

Public Health Assessments

What is ATSDR?

8

ATSDR is the Agency for Toxic Substances and Disease Registry, a federal public health agency. ATSDR is part of the Public Health Service within the U.S. Department of Health and Human Services. Created by Superfund legislation in 1980, ATSDR's mission is to prevent or mitigate adverse human health effects and diminished quality of life resulting from exposure to hazardous substances in the environment.



What is a Public Health Assessment?

An ATSDR Public Health Assessment gathers information about hazardous substances at a site and evaluates whether exposure to those substances might cause any harm to people. Public Health Assessments consider --

- o what the levels (or "concentrations") of chemicals are at the site
- o whether people on or near the site might be exposed to the substances and how (through "exposure pathways" such as breathing air, drinking or contacting water, contacting or eating soil, or eating contaminated food)
- o what harm the substances at the site might cause to people (or the chemicals' "toxicity")
- o whether working or living near the site might affect people's health

To make those determinations, ATSDR looks at three primary sources of information --

- o **environmental data**, such as information on the chemicals at the site and how people could come in contact with the chemicals
- o **health data**, including information on community-wide rates of illness, disease, and death compared with national and state rates
- o **community concerns**, such as citizen reports about how the site affects their health or quality of life

How Are Public Health Assessments Used?

Public Health Assessments advise the U.S. Environmental Protection Agency and states on actions to reduce or prevent people's exposure to hazardous substances. They are used to develop Public Health Advisories and other recommendations to protect the public's health. They are also used to identify health studies or other actions -- such as environmental health education for the community and its health care providers -- that might be needed.



What Is the Community's Role in a Public Health Assessment?

The community has a key role to play in a Public Health Assessment and any activity that may follow. Throughout the Public Health Assessment, ATSDR talks with people living near the site--citizen groups, local leaders, and health professionals, among other community members--about their knowledge of the site and their health concerns related to the site. Health concerns are addressed in every Public Health Assessment for every site.

Two-way communication between the public and ATSDR is vital to a successful Public Health Assessment. For that reason, ATSDR has several mechanisms to keep the public involved and informed and to solicit information from the community, such as --

- o Public Availability Meetings where community members can meet individually with ATSDR staff.
- o Public Meetings during which community members can express ideas in a larger forum.
- o Community Advisory Panels, which work to inform ATSDR about community concerns and health information and, in turn, to inform the community about ATSDR activities and the status of the Public Health Assessment.
- o Other communication channels, such as contact with local citizen groups, political leaders, and health professionals, as well as articles in local newspapers and on television and radio stations.
- o Before the Public Health Assessment is complete, it is available in the community during the Public Comment Period. The Public Comment Period gives the community the opportunity to tell ATSDR how well the Public Health Assessment addresses concerns. To provide information back to the community, ATSDR responds to public comments in the final Public Health Assessment.

To Get More Information

Call or write:

Lydia Ogden Askew
Community Involvement Liaison
ATSDR-Division of Health Assessment and Consultation
1600 Clifton Road, NE (E32)
Atlanta, Georgia 30333
404/639-0609 (during the workday)
404/330-9543 (24 hours)



Agency for Toxic Substances
and Disease Registry
Atlanta GA 30333

PARTIAL LIST OF SERVICES ATSDR CAN PERFORM

MANDATED:

Public Health Assessments
Exposure and Disease Registries
Emergency Response
Toxicological Profiles
Health Education
Applied Research
Citizen Petitions

COMMENT:

Review Risk Assessments
Work Plans
Evaluate Data & Sampling Plans
Remedial Investigations
Feasibility Studies
Records of Decision
Health Outcome Data
Medical Studies
Health & Safety Plans

ARRANGE:

Educational/Informational
Services to Health Care
Providers
Medical Examinations
Epidemiologic & Pilot Studies

COORDINATE:

Health Assessment Activities
Site Visits
Federal, State, & County
Medical Responses

ATTEND:

Scoping Meetings
Public Meetings
Site Visits
Availability Sessions
Technical Reviews

PROVIDE:

Consultations:
Emergency
Non-Emergency
Referrals
Health Information to:
Elected Officials
State & Local
Health Depts.
Environmental
Agencies
Public & Others
Testimony/Hearings

DETERMINE:

Need for Additional
Health Studies
and/or
Environmental
Follow-up

SITES:

Emergency/Remedial
RCRA
Federal Facilities
Citizen Petitions

REGIONAL REPRESENTATIVES:

WILLIAM NELSON (415) 744-2194
GWEN ENG (415) 744-2193
LYNN BERLAD (415) 744-2220
FAX (415) 744-1797
PAGER (415) 708-9732

ADDRESS:

ATSDR
75 Hawthorne St.
Mail Stop H-1-2
San Francisco, CA
94105

ATSDR'S ACTIVITIES AND VIEWS ON EXPOSURE ASSESSMENT

BARRY L. JOHNSON AND DENNIS E. JONES

Department of Health and Human Services, Public Health Service
Agency for Toxic Substances and Disease Registry
Atlanta, Georgia

INTRODUCTION

As awareness of environmental pollution has increased, concern for public health has increased correspondingly. This concern has been translated into action by legislative bodies, resulting in laws and regulations designed to manage environmental pollution and to prevent its adverse effects on ecological systems, the environment, and human health. At the core of the public's concern is the fear that contact with toxic substances in the environment will have adverse effects on human health. Assessment of human exposure, therefore, becomes a centerpiece in efforts to identify and prevent adverse health consequences resulting from contact with hazardous substances.

This paper describes the views and programs of the Agency for Toxic Substances and Disease Registry (ATSDR) that relate to human exposure assessment. ATSDR is one of eight agencies that constitute the Public Health Service, which in turn is part of the U.S. Department of Health and Human Services. ATSDR was created by the Comprehensive Environmental Response, Compensation, and Liability Act of 1980 (CERCLA), otherwise known as Superfund. ATSDR's mission is to prevent or mitigate the adverse human health effects and diminished quality of life resulting from exposure to hazardous substances in the environment (ATSDR, 1991).

To prevent or mitigate adverse health effects resulting from exposure to environmental hazards, it is imperative to identify any *adverse health effects*. Equally important is the ability to detect *environmental exposures* that have the potential to produce such effects. ATSDR has developed and implemented several programs designed to address critical needs in assessing human exposure to hazardous substances. What follows is a description of Agency programs relating to exposure assessment; how and why they were implemented, their current status, and what ATSDR foresees as future needs in exposure assessment programs.

ATSDR APPROACH

Before examining ATSDR's program specifics, it is important to point out some aspects of the Agency and its needs that make ATSDR's approach to exposure assessment somewhat different from that of other federal agencies.

1. Address all correspondence to: Dennis E. Jones, ATSDR, Mail-Stop E-48, 1600 Clifton Road, NE, Atlanta, Georgia 30333.

ATSDR is not a regulatory agency. Nonetheless its activities do have impact on regulatory agencies, and, in turn, the Agency is affected by regulatory actions of those agencies. However, ATSDR usually examines and evaluates exposures from a different perspective than do agencies that have actual regulatory authority, such as the Environmental Protection Agency (EPA) and the Occupational Safety and Health Administration.

There are many different approaches and aspects to assessing exposure to hazardous substances, covering the full gamut of possible exposure scenarios—from assessment of past exposures to predicting future exposures. In addition, exposure assessment must include a very broad spectrum of methods—from simulation models that predict environmental media levels, to the use of human disease incidence rates that infer probable environmental exposure levels.

One of the primary purposes of agencies such as EPA is to establish and enforce regulatory safeguards. These safeguards usually specify standards or limits for hazardous substances in various environmental media such as air, soil, or water (EPA, 1988; 1989). Such safeguards are established to prevent or at least limit risks to human health, the environment, and ecological systems.

Not surprisingly, standards developed by governmental regulatory agencies for chemicals in the environment have engendered considerable controversy among such diverse groups as chemical manufacturers, consumers, transporters, waste handlers, biomedical researchers, and environmentalists. This controversy was probably best summarized by the National Research Council of the National Academy of Sciences in a 1983 risk assessment monograph: "Much of the recent controversy is general; it reflects the conflict in values between different groups in society, particularly regarding the relative importance of economic factors and health protection in the formulation of regulatory decisions" (NAS, 1983, pg. 14). But, controversial or not, regulatory standards are a staple in the environmental arena and serve as benchmarks for pollution control and strategies for environmental restoration.

What does all this have to do with ATSDR's exposure assessment activities? Regulatory agencies must, almost by necessity, focus primarily on contaminant levels in environmental media. Moreover, these regulatory functions seem to give emphasis to current or future exposure levels in order to trigger regulatory actions when needed.

In contrast to regulatory agencies, ATSDR's approach to exposure assessment attacks the problem from the opposite direction. Rather than using environmental media levels as a means to predict health impact, ATSDR's *idealized approach* is to assess the health status of a potentially exposed population and use this assessment as a means to determine the level of environmental exposure. EPA generally asks, "Are the environmental concentrations of concern now, or are they predicted to be so in the future?" ATSDR, however, prefers to examine the health status of the population and to establish whether there has been any exposure of this population to hazardous substances at levels of public health concern.

These two approaches by which ATSDR and regulatory agencies assess exposure are neither inclusive nor exclusive but show considerable overlap. This is particularly evident in the case of ongoing exposures where conditions may dictate both regulatory action and health intervention protocols.

With an emphasis on assessing exposure from a health-status perspective, this survey paper summarizes ATSDR's in-house programs and extramural research activities designed to accomplish this "idealized" approach to exposure assessment.

ATSDR'S EXPOSURE ASSESSMENT PROGRAMS

This paper describes the principal ATSDR programs that concern exposure assessment. The first program described is a five-year cooperative agreement between ATSDR and the National Research Council (NRC) of the National Academy of Sciences. Also described are intramural programs involving public health assessments of Superfund sites, epidemiological investigations, exposure registries, and applied research involving exposure analysis. These programs originated within the Agency but have since been implemented in cooperation with several state health and/or environmental departments.

NRC STUDIES AND BIOLOGICAL MARKERS

Several of the NRC studies commissioned by ATSDR fall into the category of biological markers. The simplest and perhaps the most meaningful definition of biological markers, given by the NRC, is "Biological markers are indicators of changes or events in human biological systems" (NAS, 1991a, pg. 115).

EPA and the National Institute of Environmental Health Science (NIEHS) are also sponsors of this effort. This co-sponsorship underscores the overlap in concerns and approaches to exposure assessment that non-regulatory agencies and regulatory agencies have. The three agencies, (ATSDR, EPA, and NIEHS) all share the same concerns for humans and the environment but with different perspectives, emphases, and statutory authorities.

ATSDR's concern with biological markers can be explained by reference to Figure 1 (adapted from Committee on Biological Markers, 1987). As previously noted, ATSDR's goal is to be able to assess exposures from the *human* perspective. Although NRC divided biological markers into three broad classes: (1) markers of exposure; (2) markers of effect, and (3) markers of susceptibility (NRC, 1991a, pg. 141), none of these constitute distinct, discrete categories, but each is part of a continuous spectrum of events in the human body.

Thus, health investigators are actually looking for specific and sensitive biological indicators—measurements of actual hazardous chemical levels, measurements of metabolic products, diagnoses of disease states, or measurements of altered physiologic states that predispose or

increase susceptibility to disease. If such biological indicators can be identified and quantified, they become extremely valuable tools for assessing exposure to hazardous substances.

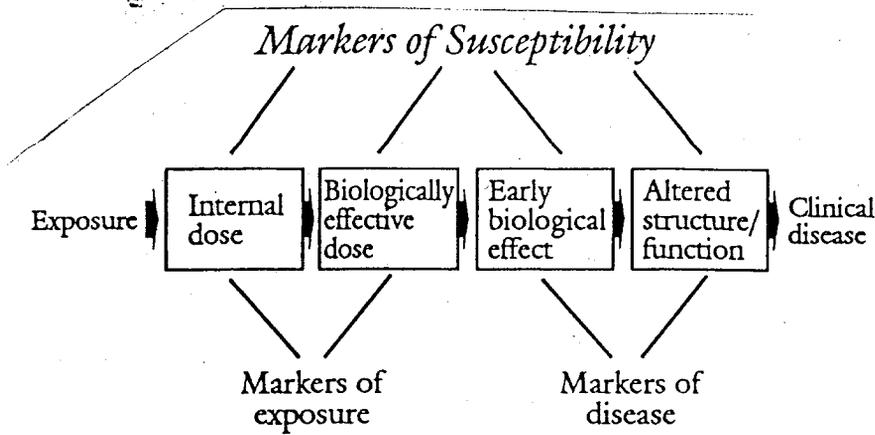


FIGURE 1. Schema for relating exposure with clinical disease.

ATSDR's sponsorship to date of biological marker studies conducted by the NRC include four specific toxicologic endpoints: (1) reproductive toxicology; (2) pulmonary toxicology; (3) neurotoxicology; and (4) immunotoxicology. These four study areas were selected on the basis of seven health conditions ATSDR has identified as priority health concerns at Superfund sites (see Table 1). ATSDR identified these seven conditions following an extensive review of the toxicologic literature and with a knowledge of what substances are released from Superfund sites (ATSDR, 1991b). As Table 1 shows, four of these priority health conditions—reproductive disorders, lung and respiratory diseases, immune function disorders, and neurotoxic disorders—have all been specifically addressed in the biological markers program.

TABLE 1. ATSDR's Priority Health Conditions

- Birth defects and reproductive disorders
- Cancers (selected)
- Immune function disorders
- Kidney dysfunction
- Liver dysfunction
- Lung and respiratory illness
- Neurotoxic disorders

The NRC program on biological markers has already produced some tangible results. Four monographs on biological markers have been completed and published by the National Academy Press: *Biologic Markers in Reproductive Toxicology* (NAS, 1989a), *Biologic Markers in Pulmonary Toxicology* (NAS, 1989b), *Environmental Neurotoxicology* (NAS,

1992a), and *Biologic Markers in Immunotoxicology* (NAS, 1992b). Summaries of the specific biological markers reviewed in these four NRC monographs are listed in the Appendices. The biological markers listed in the Appendices illustrate that progress is being made by researchers and medical providers in developing markers relevant to organ-specific health endpoints. ATSDR will incorporate some of these biomarkers in its exposure and health effects studies of communities around sources of release of hazardous substances. Reference to the four NRC monographs should be made to obtain background information and details on the biological markers delineated in the Appendices.

OTHER NRC STUDIES

Programs that bear on exposure assessment, particularly as it relates directly to human health, include the project, "Human Exposure Assessment for Airborne Pollutants", commissioned by ATSDR and whose purpose is to "...study advances in assessing exposure to airborne contaminants" (NAS, 1991a, pg. vii). This report "describes a framework and methods for assessing and analyzing the totality of exposures of an individual to air contaminants in the course of all activities over specified increments of time" (NAS, 1991a, p. 2). NRC clearly articulates the necessity for total exposure assessment, and although this report focuses on air pollutants, the principles of exposure measurement and characterization described there are applicable to other contaminated environmental media.

In a continuing effort to address exposure assessment issues, ATSDR and the NRC's Board on Environmental Studies and Toxicology cosponsored a two-day symposium in May 1990. This symposium, entitled "Frontiers in Assessing Human Exposure to Environmental Toxicants," was designed "...to bring current knowledge and current difficulties to public and scientific attention" (NAS, 1991b, pg. vii). A monograph by the same name, covering the events and findings of the symposium, was published in 1991 by the National Academy Press. The symposium concluded, "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 right of persons to act in their own best interests" (NAS, 1991b, p. 32). The conference advocated greater attention to actual exposure measurements of persons exposed to toxic substances and the development of resultant databases.

Another ATSDR/NRC joint project led to the monograph *Environmental Epidemiology: Public Health and Hazardous Waste*, Volume 1 (NAS, 1991c). This study "...examines and evaluates the published scientific literature on health effects that could be linked with exposure to hazardous-waste-disposal sites, and develops recommendations about major data gaps that need to be remedied in order to advance the field" (NAS, 1991c, pg. vii). This monograph describes the importance of exposure analysis in determining the effects of hazardous waste on human health. In addition, NRC advocates the conduct of more health studies of communities around waste sites in ways that permit systematic database development.

Another NRC study produced a monograph entitled *Animals as Sentinels of Environmental Health* (NAS, 1991d). This study was designed to "...determine how animals could be used for ecological and human health risk determinations as well as provide an early-warning system for risk assessment and management" (NAS, 1991d, pg. vii). This project bridges the gap between environmental media analysis and human analysis. The NRC concludes, "Domestic and wild animals can be used to identify and monitor a wide range of environmental hazards to human health and ecosystems" (NAS, 1991d, p. 14). ATSDR has no plans to initiate an animal health surveillance system, but will consider the acquisition of this kind of data in support of specific human health investigations.

The importance of animal sentinels to both environmental health and human health is brought home if we remember Rachel Carson, who, in her 1962 publication, *Silent Spring*, first brought national attention to the hazards of environmental contamination on ecological systems (Carson, 1962). Indeed, this work is often cited as the initiating force behind many current federal environmental protection and environmental health programs.

INTRAMURAL PROGRAMS

Public Health Assessments

In addition to the NRC-conducted studies funded by ATSDR, the Agency has several intramural programs bearing on human exposure assessment. An important in-house activity is the development of Public Health Assessments for hazardous waste sites. A Public Health Assessment is ATSDR's evaluation of environmental contamination data, health outcomes, and community health concerns to determine the significance of individual sites. As mandated by the Superfund Amendments and Reauthorization Act of 1986, a Public Health Assessment must be prepared for every site on the National Priorities List and in response to citizens' petitions.

Almost every Public Health Assessment contains considerable information on contaminant concentrations in various environmental media, usually provided to ATSDR by EPA or other federal departments (e.g., Department of Energy). ATSDR has now combined all the environmental contamination information from about 1,600 sites into an extremely useful database called HAZDAT. For example, HAZDAT can be used to select those sites that can be aggregated for the purpose of multisite investigation.

A unique and meaningful portion of the Public Health Assessment with regard to public health is the Public Health Action section. This recently developed and implemented section did not appear in our earlier Health Assessments.

The Public Health Action Section can best be compared to a public health procedures, policy, and implementation plan, and it works in the following way. ATSDR has a standing panel of biomedical health professionals known as the Health Activities Recommendation Panel, (HARP). This panel reviews every Public Health Assessment to determine what follow-up

health actions are indicated. The Public Health Action section basically reflects the recommendations of HARP which generally fall under one of two categories:

- (1) recommendations for follow-up health investigations, or
- (2) recommendations for follow-up educational actions.

There are also two different types of follow-up public health investigations: (1) studies using biological markers of exposure—for example, blood lead studies, and (2) studies of biomedical effects—such as investigations of clusters of adverse health symptoms or disease. Likewise, follow-up educational actions take the form of educating both the health professionals associated with the site and the general community potentially affected by the site. Educational outreach programs explain how a person can be exposed to hazardous substances and how to reduce personal exposures.

Exposure assessment issues are very important to ATSDR's follow-up health actions at Superfund sites. During fiscal year 1991, ATSDR's Health Activities Recommendation Panel reviewed 261 individual Public Health Assessments. Of these, approximately 40%, or more than 100 sites, were recommended for follow-up health studies (Table 2). These health studies included human exposure studies, symptom prevalence investigations, and cluster studies. Many of these health studies are in the planning stages and will be conducted in cooperation with state health departments.

TABLE 2. HARP Recommendations; FY91

261 Individual Public Health Assessment Reviews
• 40% referred for follow-up health studies
• 20% referred for health professional education
• 36% referred for community health education
• 4% referred for substance specific research

EPIDEMIOLOGIC INVESTIGATIONS

In 1987 ATSDR undertook, in cooperation with state agencies, a series of human exposure assessments, surveillance projects, and epidemiologic health investigations of persons who may be at increased risk of exposure to hazardous substances released from sites. To date the Agency has conducted 37 pilot health studies (principally exposure assessments), 18 epidemiology investigations, and 20 surveillance projects. The aggregate findings from this work are currently being evaluated.

Findings from ATSDR's exposure assessment studies show that group mean exposures have generally been low compared with occupational exposures to the same substances. However, the Agency has observed that each exposure assessment must consider the distribution of all

exposures within the community investigated. Where individuals exceed health-based exposure standards or guidelines, ATSDR works with state and local authorities to reduce the exposure for those individuals.

Although a complete description of findings from these studies is beyond the scope of this paper, three generalizations are possible. First, each site and community study is different in ways that must be factored into the exposure assessment. For example, children may be the sole population of concern in certain communities because of exposure and behavioral factors. Second, total exposure assessment should be the goal of any investigation (Johnson, 1992). For instance, a study of children exposed to lead released from a Superfund site must also consider other possible sources of lead exposure, for example, lead in paint in older houses. Third, knowledge is generally inadequate of the relationship between levels of contaminants in environmental media and concentrations of primary or metabolic correlates in human biological media.

ATSDR has made a significant change in its intramural approach to conducting human exposure assessments. The Agency's Division of Health Assessment and Consultation is beginning to implement site-specific health investigations, including exposure assessments, as a follow-up to its Public Health Assessments. At the same time, the Division of Health Studies is moving away from such singular, site-specific investigations, toward multi-site research studies. These studies will evaluate total exposure patterns to the same hazardous substance at multiple sites. Furthermore, these studies will afford the opportunity to evaluate composite health outcomes at several sites where people are exposed to the same chemical and also to multiple chemicals. The premise is that linking raw data from multiple sites will give these studies much greater statistical power and thus enhance the Agency's ability to discern meaningful associations between disease and exposure to hazardous substances.

NATIONAL EXPOSURE REGISTRY

The Agency's National Exposure Registry is closely linked to both ATSDR's Public Health Assessment Program and our Epidemiologic Studies Program. Superfund legislation directed ATSDR not only to perform Health Assessments and Health Studies at Superfund sites but also to develop a national registry of persons exposed to substances released from these sites (Johnson, 1990). (An exposure registry is defined as a list of persons and their health-related characteristics who have exposure to a common chemical.) Each registry contains information about the registrants' self-reported health status and other vital information. ATSDR has developed exposure subregistries for persons exposed to dioxins, trichloroethylene (TCE), and benzene, and a subregistry is planned for persons exposed to chromium.

For example, the TCE subregistry lists 4,883 persons from 13 Superfund sites in Michigan, Illinois, and Indiana; the dioxin subregistry lists 250 persons from four different sites—all in the Times Beach, Missouri, area; and the benzene subregistry currently lists approximately

1,200 persons, all from sites in Texas, and is soon to be updated to approximately 5,000 persons with the addition of sites in New York and another state to be determined.

ATSDR believes these subregistries will be a valuable resource for advancing our understanding of the link between exposure and disease. They should provide many of the same advantages that multi-site analysis promises to bring to our health studies. The actual health outcome data will complement and may, in some instances, replace our reliance on extrapolations from animal toxicology studies and occupational health investigations to predict the effects of long term exposure to low concentrations of toxicants.

TOXICOLOGICAL PROFILES AND DATA GAP RESEARCH

A sense of priority has often been lacking in setting an agenda for research on environmental hazards. The Superfund statute prescribes an applied research program to fill key data gaps for priority substances. First, ATSDR and EPA must jointly rank hazardous substances released from Superfund sites. Second, using the list of priority substances, ATSDR is mandated to prepare and periodically update a Toxicological Profile on each substance. (Each profile contains information on how to assess exposure to the substance, e.g., analytical methods to measure the substance in biological media.) Third, using the Profiles, ATSDR is required to initiate a program of research to fill key gaps in knowledge about the substances' effects on human health (Johnson, 1990).

For example, Table 3 contains a list of the top 10 hazardous substances from a list of 275 substances (ATSDR, 1991c), together with what ATSDR considers to be the key data gaps for each substance (ATSDR, 1991d). For most ranked substances, research is needed to improve exposure measurements. Data gaps will be filled through a combination of Agency-funded studies, private industry voluntarism, and EPA directives under the Toxic Substances Control Act or the Federal Insecticide, Fungicide, and Rodenticide Act (ATSDR, 1991d). If fully implemented, this Superfund program of applied research to fill key data gaps holds the promise of significantly advancing our collective knowledge on the toxicity and human health effects of toxicants in the environment, including our ability to measure and relate human uptake of priority toxicants.

FUTURE DIRECTIONS

Exposure assessments are important to almost all aspects of ATSDR's activities. As our ongoing programs indicate, the Agency has a continuing commitment to improve and advance the understanding of human exposure assessment. Future directions and focus for the Agency's exposure assessment efforts have been taken from proposals put forth by such organizations as the Office of Science and Technology Policy, the Office of Management and Budget, EPA, and the National Research Council of the National Academy of Science (OSTP, 1985; OMB, 1991; ISGC, 1986; NAS, 1991b) and then synthesized into a program consistent with the ATSDR mission.

TABLE 3. Key Data Needs for Superfund Top 10 Priority Substances

SUBSTANCE	DATA GAPS
1. Lead	<ul style="list-style-type: none"> a) Epidemiological studies of special emphasis health endpoints and dose-response data a) Mechanistic studies on the neurotoxicity of lead
2. Arsenic NOTE: a) gaps are of higher priority than b) gaps	<ul style="list-style-type: none"> a) Comparative toxicokinetics b) Half-lives in surface water, groundwater b) Bioavailability from soil
3. Mercury	<ul style="list-style-type: none"> a) Epidemiologic studies of special emphasis health endpoints a) Multigeneration reproductive toxicity b) Immunotoxicity via oral exposure b) Carcinogenicity via oral exposure
4. Vinyl Chloride	<ul style="list-style-type: none"> a) Epidemiologic studies of special emphasis health endpoints a) Dose-response data in animals for acute-duration inhalation exposure a) Multigeneration reproductive toxicity via oral exposure b) Dose-response data in animals for chronic-duration inhalation exposure b) Mitigation of vinyl chloride-induced toxicity b) Two-species developmental toxicity via inhalation exposure
5. Benzene	<ul style="list-style-type: none"> a) Epidemiologic studies of special emphasis health endpoints a) Dose-response data in animals for acute- and intermediate-duration oral exposure a) Two-species developmental toxicity via oral exposure a) Neurotoxicity via oral exposure
6. Cadmium	<ul style="list-style-type: none"> a) Epidemiologic studies of special emphasis health endpoints
7. PCBs	<ul style="list-style-type: none"> a) Epidemiologic studies of special emphasis health endpoints a) Dose-response data in animals for acute- and intermediate-duration oral exposures b) Photodegradation in air and water b) Bioavailability in air, water, and soil c) Dose-response data in animals via inhalation exposure

8. Chloroform	a) Epidemiologic studies of special emphasis health endpoints a) Dose-response data in animals for intermediate-duration oral exposure
9. Benzo(b)fluoranthene	Not yet determined
10. Trichloroethylene	a) Epidemiologic studies of special emphasis health endpoints a) Dose-response data in animals for acute-duration oral exposure b) Neurotoxicity via oral exposure b) Immunotoxicity via oral exposure

First, a continuing exploration and use of biological markers is needed. The artificial division between markers of exposure and markers of disease must be eliminated because biological markers encompass a truly continuous spectrum of events. Specific chemical metabolites, particularly those with stable half-lives or those that sequester in or bind to tissues, must be identified and measured. In addition, we must be able to identify subtle, chemically-induced tissue changes, particularly those shown to be preclinical indicators of disease. Moreover, establishing the relationship between these preclinical indicators and subsequent disease would greatly increase our ability to estimate the probability of future disease. This would also provide an unparalleled opportunity to assess the effectiveness of public health intervention strategies.

Next, and closely related, is the need for information on chemical-specific pharmacokinetics. If we cannot accurately predict chemical uptake, distribution, metabolism, and elimination, it is impossible to truly predict subsequent health consequences with any degree of accuracy.

We must continue and expand efforts in the study of Quantitative Structure Activity Relationships (QSAR). Although QSAR is usually associated with mechanism-of-action type studies, it is equally important to exposure assessment. An estimated 50,000 to 70,000 chemicals are manufactured yearly in the United States and thus serve as candidates for environmental exposures (Saxena and Fisher, 1981). Obviously, it would be impossible to evaluate the environmental and health effects of each chemical individually. The only viable alternative is QSAR studies such as those used effectively for years in pharmacology and medicinal chemistry. Properly conducted QSAR studies should provide the opportunity to predict not only pharmacokinetics but also health outcomes for entire chemical classes. In addition, the proper application of structure-activity principles has been and should continue to be a valuable tool for environmental modelling.

Another important need is for accurate, normal baseline data. Such data include normal levels in environmental media, normal tissue levels, and normal physiologic values, whether they be chemical concentrations, ingestion amounts, breathing rates, or enzyme levels. The range and

distribution of these normal background values should also be accurately determined. ATSDR is funding the development of reference-range values for 38 hazardous substances measured in biological media. This work is part of the National Center for Health Statistics's population-based survey, the National Health Examination and Applied Nutrition Survey (Johnson et al., 1990). This reference data will be enormously useful when evaluating persons at risk of consequential exposure to one or more of these 38 substances.

Closely tied to this need for accurate assessment of background data is the need for probabilistic approaches to assessing exposure (CRA, 1990; NAS, 1991b). Today, exposure is commonly estimated on the basis of single-scenario-point estimates (EPA, 1988; EPA, 1989). For example, an average 70 kg human is assumed to have lived at a site for 70 years and to have ingested daily 2 liters of water contaminated at a specific chemical concentration; exposure is then calculated from these values. However, each of these estimates—body weight, age, years residence in close proximity to the site, water consumption, and even chemical concentration in the water—has a range and distribution. The appropriate use of these various distributions through probabilistic models should provide much more accurate and meaningful population-based estimates of minimum, maximum, and average exposures. These scenarios should, to the extent feasible, be tailored on a site or context-specific basis.

Finally, and perhaps most importantly, we as health and environmental professionals must be willing to put ourselves to the test. The environmental actions and health responses we employ today are based on several hypotheses, many of which have scant, unvalidated scientific support. However, as we continue to expand our knowledge and abilities in the field of exposure assessment, new and useful tools should become available to test these hypotheses. As a result, risk assessments and science policies can be adjusted in light of new and better scientific data, but we must be willing to act appropriately and decisively on what we learn.

For example, if new techniques reveal that exposure or disease is greater than we had previously estimated—as we have found with lead exposure—we must acknowledge that fact and subsequently develop and implement whatever new and more stringent control measures are necessary. Likewise, if we find, through applying new techniques, that human exposure is not as great as previously anticipated, then we should be equally willing to curtail or adjust our control standards and remedial measures, as appropriate.

Resources available for controlling environmental hazards are limited. If we use new knowledge from exposure analyses to key on the most important issues, and direct our resources accordingly, we can achieve the most good for both human health and the environment.

REFERENCES

- AGENCY FOR TOXIC SUBSTANCES AND DISEASE REGISTRY (ATSDR). (1991). Goals, Objectives, Milestones: 1991. U.S. Department of Health and Human Services, Public Health Service, Agency for Toxic Substances and Disease Registry, Atlanta, GA.

- AGENCY FOR TOXIC SUBSTANCES AND DISEASE REGISTRY (ATSDR). (1991b). "Health Studies of Priority Health Conditions." Federal Register 58(127): 30393-30395.
- AGENCY FOR TOXIC SUBSTANCES AND DISEASE REGISTRY (ATSDR). (1991c). "The Revised List of Hazardous Substances that will be the Subject of Toxicological Profiles." Federal Register 56: 52168-52173.
- AGENCY FOR TOXIC SUBSTANCES AND DISEASE REGISTRY (ATSDR). (1991d). "Identification of Priority Data Needs for 38 Priority Hazardous Substances." Federal Register 56: 52180-52185.
- CARSON, R. (1962). Silent Spring. Houghton Mifflin, New York.
- CENTER FOR RISK ANALYSIS (CRA). (1990). Annual Report 1990, Center for Risk Analysis, Harvard School of Public Health, Boston, MA.
- COMMITTEE ON BIOLOGICAL MARKERS OF THE NATIONAL RESEARCH COUNCIL. (1987). "Biological Markers in Environmental Health Research." Environ. Health Persp. 74: 3-9.
- INTERAGENCY STAFF GROUP ON CHEMICAL CARCINOGENS (ISGC). (1986). Chemical Carcinogens: "A Review of the Science and its Associated Principles." Environ. Health Persp. 67: 201-282.
- JOHNSON, B.L. (1990). "Implementation of Superfund's Health-related Provisions by the Agency of Toxic Substances and Disease Registry." Environ. Law Reporter 20: 10277-10282.
- JOHNSON, B.L. (1992). "A Precip on Exposure Assessment." J. Environ. Health. 55: 6-9.
- JOHNSON, B., STRAIGHT, M., GRISSOM, R., GIFT, J., and HOLLER, J. (1990). "Monitoring Human Exposures that Involve Hazardous Waste." In: Biological Monitoring of Exposure to Industrial Chemicals (V. Fiserova-Bergerova, and M. Ogata, eds.). American Conference of Governmental Industrial Hygienists, Cincinnati, OH.
- NATIONAL ACADEMY OF SCIENCES (NAS). (1983). Risk Assessment in the Federal Government: Managing the Process. National Academy Press, Washington, DC.
- NATIONAL ACADEMY OF SCIENCES (NAS). (1989a). Biologic Markers in Reproductive Toxicology. National Academy Press, Washington, DC.
- NATIONAL ACADEMY OF SCIENCES (NAS). (1989b). Biologic Markers in Pulmonary Toxicology. National Academy Press, Washington, DC.
- NATIONAL ACADEMY OF SCIENCES (NAS). (1991a). Human Exposure Assessment for Airborne Pollutants: Advances and Opportunities. National Academy Press, Washington, DC.
- NATIONAL ACADEMY OF SCIENCES (NAS). (1991b). Frontiers in Assessing Human Exposures to Environmental Toxicants. National Academy Press, Washington, DC.
- NATIONAL ACADEMY OF SCIENCES (NAS). (1991c). Environmental Epidemiology: Public Health and Hazardous Waste. National Academy Press, Washington, DC.
- NATIONAL ACADEMY OF SCIENCES (NAS). (1991d). Animals as Sentinels of Environmental Hazards. National Academy Press, Washington, DC.
- NATIONAL ACADEMY OF SCIENCES (NAS). (1992a). Environmental Neurotoxicology. National Academy Press, Washington, DC.
- NATIONAL ACADEMY OF SCIENCES (NAS). (1992b). Biologic Markers in Immunotoxicology. National Academy Press, Washington, DC.
- NEW YORK ACADEMY OF SCIENCES. (1990). "Trends in Cancer Mortality in Industrial Countries." Ann. N.Y. Acad. Sci., 609.
- OFFICE OF MANAGEMENT AND BUDGET (OMB). (1991). "Current Regulatory Issues in Risk Assessment and Risk Management." Regulatory Programs of the United States Government, 13-26, Washington, DC.
- OFFICE OF SCIENCE AND TECHNOLOGY POLICY (OSTP). (1985). "Chemical Carcinogens: A Review of the Science and its Associated Principles." Federal Register 50: 10371-10442
- SAXENA, J. and FISHER, F. (1981). Hazard Assessment of Chemicals: Current Developments, Vol. 1. Academic Press, Inc., New York.
- U.S. ENVIRONMENTAL PROTECTION AGENCY (EPA). (1989). Exposure Factors Handbook, Office of Health and Environmental Assessment, EPA/600/8-89/043, Washington, DC.
- U.S. ENVIRONMENTAL PROTECTION AGENCY (EPA). (1988). Superfund Exposure Assessment Manual, Office of Emergency and Remedial Response, Office of Solid Waste and Emergency Response, EPA/540/1-88/001, Washington, DC.

APPENDIX A

Biological Markers for Pulmonary, Reproductive, and Neurotoxicity¹

NEUROTOXICITY (NAS, 1992a, p. 45)	PULMONARY TOXICITY (NAS, 1989b, pp.4-7)	REPRODUCTIVE TOXICITY (NAS, 1989a, pp. 6-12)
<p>General Neuronal Measures:</p> <p>Cell number Tetanus-toxin binding Neurofilament protein Neuronal structure</p>	<p>Exposure:</p> <p>Tissue samples Respiratory phenomena Respiratory tract dosimetry</p>	<p>Pregnancy:</p> <p>Implantation: hCG assays early pregnancy factor assays immunologic assays Organogenesis conceptus characteristics Fetal and neonatal periods: dysmorphisms CNS function fetal chest-wall movement fetal cardiovascular function plasma markers: human placental lactogen alpha-fetoprotein amniocentesis and chorionic villus sampling</p>
<p>General Glial Measures:</p> <p>Glial fibrillary acidic protein Oligodendrocyte probe</p>	<p>Physiologic Changes in Respiratory Function:</p> <p>Changes in respiratory function Increased airway reactivity Clearance of particles Increased permeability of air-blood barrier</p>	<p>Male Reproduction:</p> <p>Pathophysiologic changes: potency fertility testicular size gonadal and pituitary steroids semen characteristics</p> <p>Genetic damage: pregnancy outcome sentinel phenotypes macromolecules in offspring</p>

¹ Detailed information about individual biological markers can found in the references cited.

APPENDIX A (cont'd)

Biological Markers for Pulmonary, Reproductive, and Neurotoxicity

<p>Transmitter Systems:</p> <p>Amino acid: excitatory inhibitory</p> <p>Cholinergic: choline acetyl-transferase muscarinic and nicotinic receptors</p> <p>Aminergic: norepinephrine serotonin dopamine</p> <p>Peptidergic: vasoactive intestinal peptide Substance P Enkephalin</p>	<p>Altered Structure or Function:</p> <p>Visual examination Microscopic examination</p>	<p>Female Reproduction:</p> <p>Sexual development and maturation and cyclic ovarian development: self-reports ovarian steroids pituitary hormones luteinizing hormone pregnancy assays: urinary human chorionic gonadotropin</p> <p>Genetic damage: ovarian tissue other relevant tissue heritable damage</p>
<p>Cell Biological Responses:</p> <p>Second Messengers: cyclic nucleotide Phosphorylation</p>	<p>Inflammatory and Immune Responses:</p> <p>Cell responses: macrophage neutrophils eosinophils protein products Components of cellular and humoral immunity Antigen-antibody complexes</p>	<p>Neurodevelopment:</p> <p>Minor physical abnormalities neurochemical factors: CNS neuro-transmitters behavioral measures: simple psycho-physical function complex functions</p>
<p>Calcium-dependent Transmitter Release</p> <p>Voltage-dependent Na⁺ or Ca²⁺ Uptake</p>	<p>Cellular and Biochemical Responses:</p> <p>Bronchoalveolar lavage: predominant cells immune cellular response Nasal lavage: lactate dehydrogenase hydrolytic and proteolytic enzymes cellular markers of inflammation Individual cell damage</p>	

APPENDIX B • Biologic Markers in Immunotoxicity

IMMUNOTOXICITY	
TIER I. All Persons Exposed to Immunotoxicants	
Humoral Immunity	
<p>Immunoglobulin class concentrations in serum (IgM, IgG, IgA, IgE) and immunofixation electrophoresis</p> <p>Natural Immunity: Antibody levels to ubiquitous antigens (e.g., anti-A and anti-B group substances in individuals of non-AB blood type)</p> <p>Secondary antibody responses² to proteins (e.g., diphtheria, tetanus, poliomyelitis) and polysaccharides (e.g., pneumococcal, meningococcal)</p>	
Lymphocytes	
<p>Enumeration of B and T cells in blood</p> <p>Surface analysis of CD3, CD4, CD8, CD20</p> <p>Secondary delayed-type hypersensitivity reaction (e.g., candida, diphtheria, tetanus)</p> <p>Alternative: Multiple antigen skin test kit</p>	
Autoantibody Titers	
Titers to red blood cells, nuclei [ANA], DNA, mitochondria, IgE [rheumatoid factor]	
TIER II. All Persons With Abnormal TIER I Test Results and a Fraction of the Total Exposed Population (To Be Determined by Statistician)	
Humoral Immunity ³	
Primary antibody response to protein and polysaccharide antigens	
Cellular Immunity ⁴	
<p>Proliferative response to mitogens (PHA, Con A) and possible antigens such as tetanus</p> <p>Primary DTH reaction (KLH)</p>	

² In immunization studies, live microorganisms should not be given to persons suspected of being severely immunocompromised

³ There is a need to develop a panel of antigens that can be used in sequential studies on a given individual since a particular antigen can be used only once to assess a primary response.

⁴ Here, too, there is a need for a panel of standard antigens for sequential testing. These could be the same as those used to assess primary antibody responses.

APPENDIX B • Biologic Markers in Immunotoxicity (cont'd)

NK cells, Monocytes, and other T and B cell Markers CD5, CD11, CD16, CD19, CD23, CD64; class II MHC on T cells by two-color flow cytometry for coexpression of class II and a T-Cell marker such as CD3
Serum Levels of Cytokines e.g., IL-1, IL-2, IL-6 Shed or secreted cellular activation markers and receptors
Class I and II MHC Antigen Typing
TIER III. Consider for Those With Abnormalities in TIER II Tests or a Random Factor of the Entire Population
If a proportion of CD 16 cells of NK cells, monocytes, or other B and T cell markers is abnormal: nonspecific killing of a tumor cell line to test for NK function If primary DTH reaction in cellular immunity is abnormal: cell proliferation in response to phorbol ester and calcium ionophore, anti-CD3 antibody, and staphylococcal enterotoxin B (experimental) Generation of secondary cell-mediated immune reactions (proliferation and MHC-restricted cytotoxicity) in vivo, e.g., with influenza virus (experimental) Immunoglobulin subclass levels in serum (IgA1, IgA2, IgG1-4) Antiviral titers (e.g., influenza, parainfluenza, cytomegalovirus, HIV) in serum (no deliberate immunization)
NAS, 1992b, pp. 109-111