toxic Substances and Disease Registry (ATSDR), recognizing this need to measure environmental parameters at least as well as diseases can be documented, commissioned the National Research Council (NRC) of the National Academy of Sciences to explore this challenge in a way that would be understandable to scientists, regulators, legislators, and the general public. The NRC convened a 2-day workshop in Washington, D.C. on May 16-17, 1990, to bring current knowledge and current difficulties to public and scientific attention (see appendix).

Measuring the sources, concentration and fate of chemicals in the environment is a task so complex that many of the scientists trying to do these measurements feel that they are pioneers. It was natural that the workshop be called "Frontiers in Assessing Human Exposure to Environmental Toxicants." The report that follows is the summary of that workshop. Dr. Barry Johnson, Assistant Administrator of ATSDR, personally stimulated this workshop. The Honorable J. Roy Rowland, M.D. (D.Ga.), expressed the interests of many legislators. Numerous state and federal regulators participated, as did several members of NRC's Board on Environmental Studies and Toxicology (BEST), under the co-chairmanship of Gilbert Omenn and Ellen Silbergeld.

The workshop was divided into three major topic areas attempting to answer the following questions: "How do people become exposed?" (chaired by Yoram Cohen), "How can we tell that people have been exposed?" (chaired by Bernard Goldstein), and "What happens after exposure?" (chaired by David Bates).

There were four major conclusions of the workshop. First, people are exposed to environmental toxicants in many ways. Dividing exposure assessment into studies of airborne, waterborne, and foodborne components cannot substitute for assessment of total exposure, with specific analysis of cross-

media roots of exposure. Second, biological markers can often help identify who has been exposed, sometimes quantifying to what. Third, we need to know the distribution of actual and potential exposures among people. It is not enough to know average exposures to a population. The policy implications of better individual exposure information were carefully examined during the workshop. Finally, many kinds of epidemiologic methods can be used to evaluate the relationship between exposures and the health outcome of those exposures, including exposure registries, disease registries, exploitation of biomarkers and opportunistic use of environmental monitoring data as clues to potential exposures.

The account of the workshop that follows was prepared by Paul Phelps, a professional science writer, with input from the participants. The NRC/BEST staff members most involved with the workshop included James Reisa, Marvin Schneiderman, Sharon Smith and Richard Thomas.

Gilbert S. Omenn, *Co-chair*
Ellen Silbergeld, *Co-chair*

Frontiers in Assessing Human Exposures To Environmental Toxicants: Report of a Symposium

OVERVIEW

Exposure is the critical connection between potentially hazardous substances (chemicals, trace elements, microbes) and human health effects. Exposure to these substances in the environment is increasingly worrisome to the American people, and the worry is often intensified by incomplete information on the nature, extent, and implications of the threat. Exposure is difficult to measure: hazardous materials are often present in very low concentrations, move unevenly through several environmental pathways, persist for varying periods of time, and finally are absorbed by humans in varying amounts depending upon individual characteristics such as age, behavior, and nutrition. Better information is needed by all parties: legislators and policy makers need better information to make good laws and regulations; public health officials need better information to detect and prevent the health effects of exposure; and the public deserves information that is understandable and an aid to people in reducing some exposures and in responding to public policies.

"Frontiers in Assessing Human Exposures to Environmental Toxicants," was a special 2-day symposium at the National Academy of Sciences in Washington, D.C., cosponsored by the Agency for Toxic Substances and Disease Registry of the U.S. Public Health Service and the National Research Council's Board on Environmental Studies and Toxicology. Many of the nearly 400 registrants were officials and scientists from federal, state, county, and local health agencies. The audience also included participants from environmental groups, academia, private industry, and congressional staff. They heard a series of case studies and panel discussions arranged around some basic questions: How do people become exposed to environmental toxicants? How can we tell that they have been exposed? And what happens after exposure?

The responses to these questions demonstrated the impressive advances that have been made in exposure assessment in the past 10 years. Possible health concerns can be addressed more accurately because analytic chemists can now detect some of these chemicals at concentrations of one part per billion or less; this means that exposures which at one time appeared to be

zero. For other chemicals, researchers have developed biologic markers—easily measured metabolic byproducts or tissue changes that serve as indicators of exposure, of the effects of exposure, or of differences in susceptibility to those effects. Using these new measurement tools, intensive monitoring programs and sophisticated research designs can produce a great deal of valuable data. Physical and mathematical models allow researchers to better integrate such information; this can assist in identifying confounding factors, predicting effects of new chemicals or future exposures, and recommending practical steps that health agencies or individuals can take to reduce group and personal exposures. By applying these techniques to large data bases, researchers may soon monitor exposures and assess health effects for entire populations. The desired goal is to optimize risk reduction across a range of agents and exposures.

Discussion and questions from the audience identified some of the challenges that remain in this field. The speakers seemed to agree that the ultimate goal of both science and policy should be *prevention* of harmful exposure at the population and community level. Researchers must strive to put practical, cost-effective measurement tools and models in the hands of government officials who are responsible for protecting public health in their communities. Speakers also agreed that both scientists and officials must do a better job of *communicating* with the public about exposure and risk. Community members had made significant contributions to technical aspects of several of the case studies, demonstrating that public participation can enhance good science, as well as good policy.

Finally, the symposium identified some components of a research agenda that should be pursued to improve and apply these innovations. One research need, for example, is for baseline data: What is a normal human, a healthy building, or a reference level for toxic exposure? Another need is integration: Researchers need to take advantage of the variety of exposure and epidemiologic techniques by broadening their research designs and modeling efforts. They need to look at more chemicals and at mixtures of chemicals, moving through multiple pathways. There must be more communication among toxicologists, epidemiologists, industrial hygienists, and others who conduct exposure assessments. Modeling efforts should be probabilistic, looking at the range and distribution of exposures; the greatest risks may be to persons at the high or low end of the distribution rather than the middle—at the high end if there is a positive dose-response relationship or at the low end if low exposure implies the lack of some essential material. Models should be tested against actual observations. Researchers also need a better understanding of the mechanisms of toxic effects at the cellular and molecular levels and of the genetic factors and other host factors affecting susceptibility. Most of all, our

society needs to emphasize reducing or eliminating exposures to toxicants through changes at the workplace, in the community, and in the home environment and through choices of carefully evaluated remediation programs.

INTRODUCTION

The View from Congress

The Honorable J. Roy Rowland (D-Georgia), one of only two medical doctors in the U.S. Congress and a leading voice on issues of environmental protection and public health, provided policy context for the symposium. Congressman Rowland asked the participants to focus on the needs and perceptions of policy makers and the general public, as well as those of scientists. "There is so much misinformation, misleading information, or lack of information," according to Rowland, "that it is difficult to make decisions about policy or about how best to deal with people who have been exposed." Citing the case of Agent Orange, Rowland pointed out that a new process can detect serum dioxin at concentrations of three parts per quadrillion, yet there is no consensus about the health effects of such low exposures.

Congressman Rowland supports a provision of the current Clean Air Act Amendments that calls on the National Academy of Sciences to review and recommend improvements in the risk assessment methodology used by the U.S. Environmental Protection Agency (EPA) in determining the health risks associated with exposure to hazardous air pollutants. Rowland urged the Academy to pay particular attention to such topics as low-level, high-level, and multiple-pollutant exposures, as well as the applicability of animal studies and the risks to humans of adverse health effects other than cancer. He also stressed the need to communicate with the public: "Talk to people in a way they understand; don't condescend to them."

Support for Exposure Research

A major user of research in exposure assessment and related toxicology is the Agency for Toxic Substances and Disease Registry (ATSDR) of the U.S. Public Health Service. Barry Johnson, assistant administrator of ATSDR, explained that his agency, created by the Superfund legislation in 1980, has the mission of preventing or mitigating adverse health effects in humans that result from exposures to hazardous substances in the environment. The 1986

Superfund amendments added several ambitious mandates to ATSDR's environmental health responsibilities.

- To conduct public health assessments of all sites on Superfund's National Priorities List (NPL), plus other sites at the request of concerned citizens or community groups.
- To maintain registries of persons exposed to specific hazardous substances and registries of serious illnesses in those persons.
- To produce toxicologic profiles of a long list of priority hazardous substances found at NPL sites.
- To cooperate with state agencies in developing health education materials for physicians and local health officials.
- To provide emergency assistance, a service that last year responded to over 2,500 requests for information or biomedical teams in support of federal and state health agencies.

Johnson explained that ATSDR also sponsors research into the effects on human health of hazardous substances escaping from waste sites and other sources—an aspect of ATSDR's Superfund role that is not always recognized. He observed that the agency's programs require information on substances to which human populations are exposed, how to measure them, and how to assess their effects on health.

The Fruits of Collaboration

ATSDR has supported an array of studies conducted in recent years by the Board on Environmental Studies and Toxicology (BEST) of the National Research Council. These studies, described by Gilbert Omenn of the University of Washington, the chairman of BEST, include recently published reports on biologic markers in reproductive and pulmonary toxicology; a study of biologic markers in immunotoxicology, to be published in 1991; and ongoing studies on neurotoxicology, advances in assessing human exposure to airborne pollutants, animals as sentinels of environmental hazards, lead exposure in critical populations, and environmental epidemiology. Omenn explained that the symposium provided a well-planned opportunity to discuss the results of some of this research in the form of case studies that allow lay audiences as well as professionals to "get our teeth into real-world problems and the capabilities and limitations of present and proposed methodologies."

Exploring the Frontier

Many scientific and industrial organizations are conducting exposure studies, using "new and innovative strategies" and producing useful results, according to Paul J. Lioy, director of the Exposure Measurement and Assessment Division of the University of Medicine and Dentistry of New Jersey, chairman of the BEST Committee on Advances in Air Pollution Exposure Assessment, and a member of BEST. "We need to develop exposure models that integrate these types of information and can be used by regulatory agencies to predict what exposure reduction strategies could be implemented in particular locations." The frontier of exposure assessment is "at the interfaces," said Lioy: the interface between environmental science and the health fields of toxicology, epidemiology, and clinical practice (see Figure 1), and also the interface between the environment and the individual. Following Lioy's lead, the symposium utilized a series of case studies organized around four central questions:

1. How do people become exposed?
2. How can we tell that they have been exposed?
3. What happens after exposure?
4. What implications do these findings have for public policy and for further research?

HOW DO PEOPLE BECOME EXPOSED?

Exposure, Fate, and Transport Modeling

The first set of case studies was introduced by Yoram Cohen, a chemical engineering professor at the University of California at Los Angeles, who stressed the complexity of measuring exposure in a system where humans can be exposed through multiple pathways (see Figure 2), and where both concentrations and subjects change over time. Models—not just mathematical models but empirical and even experimental representations—provide the framework for gathering data and refining the theoretical models that are the foundation of our assessment methodologies. In this sense, according to Cohen, all three of the case studies that followed were modeling studies of exposure and dose: for heavy metals in Colorado, for volatile organic compounds (VOCs) in West Virginia, and for nitrogen dioxide in Boston.

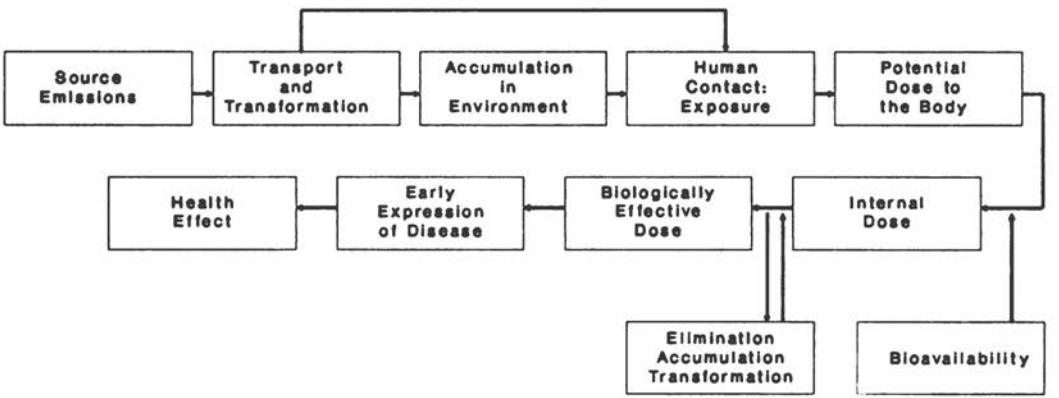

FIGURE 1 Continuum for the emission of and exposure to a contaminant and the expression of a health effect. Source: Lioy, 1990. Reprinted with permission from *Environmental Science & Technology*, copyright 1990, American Chemical Society.

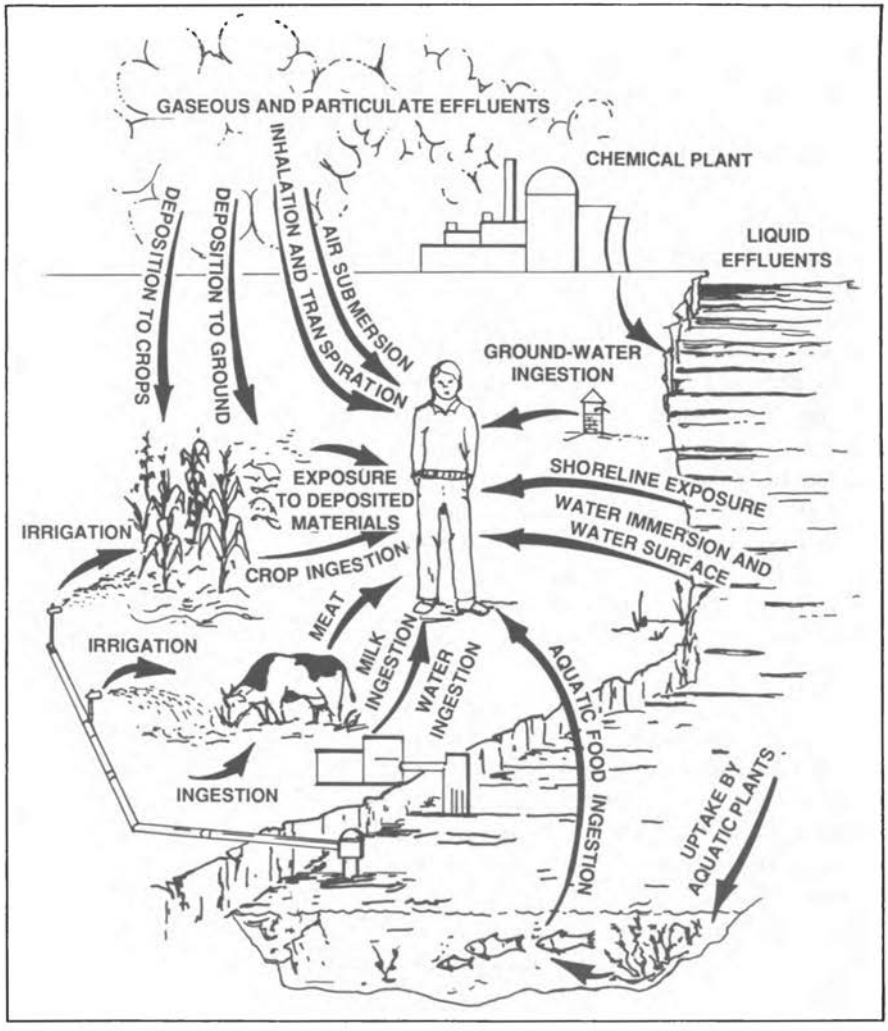

FIGURE 2 Multiple environmental pathways of toxicant exposure to humans. Source: U.S. Department of Energy, 1989.

Heavy Metals in Colorado

Leadville, Colorado, has been the site of major mining, milling, and smelting of precious and base metals since 1860. In 1983, the Yak Tunnel-California Gulch site was put on EPA's National Priority List, and in 1986 a soil survey found elevated levels of lead, arsenic, and cadmium in the residential areas of the town. A 1987 exposure study, sponsored by ATSDR, was designed to determine the levels of heavy metals in the blood and urine of individuals (particularly young children) and to identify environmental or behavioral factors that might predict exposure levels. Researchers not only took biologic samples but also collected dust samples in and around the homes and gathered information on activities that might be associated with higher exposures.

The results, reported by Willard Chappell of the University of Colorado at Denver, demonstrated the difficulties of modeling. Urinary arsenic and cadmium levels were not elevated, suggesting that exposure to these compounds was not excessive in Leadville. Few of the young children in the study exceeded the present screening guideline for blood lead levels, which is 25 μg of lead per deciliter of whole blood; the community as a whole appeared to have little lead-linked toxicity. Chappell speculated that altitude may play a role in lead risk; at 10,200 feet, Leadville is at the highest altitude of any incorporated city in North America. Among children ages 6 years or less, the mean blood lead levels were lower in children from Leadville than in children from Helena, Montana, and Telluride, Colorado, a few years earlier. Chappell noted that comparisons are very difficult to make because of dramatic decreases in blood lead levels over the past decade due to reductions in lead used in gasoline and in food containers. An EPA model was developed to account for the effect of reductions in lead in gasoline and food containers. The model predicts that geometric mean blood level for children two years of age in 1990 will be 3.0-4.7 μg/dL compared with 14.9 μg/dL, which was found by the NHANES II study in 1978. This is an average annual decrease of 1 μg/dL per year. Thus, comparison of the 1987 Leadville results with studies done more than a decade ago may be meaningless. Nevertheless, the Leadville study could recommend a number of practical steps to help residents to reduce exposure. Chappell also pointed out that several ongoing prospective studies reveal effects on cognitive function at levels of lead as low as 10-15 μg of lead per deciliter of blood.

According to Chappell, the Leadville study demonstrated that the concept of the "most exposed individual" (MEI) currently used by EPA as a basis for standard setting is potentially flawed and could lead to inappropriate policy decisions. In many cases a well-defined MEI may not exist, and in others the

exposures implied by MEI modeling are much higher than actually experienced. The definition also varies across pathways, which complicates comparisons. Chappell urged that regulators use estimates of the *range* of exposures to help define the *distribution* of risks. This would allow policy makers to make consistent choices—for example, to protect the same proportion of the exposed population (e.g., 99%) from different toxicants or toxicants delivered through different pathways.

Volatile Organic Compounds in West Virginia

An even more complex exposure study is in its third and final stage in the Kanawha Valley of West Virginia. A narrow, 35-mile-long valley with poor air circulation, the area has for decades been home to one of the densest concentrations of chemical processing plants in the United States. Following the Bhopal, India, accident of 1985 and the investigation of releases of chemicals at Institute, West Virginia, the community became increasingly concerned about potential health problems associated with residents' exposures from the valley's 17 chemical plants. In response, the National Institute for Chemical Studies (NICS), an industry group, conducted a "safeguard study" that described the various chemicals, recorded the amount of each chemical used or produced at each plant, and described each plant's accident history. A multimedia screening study, conducted by EPA in early 1986, identified airborne emissions as producing pollutants of greatest concern, setting the stage for the current study, which was cosponsored by NICS and EPA.

Phase one, designed to determine whether residents were being exposed to high levels of VOCs, monitored emissions during 1987 and 1988 at four outdoor sites and inside 35 residences scattered across the valley. Measurements at outdoor sites indicated that six of the 19 VOCs being monitored were present at elevated levels, but concentrations varied considerably among the four outdoor sites, and concentrations were often highest at a site remote from the point of emissions. Moreover, concentrations of most VOCs were higher indoors than outdoors, an important finding given that most people spend 80-90% of their time indoors. Previous studies conducted by EPA had shown that many commonly used household products are sources of VOCs. Phase two, now being completed, is an epidemiologic survey of the health status of all children in the third through fifth grades of Kanawha County schools—totaling approximately 9,000 children. Phase three, to begin during 1990, will continue monitoring, using health and activity diaries, lung function testing, and an epidemiologic survey of acute health problems.

The initial findings of this study, as reported by Lewis Crampton, associate

administrator of EPA and former director of NICS, reveal as much about how to conduct an exposure assessment as they do about actual exposures. "The monitoring actually didn't show very much." According to Crampton, "There was no smoking gun at any of the plants," yet the monitoring was useful in that it gave tangible evidence of official (regulatory agency) concern. "The way it was done gave people confidence in what was going on," he asserted. Researchers tried to make the study "user-friendly to West Virginia residents" by including community representatives in designing the study, educating local media, and holding public meetings to discuss results. The community responded with remarkable cooperation, especially during the health survey, which had an unprecedented 97% response rate. Chemical companies were cooperative as well, and the study identified three VOCs—benzene, carbon tetrachloride, and chloroform—as possible targets for exposure reduction at their plants in the valley. Some of the informal discussions about this case warned against the possible distortion or premature interpretation of the science.

Nitrogen Dioxide in Boston

The third case study, described by P. Barry Ryan of the Harvard School of Public Health, used a physical model to estimate the distribution of exposures for an entire population. In the "microenvironmental" exposure model described by Ryan, total exposure is the sum of the partial exposures resulting from time spent in different environments having varying concentrations of a contaminant. Researchers took samples of nitrogen dioxide (NO_2) from various locations in and around 581 Boston-area residences (including those with either gas or electric kitchen ranges) at different times of year in 1985. The time component was based on activity logs, in which 300 subjects recorded time spent in different microenvironments—sleeping, cooking, commuting, and so forth. Because cooking on gas ranges resulted in high concentrations of NO_2, the study team also collected peak-exposure data by using personal monitors worn during approximately 100 meal preparations. The results indicate that people spend about 65% of their time inside the home, doing something other than cooking, 25% is spent in other indoor environments, and only 10% of their time is spent outdoors. Homes with gas ranges had higher concentrations of NO_2 than homes with electric ranges—a mean of 29 parts per billion (ppb) in the living rooms of gas-range homes compared with 9 ppb in electric-range homes. Concentrations were more variable, in part because of the variable times spent in cooking, and often much higher in gas homes, however; personal monitoring showed that while individuals were cooking on gas ranges, they were exposed to short-term peak concentrations of 300-500

ppb. Consequently, the models were run in both "deterministic" and "probabilistic" modes, using both point estimates and ranges of exposure in a given microenvironment.

By combining the modeling results, Ryan was able to suggest the likely distribution of exposures expected in a population of individuals with either gas or electric ranges in their homes. Figure 3 gives the distribution of exposures (anywhere in the home). The estimated exposure in gas homes from the modeling was 36 ppb, although a large fraction had exposures two or more times the mean. The mean exposure for the electric home population was much lower, 16 ppb, but the shape of the distribution was similar—many with lower exposures, others twice the mean or higher. The probabilistic approach, which Ryan believed yielded better estimates of the population distribution, gave similar mean exposures but implied greater variability. Like Chappell, Ryan advocated a probabilistic approach as a basis for "population-based" regulation, "protecting 95% of the population, or 99%, or 99.99%, whatever you choose."

Discussion

Discussion of the first three case studies centered on what has been learned and what remains to be accomplished in exposure modeling. Models are useful for predicting exposure and for integrating empirical data into a comprehensive framework that can identify major controlling factors, according to Joan Daisey, head of the Indoor Environment Program at Lawrence Berkeley Laboratory. Because we spend most of our time indoors, however, researchers must investigate the pathways through which pollutants enter homes, as well as those originating inside homes. Models and experiments are needed to link indoor and outdoor environmental pathways (Figure 2). She also called for attention to the individual behaviors that affect our exposures, such as smoking, and greater attention to persons exposed to the upper end of the exposure distribution.

The case studies show "how far we've come from the early days" of exposure modeling, according to Thomas Burke, former New Jersey official, now at The Johns Hopkins University. Nevertheless, some researchers are not expanding their horizons and thus are still "looking for the keys under the lamp post"—investigating the things for which they already have good data and neglecting other parts of "the vast world of potential exposure," where some of the newer techniques would help investigations. Modeling studies often lack comparison populations. They do little to help us understand peak exposures, and they are still crude tools for reconstructing historical community exposure patterns,

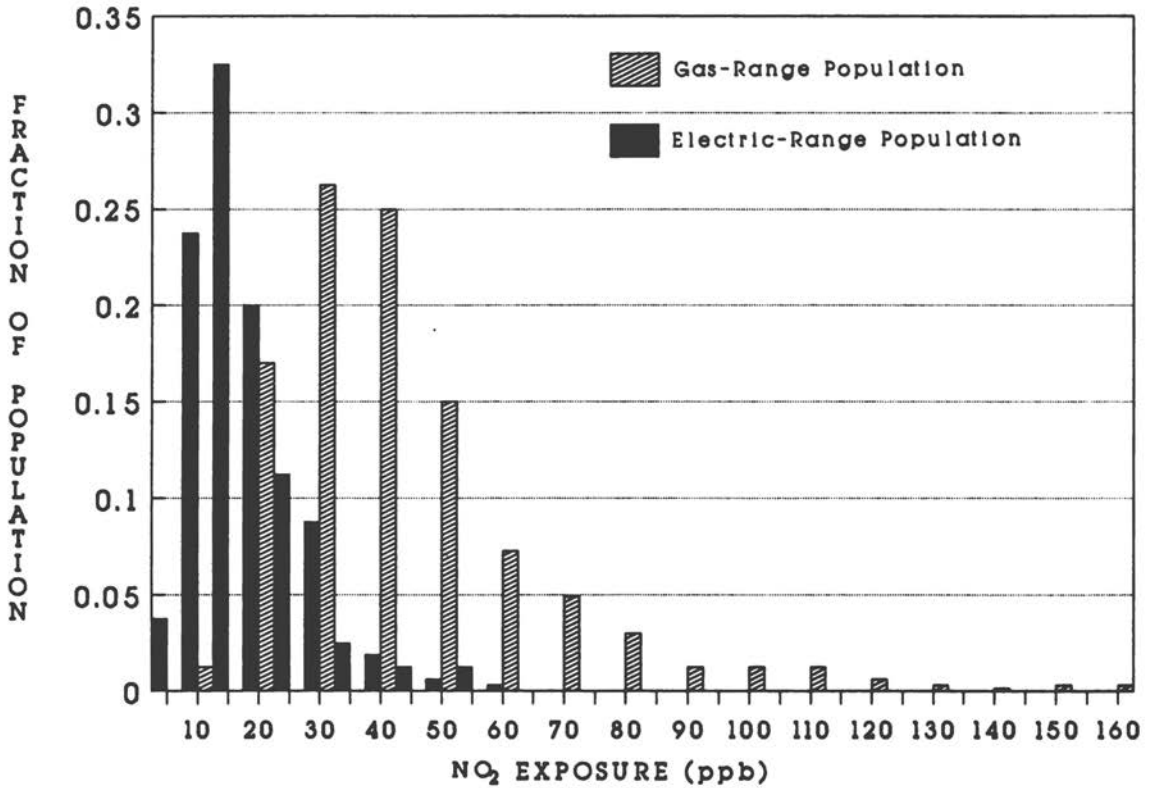

FIGURE 3 Simulated exposures to NO_2 (model) for persons in electric-range and gas-range homes in Boston SMSA. Source: Ryan et al., 1988.

often 20 or more years in the past, that may have precipitated what we now see as health problems in our communities. Above all, according to Burke, we need to put understandable models and usable field instrumentation in the hands of local health officials, who often must make decisions in the absence of specific exposure evaluations.

HOW CAN WE TELL THAT PEOPLE HAVE BEEN EXPOSED?

Markers and Surveillance

The second set of case studies was introduced by Bernard Goldstein of the University of Medicine and Dentistry of New Jersey, a former member of BEST and chairman of its biologic markers studies. He focused on what he called "the crucial uncertainty–how do we know that someone really is exposed? Without knowing that, how are we able to act?" In the past we have often acted on the supposition that people were exposed, but in many cases we have both overestimated the average exposure and underestimated the exposure to specific individuals. Because of these uncertainties, often "we are unable to identify those individuals who are really at risk."

The case studies that followed, therefore, involved attempts to identify markers for known levels of exposure, and then from the measurement of markers to extrapolate to people with unknown levels of exposure. Goldstein added that a good biologic marker not only should be easily measured and directly related to the toxicant but also should be related to it in a known way. "We want those biologic markers of exposure that fit in best with the mechanism of effect." In the case of lead, however, "one of the things we don't really know is how lead affects the central nervous system." Research in this area of toxicology could facilitate the development of better biologic markers of exposure.

Biologic Markers for Lead Exposure

Lead toxicity remains a major public health concern in the United States, according to Bruce Fowler of the University of Maryland, and toxicity has been reported at low exposures. Thanks to the phaseout of leaded gasoline, most of us now have blood lead concentrations of 5-10 μg/dL, but even these levels in young children appear to have permanent effects on the intelligence quotient and a number of organ systems. The current screening test (erythrocyte protoporphyrin) is relatively insensitive at these low concentrations, and

blood tests in general reflect only recent exposures; previous tests have shown that over 95% of the body burden of lead in adults and about 70% in children is deposited in the skeleton.

Because the "lifetime load" that accumulates in the skeleton can be released back into the system (e.g., during periods of bone remoulding as in pregnancy or menopause), researchers are developing sensitive in vivo techniques to obviate a need for an invasive procedure such as bone biopsy for measuring lead in bone. Fowler described one technique, x-ray fluorescence, that has been used in long-term studies of smelter workers in Europe. An experimental technique, analytic speciation of porphyrins with high-performance liquid chromatography, offers the possibility of complementing existing tests for lead exposure.

"A little further out on the horizon," according to Fowler, is a far more sensitive urinalysis technique based on radioimmunoassays for lead-binding proteins found specifically in the kidney of rats—alpha-2-microglobulin, a member of the retinol-binding protein gene family that is also found in humans. Because high levels of lead appear to influence the excretion of this protein, it may prove to be a useful biologic marker for exposure to lead following chronic low-level exposure. Excretion of this protein is coupled with profound lead-specific changes in gene expression that occur as a result of relatively low-level lead exposure. This radioimmunoassay may provide researchers with a better understanding of why individuals vary in their sensitivity to lead and, ultimately, with a test that will identify individual susceptibility and risk.

Tissue Monitoring—Pesticides in Breast Milk

Biologic markers can be used for surveillance and for establishing reference levels of toxic exposure. Donald Mattison, of the University of Pittsburgh Graduate School of Public Health (formerly of the University of Arkansas School for Medical Sciences), described one such case study in which human breast milk was used as a source of markers for exposure to pesticides. The Food and Drug Administration discovered in 1986 that Arkansas dairy products were contaminated with heptachlor, a potential human carcinogen. Heptachlor tends to persist in human fatty tissue and is eliminated through breast milk, thereby exposing infants. In response to concern from pregnant and nursing mothers, the Arkansas Department of Health offered to analyze breast milk for evidence of exposure not only to heptachlor but also to 12 other widely used pesticides with similar characteristics (see Table 1). For all of these pesticides, concentrations in breast milk are possibly a reasonable

TABLE 1 Breast milk pesticide concentrations reported as ppm on fat basis among samples with quantifiable concentrations

Compound	Number (%) Quantifiable of 942		Mean (± SD) and Range for Those Quantitated		
Heptachlor	49	(5)	0.03	± 0.02	(0.01 - 0.13)
Heptachlor Epoxide	694	(74)	0.06	± 0.05	(0.01 - 0.46)
Oxychlordane	792	(84)	0.06	± 0.04	(0.00 - 0.60)
t-Chlordane	15	(2)	0.18	± 0.14	(0.03 - 0.53)
cis-Chlordane	15	(2)	0.15	± 0.11	(0.05 - 0.42)
t-Nonachlor	728	(77)	0.08	± 0.07	(0.01 - 0.89)
Dieldrin	16	(2)	0.07	± 0.06	(0.03 - 0.29)
pp-DDT	181	(19)	0.20	± 0.16	(0.05 - 1.61)
op-DDT	4	(0.4)	0.11	± 0.04	(0.05 - 0.16)
pp-DDE	940	(100)	0.95	± 1.65	(0.02 - 26.41)
pp-DDD	2	(0.2)	0.10	± 0.04	(0.07 - 0.14)
α-BHC	10	(1)	0.02	± 0.01	(0.01 - 0.04)
β-BHC	252	(27)	0.11	± 0.12	(0.03 - 1.27)
Lindane	7	(0.7)	0.07	± 0.05	(0.02 - 0.18)
Arochlor	6	(0.6)	1.57	± 0.45	(0.80 - 2.09)
HCB	58	(6)	0.03	± 0.02	(0.01 - 0.10)
% Aldrin	788	(84)	85050	± 16.90	(15 - 164)
% Fat	942	(100)	3.40	± 1.60	(0 - 14)

Number quantifiable = number of samples in which the indicated compound was present above the limit of quantitation.

% Aldrin = percent recovery; aldrin was used as an internal standard in most samples analyzed.

% Fat = percent fat determined in the sample.

surrogate for concentrations in the mother's adipose tissues and thus are an acceptable biologic marker for exposure of the mother and for the direct exposure of the nursing infant.

Of 942 women in the Arkansas study, 49 (5%) had quantifiable levels of heptachlor in their breast milk, and 694 (74%) had quantifiable levels of its more persistent metabolite, heptachlor epoxide (HE). (Quantifiable concentrations are those above the threshold of detection, 1.5 ppb in whole breast milk.) The means of the quantifiable concentrations were 31 ppb heptachlor and 61 ppb HE, both of which are near the lower level of concentrations reported in earlier studies conducted in the southeastern United States. However, many of the samples also showed quantifiable concentrations of several other pesticides and their metabolites–84% had concentrations of oxychlordane, for example, and almost 100% had para-para-DDE, although both are near the lower level of concentrations previously reported.

Mattison cautioned, however, that although these xenobiotics were present, it was difficult to establish how much of the exposure resulted from dairy product contamination. All of the women consumed milk and other dairy products on a daily basis, for example, but 64% of the women lived in homes treated for termites, half of them within 12 months of the time of the breast milk sample. The relatively low range of concentrations was reassuring, according to Mattison, and although "there are some very highly exposed individuals in this population," they may represent "an exposure scenario to other than dairy products." Many questions clearly remained to be answered, but this study created a registry of 1,000 women and their children that will be a resource for future studies.

Animal Sentinels for Polychlorinated Biphenyls

An experiment in evaluating biologic markers for exposure to polychlorinated biphenyls (PCBs) in domestic animals was described by Michael Goldschmidt of the University of Pennsylvania. The Paoli Rail Yard in southeastern Pennsylvania is a major service and repair station that became heavily contaminated with the PCB Askeril between 1951 and 1979. Numerous on- and off-site surveys have found high concentrations of PCBs in the soil, runoff, and groundwater around the yard. Serum concentrations in local residents were as high as 24 ppb, with a mean of 4 ppb.

The study described by Goldschmidt was designed to test the following hypotheses:

- Dogs and cats share with their owners a potential for exposure to hazardous chemicals, and because they develop more rapidly, they will display adverse health effects earlier than humans.
- Ovarian morphology, in particular, can be correlated with tissue concentrations of PCBs and thus with exposure; therefore, ovaries from female pet dogs and cats that are spayed can be used as a sentinel system for adverse reproductive effects in humans who are exposed to toxic chemicals in the same environment.

With the owners' permission, ovaries were collected at local veterinary hospitals and analyzed for PCBs and for signs of abnormal or atretic follicles. Researchers also interviewed the owners for information relating to exposure.

The results of this observational study did not support the hypotheses. Most of the pets were spayed so young—between 12 and 24 months for dogs, and usually less than 12 months for cats—that the animals had very little exposure to their external environment. Only three dogs and three cats were found to have PCBs in their ovarian fat tissues, and although two of the cats lived within half a mile of the Paoli Yard, their owners reported that these animals had never been outside. Ironically, tests on what should have been a control population—a colony of laboratory cats at the University of Pennsylvania, cats that likewise never went outdoors—showed higher concentrations of PCBs, even in two older female cats with excellent breeding records. In both cases the source of the PCBs is unknown. Based on this small sample, it would appear that the measured levels of PCBs had no effect on reproductive activity. If a population of exposed, older animals could be found, Goldschmidt said it would probably be worth a further attempt at this "sentinel animal" approach.

Surveillance—Reproductive Outcomes

The final case study was presented by Godfrey Oakley of the Centers for Disease Control (CDC), who explained that his job often involved "starting with sick people and trying to find out about the exposures." CDC maintains registries of a variety of reproductive outcomes—birth defects, mental retardation, cerebral palsy, very low birth weight—all of which represent major public health burdens and many of which are presumed to have environmental causes. The registries serve both as an early warning system, alerting officials to adverse effects, and as a means for identifying the cause in time to avert a crisis.

Oakley cited the use of the Lyons, France, Birth Defects Registry to dem-

onstrate a connection between an environmental toxicant (valproic acid, an anticonvulsant medication) and a specific reproductive outcome (spina bifida). In another study, CDC researchers demonstrated that women who took multivitamins on a regular basis were only half as likely to have a baby with spina bifida as those who did not take multivitamins. On the other hand, CDC's study of birth defects in the Kanawha Valley during the years 1970-1974 found no association between cases of central nervous system malformation and proximity to polyvinyl chloride production; in fact, the cases tended to cluster to the northeast of the plant, upwind and upstream from the likely sources of toxic pollution. A more recent study of Vietnam veterans was the largest case control study for birth defects ever undertaken, including some 250,000 births; according to Oakley, it showed no association between presumably being exposed to Agent Orange and fathering a baby with birth defects.

Opportunities for improved surveillance, according to Oakley, include multicenter case control studies, expansion and coordination of state registries, and use of mid-pregnancy blood samples for additional toxicologic screening. He also advocated investigation of natural substances as well as man-made chemicals. However, he warned against the belief that great advances would come from the study of spontaneous abortions, which he called "the fool's gold of reproductive toxicology and epidemiology." Some workers in the field do not agree. Prospective studies of conceptuses from serial urine samples (monitoring for specific hormone) in women would suggest otherwise.

Discussion

Discussion of markers and surveillance centered on the need to go farther, to push back the frontiers. Emil Pfitzer of Hoffmann-LaRoche pointed out that BEST's definition included three types of biologic markers: markers for exposure, markers for the effects of exposure, and markers for susceptibility to the effects of exposure. Thanks to advances in analytic chemistry, it is now possible to measure internal exposure at the molecular level; investigators are also becoming more aware of the effects of exposure at very low doses, but they have not done as much in terms of identifying populations at risk. The challenge, according to Pfitzer, is to develop more specific tools as well as more sensitive ones. James Melius, speaking from his perspective as an official in the New York State Department of Health, stressed the need for multiple approaches—measuring exposure, identifying health effects, investigating the causes of those effects—and the need to integrate and coordinate these different approaches. In the face of limited resources, the practical question

becomes what exposure tools are needed to optimize protection of the public health.

WHAT HAPPENS AFTER EXPOSURE?

Population-Based Data Analysis Techniques

Whatever the challenges of measuring exposure, the problems of measuring and understanding health outcomes are just as difficult and complex, according to David Bates of the University of British Columbia and a member of BEST. The data often indicate that something is happening, he explained, but not what or why. Hospital admissions for asthma have doubled in the last 8 years, for example, but this increase could reflect changes in treatment rather than increased prevalence or severity. Some outcomes are more difficult to measure than others—cancer is fairly easy to detect and certify, compared with reproductive effects such as reduced fertility, small differences in intelligence quotient (e.g., due to lead), or decreases in visual field (e.g., due to mercury), particularly in minority populations.

Nevertheless, Bates said, "We're absolutely bound to undertake epidemiological and environmental studies—there is no other option that will tell us whether exposures are or are not having an effect on human populations." Previous speakers had described studies in which small, selected populations were monitored closely to determine exposure. Large population studies are far more effective, however, in determining whether that exposure is having an effect, in setting minimum effect levels, and in identifying susceptible groups. Large studies can also be very cost-effective. If the data are already available, "statistical analysis of banks of data is really relatively cheap." The four case studies that followed were examples of the effective and ingenious use of a variety of data bases for determining the health outcomes of exposure to environmental toxicants.

Direct Measurement of Chemicals in the Environment

The first case study, presented by Jed Waldman of the University of Medicine and Dentistry of New Jersey, demonstrated the challenge of collecting and analyzing detailed exposure data for even a limited at-risk population. The Total Human Environmental Exposure Study (THEES) is a four-year project that includes microenvironmental and personal monitoring and the development of models for exposure to a single pollutant—benzo(*a*)pyrene (BaP), a typical combustion product and a known carcinogen. Human expo-

sure to BaP can occur through multiple media and pathways, including the air (inhalation), skin contact with soot and soil, or ingestion of contaminated water or char-broiled foods. The study site, Phillipsburg, New Jersey, contains an iron foundry that is a suspected source of BaP; most of the monitoring stations were within 500 meters of the foundry.

Preliminary measurements indicated that inhalation and dietary exposure were the principal pathways; data collection included five outdoor and 13 indoor monitoring stations and also personal monitoring devices, activity logs, samples of all meals, and twice-daily urine samples from a total of 24 subjects in 10 households during three separate 14-day periods in 1987 and 1988. The unusually large and detailed data base generated by THEES provided an accurate profile of a single pollutant moving along different pathways in different media. It also showed, however, that there are many components to personal exposure, and that personal behavior can play a major role in determining total exposure.

As in other studies, THEES showed that exposure to pollutants varies over time: concentrations in winter were often 10 times those in summer or fall. Outdoor concentrations were the principal determinant of indoor BaP concentrations, but some personal activities greatly increased personal exposure from inhalation. Examples included cooking, exposure to space heaters and tobacco smoke, using arc welders on the job, and living near a diesel route. In some cases, a single peak exposure was high enough to cause a marked increase in the mean value for an entire 14-day period.

The data showed that an individual's choice of food and how it is prepared can have an even greater impact on exposure. The range and magnitude of dietary exposures (from 2 to 500 ng/day) were much greater than those of inhalation exposures (from 10 to 50 ng/day), and some individuals had 10- or even 100-fold higher exposures through the dietary route. "A nice char-broiled porterhouse steak can crank up a person's dose for a week," according to Waldman; what he called a "dosing meal" causes a spike in the levels of BaP metabolites in the urine, providing a possible biologic marker for peak exposures.

Questionnaires

The second case study illustrated the use of questionnaires to characterize a situation in which both the exposure variables and the outcome variables are difficult to define. Building-related occupant complaint syndrome or "sick-building syndrome" often involves vague and transient symptoms, according to Brian Leaderer of Yale University. The symptoms can include headache, eye irritation, dry throat, sinus congestion, shortness of breath, skin irritation,

nausea, and fatigue—many of which decrease when the worker is away from the workplace. The cause of these complaints is believed to be a complex interaction of chemical and biologic pollutants, building environmental systems (especially poor or contaminated ventilation), physical factors, individual characteristics, and social dynamics, including stress and emotional factors. Factors that might limit the ability to identify specific causes are the relatively low levels of contaminants, often in combination, and the lack of normative data—no operational definition of a "healthy building." In addition, it may be necessary to attempt to uncover possible interactions of pollution, or perceived pollution, with more subtle psychological or emotional factors.

Leaderer described the protocol for a large-scale study of four federal office buildings in Washington, D.C., carried out in February 1989. There was a history of different levels of complaints at the four buildings. The first stage of the study was to ask all 8,000 of the workers in the four buildings to complete a confidential, one-hour questionnaire designed to elicit information on 33 health symptoms, possible risk factors (including allergies), level of comfort or discomfort, perceived source of discomfort or health effects, job stressors, and personal information. Responses led researchers to identify 209 locations with the highest and lowest rankings for health symptoms or comfort; these locations were then monitored for temperature, relative humidity, carbon dioxide, and a range of pollutants, including suspended particulates, tobacco smoke products, volatile organic compounds, and microbiologicals. Phase two included a second questionnaire administered to 1,300 subjects whose workstations were within 25 feet of the monitoring stations.

Monitoring results have been released, and the final report of this study was due September 1990. Leaderer reported, however, that preliminary analysis of the questionnaires indicates a real and complex problem. Sixty-four percent of respondents reported experiencing one or more of the health symptoms "often" or "always" during the past year, and 30% thought the symptom had become worse in the past year. High percentages associated these symptoms with the work environment and believed that the work environment impaired their ability to perform their work. Carpet dust, paint smells, other chemicals, and tobacco smoke were most frequently perceived as the cause of health symptoms; air movement was the comfort factor that respondents most wanted to enhance—many employees had brought portable fans into the workplace.

Leaderer said that he learned during this study that "one has to be extremely sensitive to the perceptions and needs of occupants of the buildings . . . both for their sake and to do a comprehensive study." Management and union officials helped to promote the study, and response rates for the initial questionnaire were 83%. "The high response rate gives us confidence in the numbers we generated."

Clusters and Registries

Two case studies came from the California State Department of Health Services (DHS), which has taken a leading role in developing health and environmental data sets and techniques for analyzing them. The first, presented by Richard Jackson, illustrated the dangers of drawing conclusions from epidemiologic evidence without also examining detailed exposure data. In the fall of 1981, health officials in Santa Clara County discovered that over 60,000 gallons of chemical solvents had leaked from an underground tank at the Fairchild camera plant in the Los Paseos area. The chemicals included 1,1,1-trichloroethane (TCA, or methyl chloroform) and 1,1-dichloroethane. A local mother, whose child had been born with a heart defect, canvassed the community (not long after the controversial Medfly spraying) and identified five other families whose babies had also been born with congenital cardiac defects. She alerted health officials and the press to this "cluster," leading to the state investigation.

The leaking tank sat 80 feet above the main aquifer supplying drinking water to homes and businesses in Los Paseos; Jackson described it as "an accident waiting to happen." The well nearest the plant on the edge of Los Paseos was found to be contaminated with TCA at concentrations up to 8,800 ppb, (compared with the current drinking standard of 100 ppb), and officials immediately shut down the well. Under pressure from the community and the media, DHS conducted a preliminary epidemiologic study in 1983 that found a doubling in the rate of miscarriages and almost a tripling in the rate of congenital defects in Los Paseos during the period of interest compared with a control area in another part of the county. The DHS study could not establish a causal link between the leak and these adverse outcomes, but the residents and the media were convinced that the toxic leak caused the birth defects. Fairchild paid a settlement to the community and another $14 million to clean up the site.

Further investigation, however, using more sophisticated exposure data, suggested that the leak was not the cause of the defects. For one thing, Jackson pointed out, the heart is formed during the first trimester of pregnancy; the concerned mother's baby was born in May 1981, meaning that its heart was forming in fall of 1980, well before most of the solvents leaked from the Fairchild tank. Hydrogeological modeling of the leak and the groundwater aquifer confirmed that TCA concentrations at the nearest well should not have reached 10 ppb until January 1981. Further computer modeling of water distribution from the contaminated well during 1981 allowed researchers to estimate the probability and levels of exposure at any location in the water

district. Average exposure was higher in the immediate area of the well than in the Los Paseos area that had been investigated previously.

Based on these new data, DHS has conducted further studies comparing reproductive outcomes in four study areas—two that were "exposed" and two that were not—for two time periods: pregnancies conceived during 1980-1981 before the contaminated well was closed and pregnancies conceived during 1982-1985 after the well was closed. In this broader investigation, the previous associations between TCA exposure and pregnancy outcomes disappeared. There was no increase in either spontaneous abortions or congenital defects in the two more highly exposed study areas relative to the control areas, and the rates of both spontaneous abortions and birth defects were lower in the more highly exposed neighboring area of Los Paseos. When the data for the two exposed areas were combined, the women whose pregnancies ended in normal live births were found to have been exposed to slightly higher estimated levels of TCA than those who miscarried. Similarly, contrary to expectation, mothers of normal infants were exposed to much higher levels of TCA than those women with live-born babies identified as suffering from some malformations (Figure 4).

These studies did not exonerate TCA (at any dose) as a reproductive hazard, but, taken together, they indicate the Fairchild leak was not likely to have caused the cluster of adverse outcomes observed in Los Paseos. Nevertheless, according to Jackson, they showed the necessity of listening to the community: It's often "the alert clinician or, more often, an alert mother who has identified a problem." More important, DHS emphasizes the need for policy makers and the public to realize that epidemiology is a long and detailed process, one that needs to be linked with exposure assessment. Epidemiology cannot be used as a quick public-relations "fix."

Jackson also pointed to the advantage of having a birth defects registry in place. California's Birth Defects Monitoring Program, which did not begin operation until 1983, now covers over three-quarters of the state's births and has enabled DHS to investigate 70 clusters. None has proved to have unequivocal environmental explanations. The registry has 22 normative and descriptive epidemiological studies under way. "That's where the real gold mine is," according to Jackson, "comparing the diseased population with the healthy population and looking for risk factors."

Population-Based Data Banks

The final case study involved an ingenious use of population data to estimate the relationship between air pollution and disease. Bart Ostro, of Cali-

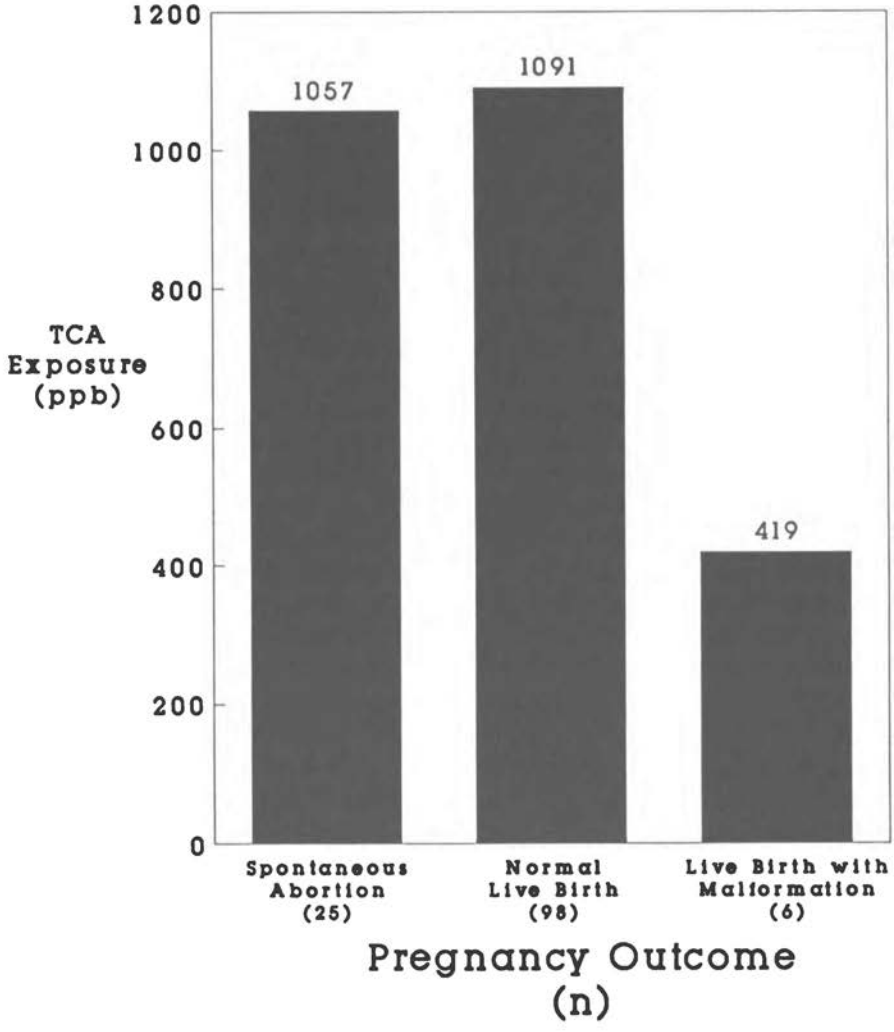

FIGURE 4. Pregnancy outcome follow-up study. Estimated TCA exposure during first month of pregnancy by pregnancy outcome. Original and exposed areas combined. Source: California State Department of Health Services, 1981.

fornia DHS, described his efforts over the past 10 years to establish dose-response information for different air-quality standards, specifically for particulate matter less than 10 μm in diameter (PM-10). Funding was unlikely for a major new study in this area, so Ostro decided to use an existing population-based data set, the Health Interview Survey (HIS), from the National Center for Health Statistics. At this time, EPA also was preparing to review a new standard for PM-10 for which few health-effects data were available. HIS includes data on the social, economic, and demographic characteristics of 150,000 individuals each year, as well as health indicators and standardized diagnoses. Ostro used the HIS illness data as a measure of health effects.

Data on air pollution were more difficult to develop. Total suspended particulates had been monitored for 20 years, but only once every six days at each location; Ostro wanted more frequent readings and readings for the smaller particles that are implicated in health effects. He found that a possible surrogate for chemical air pollution, broadly characterized as "regional haze," is dominated by particles below 1 μm (fine particles [FP]); under certain conditions, the level of FP is also inversely related to visibility. Every airport in the United States is required to record visibility at least once every three hours; the National Climatic Center maintains a computerized data base that would provide the source for estimating FP levels. After a series of quality control steps, Ostro developed a 6-year (1976-1981) data base that included 12,000 adults per year in 68 cities for which he had both HIS data and airport visibility data for the period.

Using multiple regression techniques, he analyzed respiratory symptoms against various explanatory factors, including FP levels and other variables (age, sex, smoking, etc.) that might confound the relationship between air pollution and health effects. An increase in the 2-week average FP concentration was consistently associated with increases in the number of workdays lost to illness, providing a partial measure of the economic costs of air pollution. Pollution was also associated with increases in the number of days when activities were restricted, especially by respiratory symptoms. Subsequent studies with the same data base have confirmed that air pollution has its greatest impact on those with pre-existing chronic respiratory conditions, that the association between air pollution and morbidity was maintained even when corrected for active or passive exposure to tobacco smoke, and that sulfates are a pollutant of particular concern.

Practical Applications

Much of the discussion that followed these case studies focused on the

need for a "mosaic" of methodologies to address questions of exposure and effects. The case studies "demonstrated the value of the variety of epidemiological resources," according to Diane Wagener of the National Center for Health Statistics. Long-term investments in "things like Health Interview Surveys and registries" will create the information base needed to answer "acute, short-term questions." Wagener and William Halperin of the National Institute for Occupational Safety and Health laid out the principal questions and the range of methodologic responses that had been discussed during the two days of the symposium (see Figure 5).

Halperin raised another problem, probably the key environmental health problem—"There can be exposures and there can be effects, but are they causally related?" Several participants recommended that studies be guided by rigorous, formal hypotheses about the mechanism linking exposure and health effect. David Bates, in dissenting, cautioned, however, that, "It's great if you know the mechanism, and we should certainly involve the toxicologists, but we shouldn't wait for them. Public policies should not wait until an association has been shown to be causal" (through definitive knowledge of mechanisms). Bates cited the history of tobacco smoke and illness in support of his call for early preventive action.

Exposure assessment and epidemiologic studies can be complex and expensive, leading to conflicts over resources. Many of these case studies illustrate attempts to develop convenient, economical measures. What may be emerging, according to Brian Leaderer, is a "middle ground" that (a) focuses on the health outcome and (b) integrates all relevant measures of exposure and effect in a cost-effective "nested design." "We're moving together," Leaderer added, "The environmental epidemiologist and the people who do risk assessment have discovered that adequate exposure assessment is needed to come to reasonable conclusions." Richard Jackson agreed on the need for interdisciplinary approaches: "You need a team—you need toxicologists, health specialists, [people in] laboratories, engineers, community members." Michael Goldschmidt agreed that "we should become collaborators in this one big field," people that Jackson called "exposure or environmental hygienists, rather than industrial hygienists, more investigatory and less regulatory-minded."

IMPLICATIONS FOR POLICY AND RESEARCH

Policy Implications

The panelists seemed to agree that there were two principal policy implications for exposure assessment presented during the symposium. (1) The goal

Health Questions	Methodological Responses: Exposure Assessment	Applied (Response) Epidemiology[a]	Epidemiologic Study[b]	Registries and Surveillance	Reference Surveys for Exposure	Reference Surveys for Health Effects	Risk Assessment
Are we exposed?	●				●		
Are we affected now?		●		●		●	
Did exposure cause effect?	●	●	●	●	●	●	●
Will we be affected later?	●		●	●	●		●

FIGURE 5 Mosaic of exposure and epidemiologic methodologies.

of both science and policy should be *prevention*, at the community and population level. (2) Scientists and policy makers alike should do a better job of *communicating* with the public about exposure and risk. Debate over precisely what to do and how to do it was lively.

Prevention

The theme of prevention had come up numerous times during the symposium, often as an element of risk management—that is, reducing or eliminating the source of the exposure and thereby mitigating its health effects. Managing risk (as opposed to estimating it) is a social and political issue, not just a scientific and engineering challenge; but as one speaker put it, "toxicological legislation is usually an after-the-fact process; how can we make it a before-the-fact process?" Another speaker suggested that current statutes and regulations may be impediments to collecting useful exposure data; government and industry do extensive monitoring for compliance and remediation, but monitoring by itself seldom advances understanding of human exposure. Gilbert Omenn observed that one reason for the creation of ATSDR and its mandate to compile toxicologic profiles and improve exposure assessment is to move beyond pure data gathering and into the fuller understanding of the implications of exposure to contaminants and health effects.

Ellen Silbergeld of the Environmental Defense Fund suggested two ways in which scientists could help to develop policies aimed at prevention: learning from the lessons of past exposure assessments, and using the information from exposure assessments to set priorities for further testing of chemicals. There are 60,000-70,000 existing chemicals and 2,000 new ones are added every year. For 80% of existing chemicals, we have no toxicologic data at all. Where do you start? Silbergeld suggested starting with exposures—either well-defined exposure histories for similar chemicals or some reasonable surrogate for exposure, such as volume of production—and increased biological monitoring. She suggested that any chemical produced in excess of one million pounds per year and with gaps in toxicologic information should have high priority for testing, as should any chemical found in human tissues, food, or "critical wildlife species." It was noted that the National Toxicology Program and the federal regulatory agencies already have a priority setting system for the program's chemical selection process—but only a relatively few chemicals are tested each year.

Oakley suggested that an efficient way to identify chemicals currently in the environment that cause adverse health effects, such as birth defects, was to determine exposure to chemicals among people with and without the adverse

health effects. Most of the substances that are known to cause adverse health effects in human beings have been identified by this approach. Yet it is not currently fashionable in environmental circles to conduct these kinds of studies. Oakley contended that the price we pay for ignoring this approach is to continue to have unnecessary disease from environmental exposures that currently are not known to cause sickness among people. Surveillance, registries, and case-control studies should be conducted in greater number, taking advantage of improved technology to measure exposures among the cases and controls.

Risk Communication

Risk communication is a necessary companion to risk assessment and risk management, according to several speakers. Scientists and policy makers alike "have a responsibility to be responsive to the community," according to Gilbert Omenn, to provide understandable answers to "real questions that affect people's lives." This mission includes efforts to educate the public on the difference between individual risks and population risks, the level of uncertainty about some risks, and the differences between current and past exposures. Policy makers, too, need better data and fuller understanding to make better decisions, laws, and regulations.

Several of the case studies demonstrated that public participation can assist in good science as well as good policy—some of the studies reported would have been impossible without active cooperation from members of the community, who almost always proved to be more sophisticated and often were more supportive than researchers had anticipated. Richard Jackson said that the Fairchild case study pointed to the danger of excessive community and media pressure on how studies are conducted. His warning—"Epidemiology is not public relations"—was echoed by Thomas Burke. Because of the constraints on university research, "environmental epidemiology is happening in state health departments, and it's happening for the wrong reasons . . . because of public worry and political pressure." His worry was shared by Joan Daisey: "We have continually been burned by the quick-and-dirty science . . . that's driven by newspaper stories and pressure to get out and measure something. We spend a lot of money doing this, and in the end we wind up with nothing."

Burke's solution to this problem is the creation of a "rational public health priority-setting process to put our epidemiological energies where they would have the biggest benefits in terms of the overall public health." A sweeping suggestion for addressing the larger social issues underlying potential toxic exposures came from Emil Pfitzer. "You should gather together a distin-

guished group of industrial people, economists, sociologists, and talk seriously about why we have the environmental problems we have today. The fact that we are a democratic society where free enterprise is the name of the game. . . might well be the basic cause of [our problems]. Are we as environmental scientists just trying to plug the hole while the basic underlying economic forces [continue]? What would society condone in the way of putting a cap on technological advances, or perhaps on improved convenience products, even if they are considered to improve the quality of life?" It was noted that nondemocratic societies and restricted market economics have recently been reported to have even greater pollution problems than the United States.

Research Needs

The participants seemed unanimous in their belief that there is a need for further exposure studies. "We are on the leading edge of a great wave of research," according to Paul Lioy, "research that will produce better data and better models, research that will provide regulators with the tools to reduce exposure and protect the public health. There's at least a B-1 bomber's worth of research needs" in this area, he added, the results of which can provide improved "cost-effective benefit to society in the next 10-15 years." The most promising opportunities for such research appear to lie in four areas: better data, improved modeling, attention to total exposure, and interdisciplinary cooperation.

Data

Several speakers pointed to the need for better data, better tools to measure exposure, and better strategies for using those tools. There is a need for "a lot of basic research on biological, physical, and chemical markers of exposure that can be applied generally and cheaply within the population," according to Lioy. At the same time, "we may have to be a little more creative in how we define our monitoring programs—maybe we need to define sentinel populations and follow them throughout a lifetime . . . or [follow] people who live in specific microenvironments." Willard Chappell added that exposure data should include both means and distributions, given the great range of personal exposures; monitoring should attempt to verify and explain the statistical "tails" and "outliers." Quality data are needed both to determine whether exposure has actually taken place and to construct models to predict and, ultimately, reduce exposure.

Models

Input data are needed not only to develop but also to validate and calibrate exposure models. Leslie Hutchinson of ATSDR reported the widespread use of unvalidated models at Superfund sites, resulting in misinformation and inappropriate public concern. Validation of exposure models is "absolutely essential," according to Barry Ryan. It would be "ludicrous" to build a model without using data already collected or to implement the model without using actual measurements to test its accuracy. Subsequent data from field studies should lead modelers to re-examine their models and criticize their assumptions. According to Yoram Cohen, "Sometimes theoretical models should not be used and field studies should be preferred," but other times "you try to adjust the model to agree with the data" and a better model emerges through calibration.

Barry Ryan had strong opinions of the desirable characteristics of modeling. He wants models that are practical, probabilistic, and portable. *Practical* models are "appropriate" to a particular situation and "adequate" in terms of accuracy. Predicting exposure within a factor of 10 may be good enough in some situations, while others require "a very finely tuned" model that can predict exposure within 10%. "However, to use a 10% model when a factor-of-10 model will do is "essentially a waste of time and resources." *Probabilistic* models provide information not only about mean exposures but also about the distribution of those exposures. "Perhaps all of the risk is tied up with the top 5% or 1% of individuals, and those are the people we really need to worry about." *Portable* models, finally, have "general availability" and move easily between agencies and systems. "We must be able to distribute these models to all the regulators and public health officials that may indeed need to use them, and show them how to implement them, and where they're accurate and where they're not accurate."

Total Exposure

Several speakers addressed the need for a broader, more comprehensive approach to what Burke called "the continuum of exposure." According to Omenn, the concept of "total exposure" highlights multiple sources and the various "mixtures of volatiles, mixtures of pesticides, mixtures of all kinds of things that are real-world exposures." Exposure studies should also be multimedia, according to Ryan, not just inhalation or ingestion but "all of the potential routes to a particular pollutant," including the pathways pollutants follow in moving between microenvironments.

Such an approach calls for new research designs that require exposure analysts to "go beyond our narrowly defined studies," according to Cohen, "and to realize that we are part of a much greater environment." Other speakers echoed this idea: Exposure assessment needs to look both upstream and downstream; modeling needs to be integrated with field studies; the indoor microenvironment needs to be connected with the outdoor environment; and peak exposure needs to be seen in the perspective of lifetime dose and in relation to the mechanisms of toxicity.

Interdisciplinary Cooperation

An adjunct of this broader perspective is the need for interdisciplinary approaches and cross-fertilization. Several speakers pointed to the potential contributions from the field of genetics, for example, particularly in understanding susceptibility to toxic effects. Cohen emphasized opportunities for using exposure assessments to guide changes in the design of chemical manufacturing processes to eliminate those emissions that have greater impact on human populations. Daisey called on environmental toxicologists and physiologists who identify potentially dangerous compounds to guide the analytic chemists who are developing methods to measure them.

CONCLUDING REMARKS

As we enter the environmental decade of the 1990s, we now have many of the scientific tools necessary to identify those persons who are exposed to toxic chemicals, determine to what extent they are exposed, determine if they are uniquely susceptible, measure the impact on society, and carry out socially responsible actions that will protect individuals and societal health while maintaining the rights of persons to act in their own best interests.

It is now possible to determine what impact toxic chemical exposure will have on public health so that preventative measures can be adopted to protect the public and enhance the quality of life. This conference provided important discussion and information for applying scientific tools to assess exposure and to address public health problems as we face the environmental issues of the 1990s.

Speakers at the conference raised issues that remain to be resolved. For example, when does pollution from a technically advancing society overbalance the gains in life style that come from the technology, and when in the history of scientific knowledge about a toxicant is the appropriate time to regulate

exposure to that toxicant—recognizing that early data can easily lead to a false positive or false negative conclusion?

As described by Gilbert Omenn in his opening remarks, the work of ATSDR, with a strong research base and sensitivity to the community needs, fears, and desires, has already pushed back the frontiers of exposure assessment and provided the scientific underpinning that can lead to better health in a better environment.

Several areas of consequence for exposure measurement were not explicitly discussed at the symposium, but nonetheless are important to future development. These include the work of occupational hygienists to refine procedures for quantifying current exposures and for estimating historical exposures, and the reports (often ancedotal) of clinical ecologists who diagnose and treat illnesses brought on or exacerbated by environmental factors.

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Appendix

SYMPOSIUM ORGANIZING COMMITTEE

GILBERT S. OMENN *(Co-chair)*, University of Washington, Seattle
ELLEN K. SILBERGELD *(Co-chair)*, Environmental Defense Fund, Washington
JOHN C. BAILAR, III, McGill University School of Medicine, Montreal
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P. BARRY RYAN, Harvard University
DIANE WAGENER, National Center for Health Statistics
JED WALDMAN, University of Medicine and Dentistry of New Jersey

PROGRAM

WEDNESDAY, MAY 16, 1990

8:00 Registration
8:30 Welcoming Remarks and Purpose: Gilbert Omenn (Chairman of BEST)
8:45 Introduction: Barry Johnson (Assistant Administrator, ATSDR)
9:00 Frontiers in Exposure Assessment and Detection: The Fruits of Collaboration: Paul Lioy

I. How Do People Become Exposed?

Exposure Fate & Transport Modeling

9:30 Introduction–Chair: Yoram Cohen
9:45 A. Sources and Pathways: Monitoring and Modeling
Case study: Leadville/GIS Study–William Chappell
10:05 B. Chemical Release Data
Case study: Kanawha Valley study–Lewis Crampton
10:25 C. Modeling: Exposure and Dose
Case study: Barry Ryan
10:45 Summation–Joan Daisey and Tom Burke
11:00 Break
11:15 Focus Address: "Public Needs and Perception"
Honorable J. Roy Rowland, M.D. (D-GA)
12:00 Lunch

II. How Can We Tell That People Have Been Exposed?

Markers and Surveillance

1:30 Introduction–Chair: Bernard Goldstein
1:45 A. Biological Markers of Exposure and Effect
Case study: Markers of Exposure (lead)–Bruce Fowler
2:05 B. Tissue Monitoring
Case study: Heptachlor in Breast Milk–Donald Mattison

2:25 C. Animal Sentinel Studies
Case study: PCBs/Paoli, PA–Michael Goldschmidt

2:45 D. Health Status/Surveillance
Case study: Reproductive Outcomes–Godfrey Oakley
3:00 Summation: Emil Pfitzer and Jim Melius
3:15 Questions
3:45 Recess

THURSDAY, MAY 17, 1990

III. What Happens After Exposure?

Data Analysis Techniques

9:00 Introduction–Chair: David Bates
9:15 A. Direct Measures of Chemicals in the Individual's Environment
Case study: BaP THEES Study–Jed Waldman
9:35 B. Questionnaires
Case study: DC Federal Offices Indoor Air Study–Brian Leaderer
9:55 C. Clusters and Registries
Case study: San Jose Water Study–Richard Jackson
10:15 D. Population-based Databanks
Case study: Bart Ostro
10:35 Summation: Diane Wagener and William Halperin
10:50 Break
11:10 Practical Applications Panel
12:10 Lunch
1:30 Policy Implications Panel
2:30 Research Needs Panel
3:30 Adjourn